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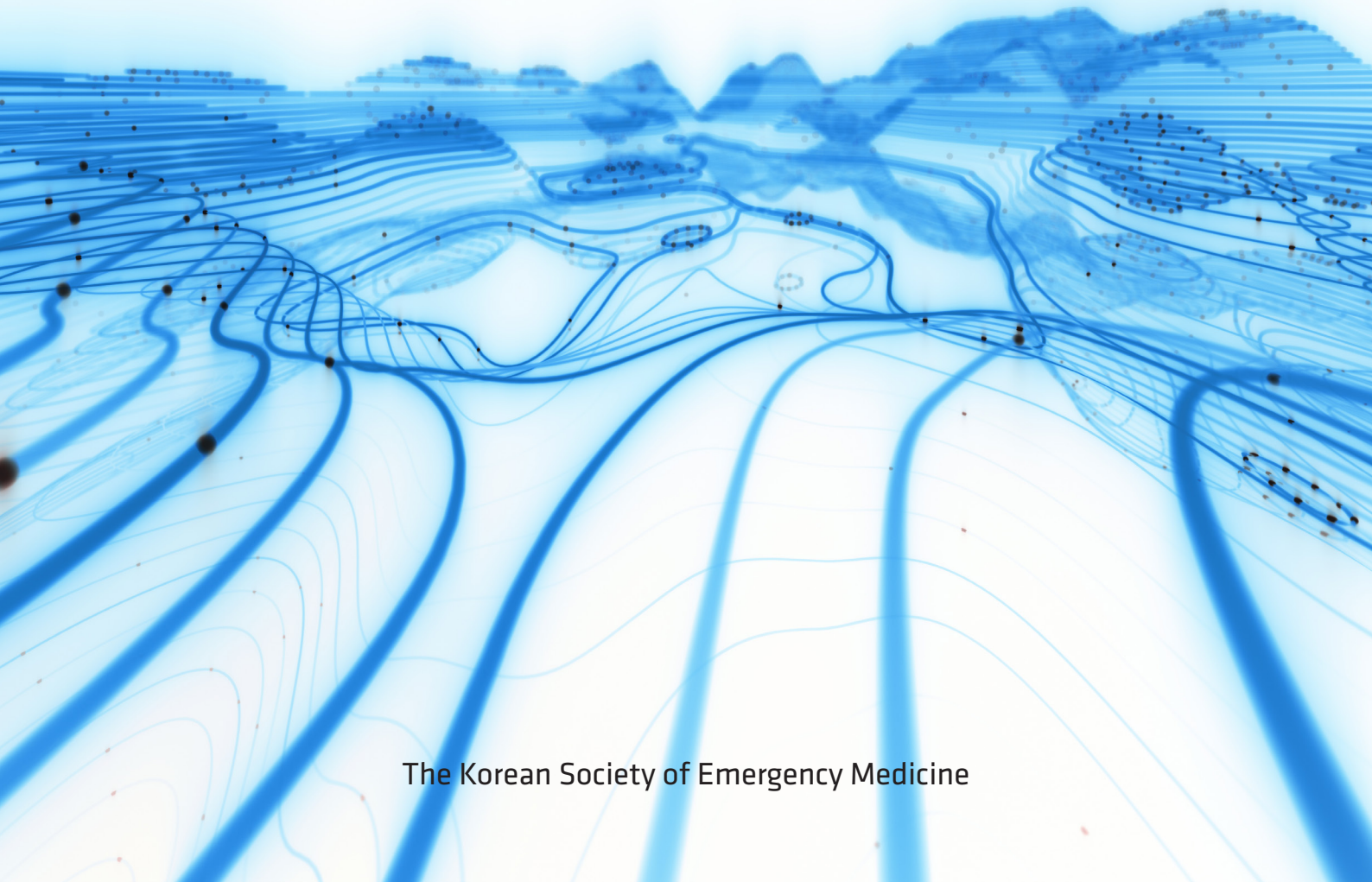

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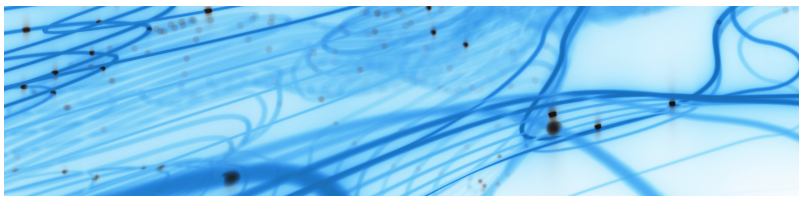

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Editorial

Artificial intelligence decision points in an emergency department

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In a crowded emergency department (ED), several crucial decisions must be made to provide effective patient care.[1,2] Prehospital decision-making, such as transport location and timing decisions, are crucial for continuity of care from prehospital to hospital levels.[3-5] Appropriate triage is required for selective and targeted care of critically ill patients.[6] To improve patient outcomes, a prompt investigation and intervention decision should be achieved.[7,8] The final disposition choice must consider patient safety.[9] Management of the overall process and the allocation of resources are also essential for ED operation.[10] Overall, the decision-making points should be considered based on patient state and ED situation.

Clinical decision support (CDS) based on artificial intelligence (AI) has recently been introduced into numerous medical fields, including emergency care. Increased data sources such as wearable devices and electronic medical records, higher computing power, and increased storage locations such as online cloud databases have contributed to the expansion of AI technology. As a result, several AI-based algorithms have been introduced for use in the ED journey.

AI-CDS can be categorized according to the decision phase of the ED journey. From the standpoint of patient care and based on a previous study, the ED journey can be classified into phases of prehospital phase, triage, investigation, intervention, and final disposition.[11] Each stage has its own decision objective and may be repeated based on the situation in the ED and the patient condition (Fig. 1).

During the prehospital period, decisions are based on the experience of the medical staff at the scene and the protocols of the local emergency medical service. However, it is difficult to make decisions with limited resources and patient information. With AI-CDS, efforts have been made to improve the accuracy of initial diagnoses based on prehospital information and data. Dispatching could also be aided by AI-CDS; for example, when the conversation between callers and bystanders shows certain context or words for critical conditions, systems would suggest higher-level providers to be dispatched. With prehospital data, a machine-learning-based prediction of hospital admission was attempted in a previous study to inform prehospital providers of patient prognosis after ED care.[12] Natural language processing techniques were implemented in prehospital paramedic reports for diagnosis of stroke.[13] A previous study predicted early sepsis using prehospital data.[14]

Nations and institutions have their own triage system for proper early care of a critical patient and effective resource distribution.[7,15] Underestimation or overestimation of triage can result in

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resource loss or deterioration of critically ill patients due to delayed care.[6] For triage, several AI-CDS system or novel AI-based methods have been introduced. There have been attempts to predict outcomes such as mortality or admission, including development of certain clinical conditions such as sepsis.[16-18] However, few studies demonstrate prospective AI-based triage research or implementation.[19,20] Attempts should be sought to match ED triage with ED resource allocation, including staff, beds, and investigatory efforts.

Prescription and interpretation of diagnostic tests are included in the investigation phase. The intervention phase consists of interventions and medication to improve patient conditions. Investigations and interventions that are time consuming and equipment restrictive should be limited. AI can assist in allocation of investigatory and treatment options or to plan expert consultations.

Investigation and intervention tools can be inputs or outputs of an AI algorithm. Some research has attempted to predict the need for computed tomography in the evaluation of disease.[21] Selected interventions can be a result of a prediction.[22] The majority of investigational studies are concerned with interpretation of diagnostic tests in relation to final diagnosis and outcome.[23-25]

In an ED, the decision for further management should be made carefully and appropriately. A patient-specific disposition, such as intensive care unit admission, is a frequently targeted outcome.[25-27] Predicting the readmission or return of a discharged patient is also essential.[28,29] Before making a final determination, these algorithms can help physicians reconsider the conditions of their patients.

Several barriers exist regarding the nature of AI. The first issue involves the data. Due to the nature of AI-based algorithms, data quality is as important as data quantity. Using low-quality data as input renders the algorithm less effective. However, unlike that from the intensive care unit, ED data collection is challenging due to rapid patient turnover and the complex environment. Additionally, patient information is easily lost along the path from injury to ward admission. Data collection should be encouraged, and data quality must be maintained.

It is well known that AI-based algorithms have a "black box" nature.[30,31] Therefore, it is difficult to determine the decision's cause or the decision-making process. To overcome the uncertainty of AI, explainable AI has recently been introduced, such as modified scoring systems or showing feature importance.[32,33] It is anticipated that explainable artificial intelligence-based predic-

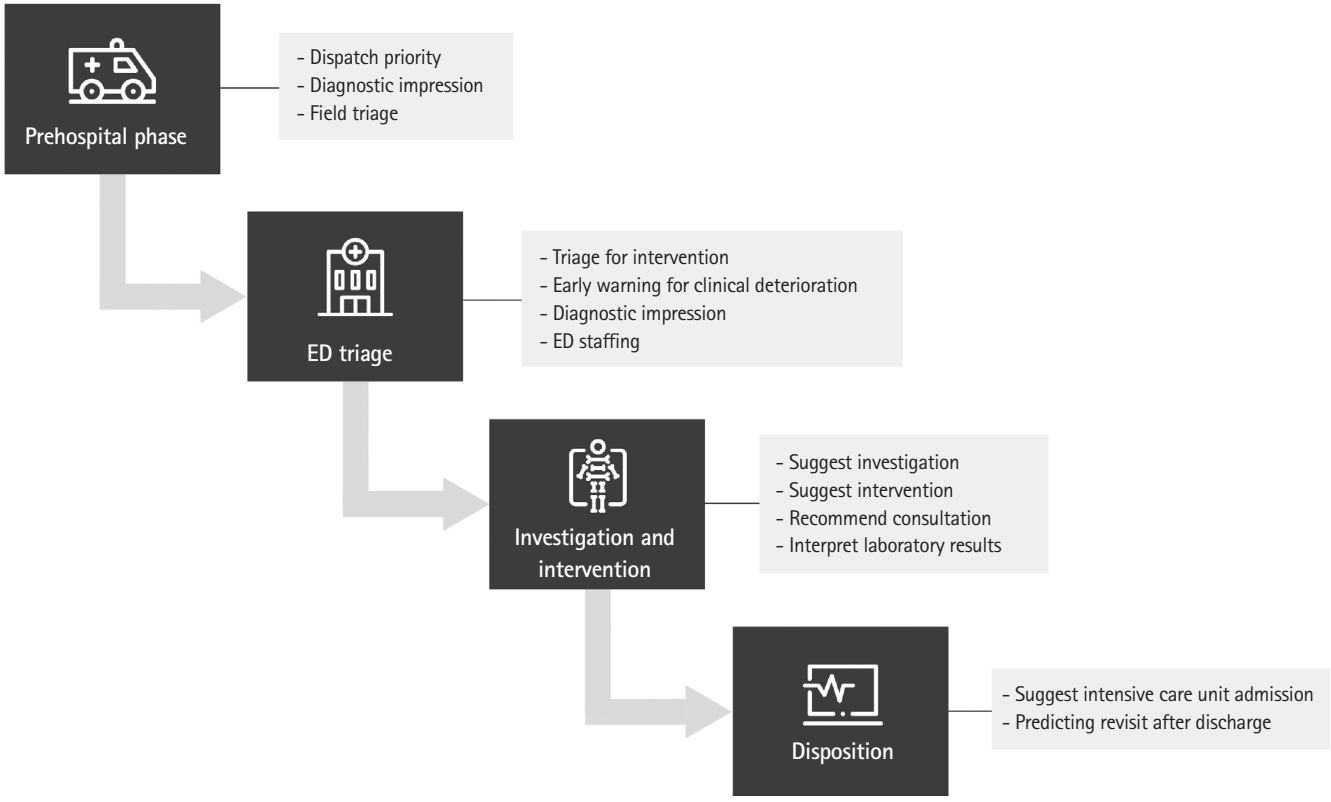

Fig. 1. Artificial intelligence-based clinical decision support points during emergency department (ED) phases. There are four points at which emergency physicians must make important decisions, where artificial intelligence can produce substantial effects.

tive models will be applicable to emergency medicine as they are implemented throughout the medical field.[34]

Recent review articles revealed that only a small number of AI-based models are utilized in actual practice, despite the development of numerous AI-based models for diverse decision phases.[35-37] The health care field is strictly managed by regulations, which is considered as the most important factor for delayed implementation of AI-CDS. For example, a randomized controlled trial is an important strategy to analyze the regulatory process, which is often difficult or impractical for AI-CDS. With these reasons, we do not frequently witness AI-CDS in practice.

Several AI-CDSs have been developed to cope with ED problems and can be categorized by the decision point in an ED: prehospital, triage, investigation, intervention, and disposition phases. Recently, only few of AI-CDS had been implemented and used in actual practice. These obstacles should be evaluated from the aspects of data, algorithm, and application. AI implementation is a practical decision that involves continuous and harmonized efforts by the ED, information technology, and data science.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Review Article

Subdissociative-dose ketamine for sickle cell vaso-occlusive crisis: a narrative review for the emergency physician

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Vaso-occlusive crisis (VOC) in sickle cell disease can cause severe pain and requires a thoughtful approach to analgesia. Considering the heightened awareness of the harm associated with opioids, an exploration of safer and more effective alternatives is overdue. Ketamine may play a role in supplementing or replacing opioid analgesia for patients in VOC. Studies on the use of ketamine for VOC are sparse, though increasing. In this review, we summarize the literature on subdissociative ketamine use for VOC to offer providers insight into the most effective and safe dosing regimens for sickle cell disease patients. Overall, the studies discussed in this review show decreased opioid use when subdissociative ketamine is provided as an adjunct and resolution of pain for most patients when subdissociative ketamine is used as the sole form of analgesia in VOC. Most studies examined intravenous delivery, and successful outcomes were established for both adult and pediatric patients in multiple clinical settings, including in the emergency department. Although more research is needed, it is clear from the published data that subdissociative ketamine may provide an efficacious addition to the clinician's toolbox for managing VOC.

Keywords Sickle cell anemia; Vaso-occlusive crisis; Subdissociative ketamine; Pain management; Hospital emergency service

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INTRODUCTION

The social and economic burdens of sickle cell disease (SCD) cannot be understated: over 100,000 people in the United States live with this diagnosis, with annual costs of emergency treatment and hospitalization totaling over $1 billion.[1] Even though many of these patients have chronic pain due to this disease, 90% of SCD hospital admissions are due to acute vaso-occlusive crisis (VOC). VOC is defined as a new onset of pain that occurred within the 10 days prior to presentation, lasts at least 4 hours, and for which there is no explanation other than vaso-occlusion from a sudden increase in cell sickling.[2] VOC can be severe and requires a thoughtful approach to analgesia that minimizes morbidity from the methods of pain control selected. Typical treatment includes hydration and medications that fall under three major classes: opioids, nonopioids, and adjuvants. Opioids, such as morphine, hydromorphone, fentanyl, and tramadol, have traditionally been used.[3] They carry with them the risks of respiratory depression, overdose, and addiction, and the lesser-known risk of opioid-induced hyperalgesia, a phenomenon of increasing pain even in the setting of increasing doses of opioids. Opioid-induced hyperalgesia arises from overactivation of N-methyl-d-aspartate (NMDA) receptors, which leads to downregulation of opioid receptors. Clinically, this results in opioid-refractory pain, lengthy hospital stays, and high pain-related readmission rates.[4] Another factor that contributes to opioid-refractory pain in SCD is neuropathic pain, thought to occur from sensitization of spinal neurons with repeated vaso-occlusive events as SCD patients reach adulthood. The presence of a neuropathic process adds further complexity to the treatment of VOC, as opioids are often ineffective for neuropathic pain.[5] Innovative therapies are needed to more effectively treat pain in VOC.

Subdissociative (also known as subanesthetic, low, or analgesic dose) ketamine may provide an alternative or supplemental analgesic option by which to address pain in VOC. However, the US Food and Drug Administration currently only approves its use as an anesthetic agent, although some guidelines support the use of subdissociative doses of ketamine for pain control in children and adults.[6] Ketamine may be of particular use in SCD VOC as it is an NMDA receptor antagonist that prevents opioid tolerance and opioid-induced hyperalgesia; for example, ketamine improved the effectiveness of morphine in pain management.[7] In addition to the NMDA receptor antagonism of ketamine, it acts at cholinergic receptors, opioid receptors, and sodium and potassium channels as well, though these interactions are suspected to play ancillary roles in its analgesic effects.[8] Multiple studies have described the efficacy and safety of subdissociative-dose ketamine for analgesia in various settings, including the emergency department (ED) and inpatient settings.[9] However, studies on the use of ketamine in VOC are sparse though increasing.[5,10-17] There is variation among these studies in terms of ketamine dose, treatment duration, and concurrent opioid use.

In this review, we summarize the literature on subdissociative ketamine for VOC to offer both ED and inpatient providers insights into the most effective and safe dosing regimens for their patients.

METHODS

A National Center for Biotechnology Information (NCBI) Medline search included all articles published through March 2022, with the following terminology: "Anemia, Sickle Cell"[MeSH] AND "Ketamine"[MeSH]. Articles were excluded if they were classified as "review," did not note the dosages of ketamine used, did not include key demographic details of the population studied such as age, were in languages other than English, or consisted of animal or cell culture experiments. We searched ClinicalTrials.gov for clinical trials using ketamine for VOC. Two reviewers (MHB and SMM) independently evaluated the eligibility of the references by reading their titles and abstracts. If there was any doubt about the relevance of the studies, we obtained full copies for further assessment. Data extraction was performed independently by both authors, and disagreements were resolved by consensus.

We focused on the use of ketamine for VOC and stratified our analysis into adult and pediatric patients (studies with subjects younger than 18 years or studies occurring in a children's hospital setting). Within these two groups, we further substratified our analysis to examine efficacy and adverse effects based on method of medication delivery and dose.

RESULTS

Our search yielded 19 articles identified through NCBI Medline and 10 trials identified through ClinicalTrials.gov. Of the 19 articles identified through NCBI Medline, three were removed for being reviews, two were removed for being study protocols, one was removed for being unrelated to sickle cell patients, and five were removed for not having drug doses or primary outcomes listed. The remaining eight articles were included in this review. Of the 10 trials identified through ClinicalTrials.gov, two were completed with results available and were included in this review, while the others were either ongoing or discontinued due to poor recruitment.

Of the studies identified, two were randomized controlled trials,[15,17] two were cohort studies,[5,18] and one was a retrospective

Table 1. Studies examining ketamine use for vaso-occlusive crisis in adult sickle cell disease patients

Study	Study type	Setting	Sample size	Mean age (yr)	Method of ketamine delivery	Medication dose	Main result	Adverse event
Meals et al.[11] (2011)	Case report	Inpatient floors	1	31	IV In conjunction with morphine PCA	Bolus of 5 mg followed by infusion of 9 mg/hr, increased to max infusion of 24 mg/hr	Decrease in opioid use after starting ketamine Resolution of pain within 4 days of starting ketamine	Self-resolved somnolence and nystagmus after ketamine bolus
Jennings et al.[12] (2013)	Case report	Inpatient floors	1	38	PO In conjunction with hydromorphone PCA	Starting dose of 15 mg PO every 6 hr, increased to 50 mg PO every 6 hr	Decrease in opioid use after starting ketamine Resolution of pain within 1 day of starting ketamine.	No serious adverse events reported
Tawfic et al.[13] (2014)	Retrospective chart review	ICU	9	27	IV In conjunction with morphine PCA	Bolus of 0.25 mg/kg followed by infusion of 0.20–0.25 mg/kg/hr	Decrease in opioid use after starting ketamine Reduction of pain score from mean 9.1 to mean 5.7 out of 10, 1 day after starting ketamine	One patient developed psychotomimetic effects, prompting discontinuation of ketamine
Gimovsky et al.[14] (2018)	Case report	Inpatient floors	2[a]	27	IV In conjunction with hydromorphone PCA	Starting dose of 10 mg/hr, maximum dose of 25 mg/hr	Patient 1: decrease in opioid use after starting ketamine; delivered at 30 wk and the child had no birth defects Patient 2: increased opioid use as she felt ketamine was ineffective; delivered at 37 wk and the child had no notable birth defects	Patient 1 had dizziness with a higher titration dose of ketamine (25 mg/hr), which resolved on return to the lower dose of 10 mg/hr
Palm et al.[16] (2018)	Case series	ICU	5	34	IV In conjunction with opioid PCA	0.18–0.30 mg/kg/hr	Decrease in opioid use per patient after starting ketamine Reduction in pain scores during infusion as	One patient experienced dizziness and vivid dreams with ketamine infusion, leading to discontinuation
Alshahrani et al.[17] (2022)	RCT	ED	278[b]	29	IV	Ketamine group: 0.3 mg/kg in 100 mL normal saline infused over 30 min Morphine group: 0.1 mg/kg in 100 mL normal saline infused over 30 min	Decrease in mean opioid use in ketamine group (0.07 mg/kg) versus morphine group (0.13 mg/kg) No significant difference in hospital admission rate	Five patients developed dizziness and four patients developed nausea and vomiting in the ketamine group

IV, intravenous; PCA, patient-controlled analgesia; PO, oral; ICU, intensive care unit; RCT, randomized controlled trial; ED, emergency department.
[a]Both patients were pregnant and in their third trimesters. [b]Ketamine group, 138 patients; morphine group, 140 patients.

chart review.[13] The remaining five studies were case reports[11,12,14] and case series.[10,16] Of the studies identified, two were conducted in the ED,[17,18] six were conducted on general inpatient floors,[5,10-12,14,15] and two were conducted in the intensive care unit (ICU).[13,16] Six studies were stratified as adult studies (Table 1)[11-14,16,17] and four as pediatric studies (Table 2).[5,10,15,18]

Use of ketamine alone versus as an adjunct to opioids, method of ketamine delivery, use of a bolus versus infusion without a bolus, starting doses, and infusion times differed among the studies. Among the adult studies, five used ketamine in conjunction with opioids.[11-14,16] Opioid use was found to decrease after the initiation of ketamine in each of these studies. In one of these studies, ketamine was given as a 0.25 mg/kg bolus followed by an infusion of 0.20 to 0.25 mg/kg/hr for uncontrolled pain with increasing doses of intravenous (IV) morphine. In this study, a midazolam bolus of 1 mg followed by an infusion of 0.5 to 1.0 mg/hr was added to reduce the emergence of ketamine reactions. Mean IV morphine use decreased by 33 mg/day after ketamine was started (P = 0.007), and pain scores, as measured by a numeric rating scale, decreased from a mean of 9.1 out of 10 before the initiation of ketamine to a mean of 5.7 out of 10, 1 day after ketamine was started (P = 0.01).[13] In another of these studies, a 10 mg/hr IV ketamine infusion was started in pregnant patients experiencing VOC unresolved with opioid therapy. In one of the two patients, ketamine treatment was effective in reducing concurrent IV hydromorphone use by 60% and resolving VOC, whereas it was not effective in the other. In both patients, deliveries occurred in the third trimester, and no notable birth defects were detected in either infant.[14] Another study in this group examined the use of oral (PO) ketamine in VOC with opioid therapy. Ketamine treatment in this study began with a starting dose of 15 mg every 6 hours, which was increased to 50 mg every 6 hours. IV morphine use was found to decrease by 1,000 mg daily after starting ketamine, and pain improved from activity-limiting to tolerable within 1 day of starting ketamine.[12]

One study compared a group receiving a single low dose of ketamine (0.3 mg/kg) in 100 mL of normal saline or a standard dose of morphine (0.1 mg/kg) in 100 mL of normal saline relative to pain scores, hospital admission rates, and cumulative dose of opioids received. Though no significant difference was found in mean pain scores or hospitalization rates at the end of the trial, the ketamine group had lower mean opioid use than the morphine group.[17]

Among the adult studies, two documented adverse effects led to treatment cessation in affected participants. In one of these studies, one patient (of nine) developed psychotomimetic symptoms after ketamine was first given as a bolus at 0.25 mg/kg and

Table 2. Studies examining ketamine use for vaso-occlusive crisis in pediatric sickle cell disease patients

Study	Study type	Setting	Sample size	Mean age (yr)	Method of ketamine delivery	Medication dose	Main result	Adverse event
Zempsky et al.[10] (2010)	Case series	Inpatient floors	5	13.4	IV Either alone or in conjunction with morphine PCA	Starting doses of 0.06–0.20 mg/kg/hr, with two patients receiving a 0.1 mg/kg bolus prior	In the patient who received an IV ketamine infusion as a lone treatment: pain control was achieved 24 hr faster than in the previous four hospitalizations In the patient who received an IV ketamine infusion in conjunction with opioid treatment: pain scores were reduced from 10 to 4.6	Patients who received boluses previous to infusion had adverse events: one experienced dysphoria and the other experienced nystagmus and unresponsiveness
Nobrega et al.[5] (2017)	Cohort	Inpatient floors	85	15	IV In conjunction with opioids	Starting doses of 0.05–0.40 mg/kg/hr, titrated up to 1 mg/kg/hr in some cases	Decrease in pain scores after ketamine infusion Greater pain reduction is seen in male patients and younger patients	No serious adverse events reported
Lubega et al.[15] (2018)	RCT	Inpatient floors	240[a]	12	IV Delivered over a 10-min infusion	1 mg/kg ketamine versus 0.1 mg/kg morphine	Reduction in numerical rating scale score comparable to a single dose of ketamine (66.4%) and morphine (61.3%) Pain resolved faster in the ketamine group (20 min) than in the morphine group (34 min)	Adverse effects experienced in 37% of those in the ketamine group, including nystagmus, dysphoria, dizziness, and increased salivation
Cooper-Sood et al.[18] (2022)	Cohort	Pediatric ED	62	19	IV In conjunction with opioids	0.2 mg/kg infused at a rate of 0.3 mg/kg/hr	Decrease in morphine equivalents used compared to previous visits Subjectively reported faster pain relief	No serious adverse events reported

IV, intravenous; PCA, patient-controlled analgesia; RCT, randomized controlled trial; ED, emergency department.
[a]Ketamine group, 120 patients; Morphine group, 120 patients.

then infused at 0.25 mg/kg/hr.[13] In another study, one patient (of five) developed persistent dizziness and vivid dreams with a 0.18 mg/kg/hr ketamine infusion.[16] Other adverse effects included horizontal nystagmus that self-resolved,[11] dizziness that resolved with a dose reduction,[14] and nausea that was controlled with antiemetics.[17]

Among the pediatric studies, one investigation examined both ketamine as a single treatment for VOC in one patient and ketamine in conjunction with opioids for others. In this study, one patient received only IV ketamine at 0.1 mg/kg/hr and had a hospital stay 24 hours shorter than a previous four hospitalizations for VOC, during which only opioids were received. Four patients in this study received IV ketamine with various dosing strategies after their pain was unresolved with opioids; the patient who received 0.1 mg/kg/hr without a bolus dose had a reduction in pain score from 10 to 4.6, whereas the patients who received boluses experienced adverse effects such as nausea and dizziness without relief of pain.[10]

Two studies examined ketamine use in conjunction with opioids. In one of these studies, IV ketamine was initiated from 0.05 to 0.40 mg/kg/hr after unresponsiveness to opioid therapy. After initiation of ketamine infusion, patients had decreased pain intensity and opioid consumption ($P=0.001$). It was additionally found that younger age ($P=0.018$) and male sex ($P=0.013$) were predictors of greater pain reduction.[5] In another study, participants first received a dose of IV opioids followed by 0.2 mg/kg IV ketamine infused at a rate of 0.3 mg/kg/hr. Thereafter, pain scores, change in opioid usage compared to previous visits, and likelihood of discharge from the ED were assessed. It was found that patients subjectively reported faster pain relief with incorporation of ketamine into treatment and had decreased morphine equivalent usage compared to previous visits ($P=0.004$). The likelihood of discharge from the ED was not affected.[18]

Last, a randomized clinical trial allocated 240 patients into two groups: one group received 1 mg/kg of IV ketamine, whereas the other received 0.1 mg/kg of IV morphine. Pain was assessed at regular intervals, and though no overall difference in pain scores was found at the end of the study, the ketamine group displayed a faster reduction in pain scores. The ketamine group also had a greater occurrence of adverse effects, with 37% experiencing nystagmus, dysphoria, dizziness, or increased salivation. Adverse effects were seen in 3% of the morphine group and included dizziness and urticaria.[15]

DISCUSSION

Subdissociative use of ketamine has increased in EDs, inpatient floors, and ICUs for a growing number of indications.[6] Ketamine is affordable and accessible in resource-limited settings, can be delivered through various routes, and, as discussed in our paper, may play a role in both supplementing or replacing opioid analgesia in conditions such as SCD VOC. In light of the opioid abuse crisis and heightened awareness of the associated harms, including constipation, respiratory depression, dependence, and withdrawal, exploration of safer and more effective alternatives is overdue, especially for patients who are frequently in pain such as those with SCD.[19]

The studies we discuss in this review suggest that the use of ketamine in VOC has many advantages. In most studies where it was used in conjunction with opioids, ketamine resulted in a decrease in opioid use. In most studies where it was used as the sole agent for analgesia, ketamine resolved pain for all but two patients who experienced adverse effects. The effectiveness of ketamine for VOC may have multiple sources: it has known beneficial mood effects that can be helpful in the SCD population, as many of these patients have a history of anxiety and depression[20]; it can prevent opioid-induced hyperalgesia through its antagonism of NMDA receptors[4]; and it has ancillary analgesic effects through its actions on cholinergic receptors and μ-opioid receptors.[8]

Though the studies examining ketamine use for VOC offer different doses, methods of delivery, and concurrent opioid management strategies, the following can be considered to maximize efficacy and minimize adverse effects. First, ketamine can be offered in the ED, inpatient floors, and ICU settings. Ketamine can be given to both pediatric and adult patients. Second, subdissociative ketamine for acute pain should not be given to those with poorly controlled cardiovascular disease, including labile hypertension, psychiatric conditions involving psychosis such as schizophrenia, severe hepatic dysfunction such as cirrhosis, and allergy to ketamine.[6] Third, ketamine can be given in a variety of ways, most commonly IV as either a bolus dose followed by a continuous infusion or a continuous infusion without a bolus. Fourth, though a study in this review used subdissociative IV ketamine successfully for VOC in pregnant women, there are limited data for use in this population. Fifth, there are no data to suggest that subdissociative ketamine is unsafe in patients with renal dysfunction. Sixth, ketamine boluses can be associated with increased side effects. Psychosensory effects increase at bolus doses above 0.3 mg/kg. If used, boluses can be given at 0.1 to 0.3 mg/kg.[21] If used as a bolus, ketamine should be given over 10 to 15 minutes to reduce psychosensory adverse effects while maintaining analgesic efficacy.[22] Although a few studies used a ketamine bolus up to 1 mg/kg for pain control,[15] this dose could be too large to be

considered subdissociative and is better suited for ED procedures such as endotracheal intubation or joint reductions. Lastly, most data for ketamine use in VOC are from IV ketamine use, and ketamine should be infused by IV. Infusions can start as low as 0.1 mg/kg/hr and should not exceed 1.0 mg/kg/hr in non-ICU settings.[23]

Though one study included in our review successfully used PO ketamine for VOC,[12] the overall evidence and guidance for PO ketamine use in acute pain are limited. When taken PO, ketamine is approximately 20% bioavailable compared to 100% in IV administration.[24] No studies examined the use of intranasal ketamine for VOC, perhaps due to the numerous patient factors that can affect bioavailability in this route, which has been shown to range from 25% to 50%.[25]

The overall safety profile of subdissociative ketamine is reassuring; large studies of continuous infusions for various pain conditions, including VOC, have shown no lasting psychotomimetic adverse effects, no hemodynamic changes requiring vasoactive agents, and no life-threatening adverse events.[26] In our review, the adverse effects seen were primarily associated with bolus dosing and infusions at higher doses.[10,11,13,14,17] While lower doses of subdissociative ketamine appear safe to use for VOC, data are limited regarding the effects of repeated exposure to ketamine. This is an area for further research, as SCD patients can present numerous times per month for treatment of VOC.

A continued examination of ketamine use for VOC is in line with guidelines that advocate a multimodal approach, defined as two or more medications that provide analgesia through different mechanisms, in SCD pain management.[27] The benefits of continuing to explore alternatives to opioids, such as ketamine, are decreased burden of opioid-related side effects and abuse on healthcare systems. We provide this review to summarize the investigations that have been conducted on ketamine as an alternative or adjunct to opioid therapy for VOC. While further trials on various populations including children, adults, pregnant patients, and those who present frequently for infusions need to be conducted to form stronger conclusions on subdissociative doses of ketamine for VOC, we offer general suggestions based on data from previous trials.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Original Article

Prediction of vasopressor requirement among hypotensive patients with suspected infection: usefulness of diastolic shock index and lactate

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Objective We evaluated the performance of diastolic shock index (DSI) and lactate in predicting vasopressor requirement among hypotensive patients with suspected infection in an emergency department.

Methods This was a single-center, retrospective observational study for adult patients with suspected infection and hypotension in the emergency department from 2018 to 2019. The study population was split into derivation and validation cohorts (70/30). We derived a simple risk score to predict vasopressor requirement using DSI and lactate cutoff values determined by Youden index. We tested the score by the area under the receiver operating characteristic curve (AUC). We performed a multivariable regression analysis to evaluate the association between the timing of vasopressor treatment and 28-day mortality.

Results A total of 1,917 patients were included. We developed a score, assigning 1 point each for the high DSI (≥ 2.0) and high lactate (≥ 2.5 mmol/L) criteria. The AUCs of the score were 0.741 (95% confidence interval [CI], 0.715–0.768) at hypotension and 0.736 (95% CI, 0.708–0.763) after initial fluid challenge in the derivation cohort and 0.676 (95% CI, 0.631–0.719) at hypotension and 0.688 (95% CI, 0.642–0.733) after initial fluid challenge in the validation cohort, respectively. In patients with scores of 2 points, early vasopressor therapy initiation was significantly associated with decreased 28-day mortality (adjusted odds ratio, 0.37; 95% CI, 0.14–0.94).

Conclusion A prediction model with DSI and lactate levels might be useful to identify patients who are more likely to need vasopressor administration among hypotensive patients with suspected infection.

Keywords Septic shock; Sepsis; Diastolic shock index; Lactic acid; Vasopressors

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Capsule Summary

What is already known

Early initiation of a vasopressor for septic shock might be beneficial in terms of more quickly correcting hypotension, maintaining organ perfusion, and limiting the amount of fluid administration. However, some controversial results have been reported; therefore, a predictive tool might help to identify patients who would benefit from vasopressor administration, rather than a "one-size-fits-all" approach to all hypotensive septic patients.

What is new in the current study

In this study, we demonstrated that the diastolic shock index and lactate levels could be used for predicting vasopressor requirement in hypotensive patients with suspected infection. We developed a simple risk assessment model using both values with fair discriminating performance. The prediction model might be helpful for identifying patients who are more likely to need vasopressor administration before or during initial fluid resuscitation. Notably, associations between the timing of vasopressor administration and 28-day mortality varied according to prediction score.

INTRODUCTION

Sepsis is a life-threatening problem defined as dysregulated host responses to an infection that causes organ dysfunction, and the overall hospital mortality rate of affected patients is > 10%.[1-4] Septic shock, which is a subtype of sepsis involving circulatory, cellular, and metabolic abnormalities, remains a critical illness associated with a hospital mortality rate of about 40%.[1,5,6] Systemic vasodilatation is a key pathophysiologic process in septic shock, and fluid resuscitation and vasopressor administration are the main treatment modalities.[7,8]

The Surviving Sepsis Campaign (SSC) guidelines recommend using norepinephrine (NE) as a first-line vasopressor, and this medication is included in the 1-hour treatment bundle.[7] Early initiation of NE for septic shock might be beneficial in terms of more quickly correcting hypotension, maintaining organ perfusion and limiting the amount of fluid administration.[9-12] However, some controversial results have been reported.[13,14] In addition, there is no clear consensus on the appropriate time to initiate vasopressors during initial fluid resuscitation, and it has not been determined which index can be used to select patients who require vasopressors early.[15] Therefore, a predictive tool might be helpful to identify patients who need NE urgently in a personalized context rather than adopting a "one-size-fits-all" approach to all hypotensive septic patients.

Measuring the diastolic arterial pressure (DAP) may be a simple way to identify patients who need NE administration because a low DAP is mainly due to reduced vascular tone.[8,16] On the other hand, the diastolic shock index (DSI), which is defined as the ratio between heart rate (HR) and DAP, has been proposed as an early predictor for identifying high-risk patients with septic shock.[17] In this study, neither isolated low DAP nor high HR showed prognostic value, but the DSI value calculated before or at the start of vasopressor treatment showed similar performance to initial lactate levels and the Sequential Organ Failure Assessment (SOFA) score in predicting mortality. Importantly, early initiation of vasopressors within 1 hour showed a survival benefit only in the higher DSI quintile group. The results suggested that a higher DSI might be a trigger for early vasopressor treatment.

Lactate has been widely used as a biomarker for tissue perfusion, a screening tool for sepsis and part of the septic shock definition.[5,7] In an observational study, hyperlactatemia ≥ 4 mmol/L was also associated with a phenotype refractory to fluid resuscitation.[18] Given these results, DSI and lactate, as widely available indices that can easily be measured, might be used to identify patients who need vasopressor treatment.

In this study, we evaluated the performance of the DSI and initial lactate levels for predicting vasopressor requirement among hypotensive patients with suspected infection in an emergency department (ED), and we developed a risk assessment scoring protocol for vasopressor use.

METHODS

Study design, setting, and population

This was a single-center, retrospective, observational study performed at Samsung Medical Center, a 1,960-bed, university-affiliated, tertiary care referral hospital in Seoul, Korea. The study period was from January 2018 to December 2019. This study was approved by the Institutional Review Board of Samsung Medical Center (No. 2022-03-070); the need for informed consent was waived because this study was retrospective and observational in nature, and patients' data were anonymized.

We included patients aged ≥ 18 years with suspected infection

and hypotension who presented to the ED. A suspected infection was defined as a case in which blood culture and antibiotic administration were conducted in the ED.[1] Hypotension was defined as systolic blood pressure of <90 mmHg. We excluded patients who had limitations on invasive care (e.g., patients who had terminal malignancy or who had previously signed a do-not-resuscitate order), who presented with cardiac arrest, who were transferred from or to another hospital, who had obviously noninfectious conditions such as trauma or bleeding, who showed hypotension 6 hours after ED arrival and who had inadequate data due to an inability to access electronic medical records.

Data collection and outcomes

Eligible cases were electronically identified based on the definition of suspected infection and hypotension. The following data were extracted from the hospital database: age, sex, comorbidities, vital signs, mental status, suspected infection focus, initial laboratory tests, vasopressor use, mechanical ventilation, ED disposition, and survival data.

DSI was defined as the quotient between HR and DAP.[17] We calculated the DSI at the time of initial hypotensive events and immediately after a rapid infusion of 300 to 1,000 mL. DSI values after vasopressor administration were not used. We used arterial blood pressure values first, but noninvasive measurements were used if an arterial line was not inserted. The SOFA score was calculated using maximum variables recorded at 24 hours from ED arrival. Missed variables for the SOFA components were considered as normal values. Septic shock was defined according to the Sepsis-3 criteria.[5] The primary study outcome was vasopressor requirement. NE was used as the first vasopressor, and the target mean arterial pressure was ≥ 65 mmHg. General ED management for sepsis was conducted according to the SSC guidelines.[7]

Statistical analysis

The study population was split randomly into derivation and validation cohorts (70/30). The results were expressed as mean ± standard deviation values or median with interquartile range (IQR) values for continuous variables and as the number of patients with percentages for categorical data. Continuous variables were analyzed using Wilcoxon rank-sum tests, while categorical variables were analyzed using chi-squared tests. For the derivation and validation cohorts, we categorized patients according to the quintile of the DSI values and initial lactate levels, and we evaluated P-value for trends with the incidence of vasopressor use. The accuracy of prediction for vasopressor requirement was assessed using the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, and their corresponding 95% confidence intervals (CIs). Optimal cutoff values of the DSI and lactate levels were calculated using Youden index. We derived a simple risk scoring system to predict vasopressor requirement using the DSI and lactate cutoff values in the derivation cohort. We used regression coefficients of the DSI and lactate level for vasopressor use to derive a score in multivariable linear regression models. We converted the coefficient into a single-integer risk score.

Afterwards, the final risk model was assessed by multivariable logistic regression analysis with variables showing differences in baseline characteristics, the AUC, and calibration plots. For sensitivity analysis, we evaluated the predictive validity of a model in which missing values of the DSI and lactate level were replaced with normal values. In addition, we investigated whether the timing of vasopressor administration was associated with the 28-day mortality rate according to the developed score obtained by multivariable logistic regression modeling. We calculated adjusted odds ratios (aORs) with predefined variables, including age, infection focus, lactate levels, and SOFA score. A two-tailed P-value of less than 0.05 was considered statistically significant. All analyses were performed using R ver. 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and Stata ver. 17.0 (StataCorp., College Station, TX, USA).

RESULTS

Study population

We assessed the eligibility of 17,736 adult patients who underwent blood cultures and antibiotic administration in the ED from January 2018 through December 2019. Patients who were transferred from or to another hospital, who had limitations on invasive care, who did not have an infection, who presented with cardiac arrest and/or who had inadequate data were excluded (n = 2,827). We also excluded patients without hypotension or with hypotension after 6 hours from ED arrival (n = 12,992). A total of 1,917 patients with suspected infection with hypotension within 6 hours from ED arrival were included in the analysis. We randomly split the data with 1,342 patients (70%) included in the derivation cohort and 575 patients (30%) included in the validation cohort (Fig. 1).

Baseline characteristics

The baseline characteristics of the overall population, the derivation, and validation cohorts are presented in Table 1. The median age was 65 years (IQR, 56–74 years), and 1,052 study participants (54.9%) were male. The 28-day mortality rate was 12.4% (n = 237). The median DSI value was 1.9 (IQR, 1.6–2.3) at the time of hypotension and 1.8 (IQR, 1.5–2.2) after fluid challenge. The

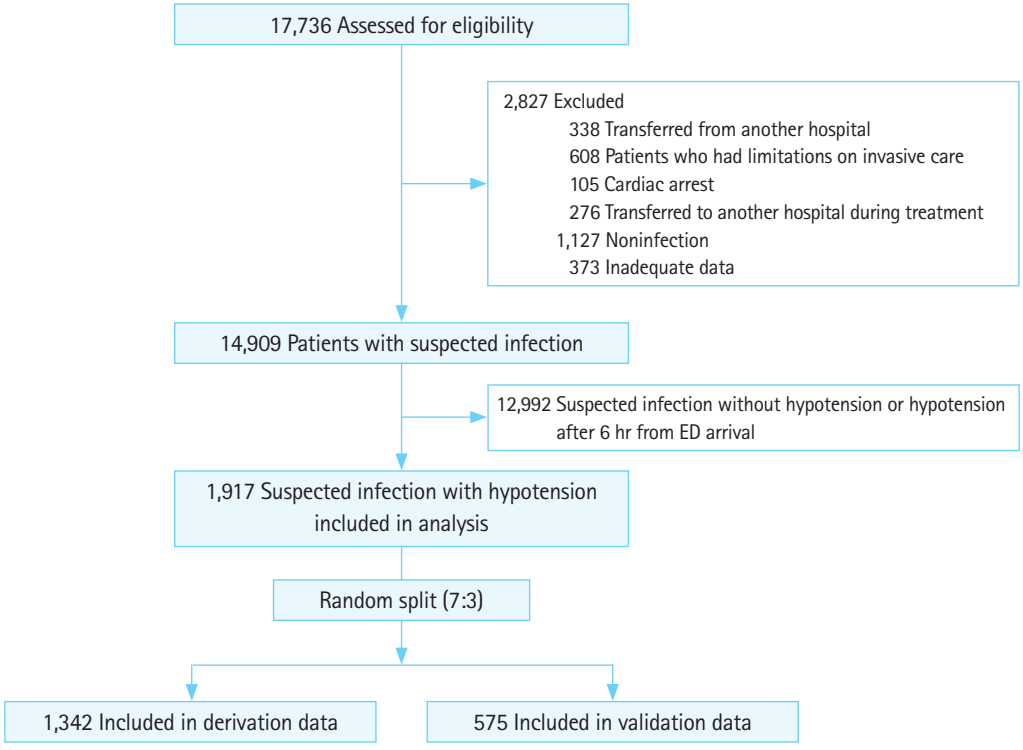

Fig. 1. Study population. ED, emergency department.

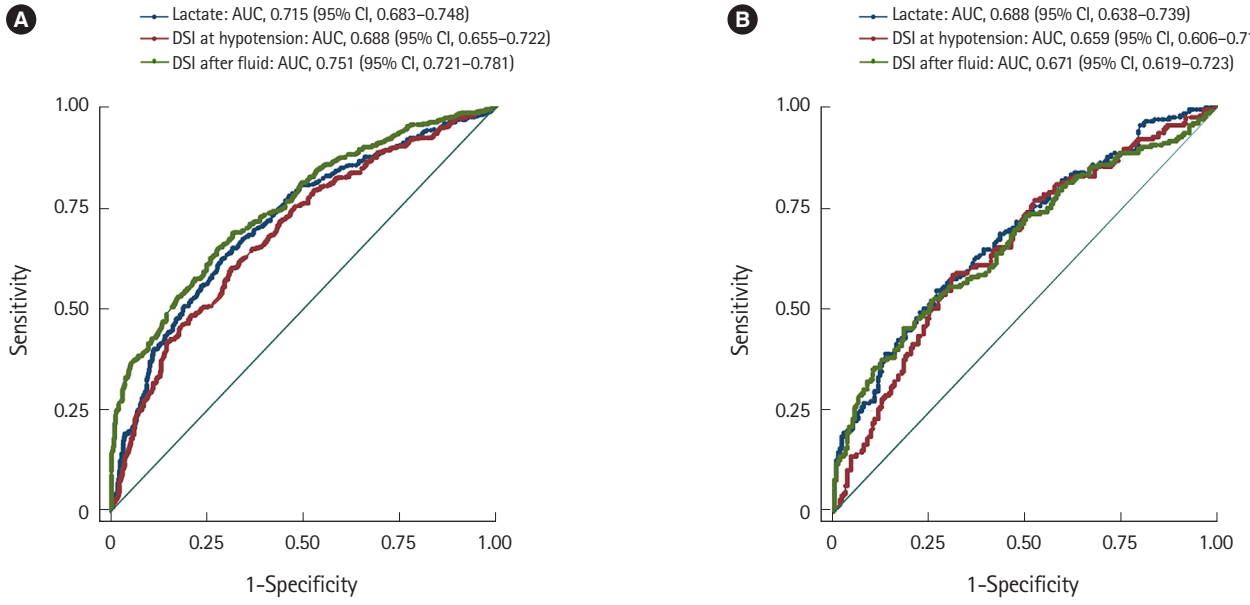

Fig. 2. Area under the receiver operating characteristic curves (AUCs) of the diastolic shock index (DSI) at the time of hypotension and after fluid challenge and initial lactate levels for predicting vasopressor requirement in (A) the derivation cohort and (B) the validation cohort. The AUC of the DSI after fluid was significantly higher than that of the DSI at hypotension (P<0.01). There was no significant difference in other post hoc comparisons. CI, confidence interval.

mean volume of initial fluid before vital sign follow-up was 838.0±261.8 mL. The median lactate level was 2.3 (IQR, 1.5–3.6), and the SOFA score on the 1st day was 5.0 (IQR, 3.0–8.0). The overall vasopressor requirement was 45.7% (n=876), with 620 patients (46.2%) included in the derivation cohort and 256 patients (44.5%) included in the validation cohort.

Table 1. Baseline characteristics of the derivation and validation cohorts

Characteristic	Overall (n = 1,917)	Derivation (n = 1,342)	Validation (n = 575)
Age (yr)	65 (56–74)	65 (55–74)	65 (56–74)
Male sex	1,052 (54.9)	734 (54.7)	318 (55.3)
Comorbidity			
Hypertension	581 (30.3)	403 (30.0)	178 (31.0)
Diabetes	459 (23.9)	307 (22.9)	152 (26.4)
Cardiac disease	333 (17.4)	234 (17.4)	99 (17.2)
Cerebrovascular disease	197 (10.3)	145 (10.8)	52 (9.0)
Chronic lung disease	170 (8.9)	117 (8.7)	53 (9.2)
Chronic liver disease	192 (10.0)	135 (10.1)	57 (9.9)
Solid cancer	1,041 (54.3)	700 (52.2)	341 (59.3)
Suspected infection source			
Respiratory infection	392 (20.5)	269 (20.0)	123 (21.4)
Intraabdominal infection	504 (26.3)	357 (26.6)	147 (25.6)
Urinary tract infection	271 (14.1)	187 (13.9)	84 (14.6)
Other or unknown	750 (39.1)	529 (39.4)	221 (38.4)
Positive blood culture	442 (23.1)	333 (24.8)	109 (19.0)
Vital sign at the time of hypotension			
Systolic pressure (mmHg)	83 (78–87)	83 (78–87)	83 (79–87)
Diastolic pressure (mmHg)	52 (47–56)	52 (47–56)	52 (47–56)
Respiratory rate (/min)	20 (18–22)	20 (18–22)	20 (18–22)
Heart rate (/min)	101 (86–117)	101 (86–118)	99 (85–116)
Vital sign after fluid challenge			
Systolic pressure (mmHg)	93 (85–103)	93 (85–103)	93.5 (85–104)
Diastolic pressure (mmHg)	55 (48–62)	54 (47–61)	55 (48–62)
Respiratory rate (/min)	20 (17–23)	20 (18–23)	19 (17–22)
Heart rate (/min)	98 (85–112)	98 (85–112)	97.5 (85–111)
Diastolic shock index			
At the time of hypotension (n = 1,768)	1.9 (1.6–2.3)	1.9 (1.6–2.3)	1.9 (1.6–2.3)
After fluid challenge (n = 1,531)	1.8 (1.5–2.2)	1.8 (1.5–2.1)	1.8 (1.5–2.2)
Lactate (mmol/L) (n = 1,865)	2.3 (1.5–3.6)	2.3 (1.5–3.6)	2.2 (1.5–3.6)
SOFA score on the 1st day	5.0 (3.0–8.0)	5.0 (3.0–8.0)	5.0 (3.0–8.0)
Vasopressor requirement	876 (45.7)	620 (46.2)	256 (44.5)
Septic shock (Sepsis-3)[a]	649 (33.9)	471 (35.1)	178 (31.0)
Time to hypotension from ED arrival (min)	56 (5–171)	52 (5–172)	32.5 (6–171)
Time to vasopressor use from ED arrival (min)	188 (94–318)	184 (89–309)	196 (100–327)
Vasopressor duration (hr)	20.8 (9.4–40.2)	20.4 (9.2–40.6)	21.6 (10.3–43.2)
Mechanical ventilation	203 (10.6)	146 (10.9)	57 (9.9)
Intensive care unit admission	469 (24.5)	326 (24.3)	143 (24.9)
28-Day mortality	237 (12.4)	169 (12.6)	68 (11.8)

Values are presented as median (interquartile range) or number (%).
SOFA, Sequential Organ Failure Assessment; ED, emergency department.
[a]Patients who met septic shock criteria according to the new Sepsis-3 definition, which are persistent hypotension requiring vasopressors to maintain a mean arterial pressure of ≥ 65 mmHg and a serum lactate level of > 2 mmol/L despite adequate volume resuscitation.

The comparison of clinical characteristics and outcomes according to vasopressor requirement in the derivation cohort is shown in Supplementary Table 1. Both DSI values and lactate levels were significantly higher in the vasopressor use group than the nonvasopressor use group (DSI at hypotension, 2.2 [IQR, 1.8–2.6] vs. 1.8 [IQR, 1.5–2.1]; DSI after fluid, 2.0 [IQR, 1.7–2.4] vs. 1.6 [IQR, 1.4–1.9]; lactate, 3.2 mmol/L [IQR, 2.0–4.9] vs. 1.8 mmol/L [IQR, 1.3–2.6]; P < 0.001 for all comparisons). The results were similar in the validation cohort (Supplementary Table 2).

Prognostic performance for vasopressor requirement according to DSI and lactate level

The AUC in predicting vasopressor use was 0.715 (95% CI, 0.683–0.748) for lactate, 0.688 (95% CI, 0.655–0.722) for DSI at hypo-

tension, and 0.751 (95% CI, 0.721–0.781) for DSI after fluid challenge (Fig. 2). The optimal cutoff values of the DSI at hypotension (2.06), DSI after fluid (1.77), and lactate (2.36 mmol/L), calculated by the Youden index, were simplified to 2.0 for both DSI at hypotension and a after fluid challenge, and 2.5 mmol/L for lactate, as rounded to the nearest 0.5 interval value. The prognostic performance of the cutoff values of DSI and lactate levels are presented in Supplementary Table 3.

Development and validation of a prediction score model

The vasopressor requirement prediction score was developed using the DSI and lactate (Table 2) and ranged from 0 to 2 points, with 1 point each assigned for the high DSI and high lactate criteria because the regression coefficients of the DSI and lactate values for vasopressor requirement were similar (model 1 in Supplementary Table 4). The prediction score was significantly associated with vasopressor requirement after adjusting confounding variables, including age, sex, hypertension, diabetes, infection source, bacteremia, SOFA score, and respiratory rate (aOR at hypotension, 1.66; 95% CI, 1.34–2.05; P<0.001; aOR after fluid challenge, 1.71; 95% CI, 1.39–2.10; P<0.001).

Table 2. Vasopressor requirement prediction score for hypotensive patients

No. of positive criteria[a]	Risk
0	Low
1	Intermediate
2	High

DSI, diastolic shock index.
[a]DSI ≥2.0 or lactate ≥2.5 mmol/L.

The proportions of vasopressor use significantly increased as the prediction score increased, both at the time of hypotension (20.6%, 44.7%, and 79.1% for scores of 0, 1, and 2 points, respectively) and after fluid challenge (29.1%, 57.1%, and 85.8% for scores of 0, 1, and 2 points, respectively) (Fig. 3), with a similar tendency present in the validation cohort (Supplementary Fig. 1).

Table 3. Multivariable logistic regression for the effect of the timing of vasopressor administration from initial hypotension on 28-day mortality according to the prediction score

Score	Adjusted OR[a]	95% CI	P-value
0 Points			
Hourly delay of vasopressor administration	0.92	0.78–1.09	0.346
Timing of vasopressor administration (min)			
>60	Reference		
30–60	4.76	1.07–21.14	0.040
<30	7.28	1.43–37.10	0.017
1 Point			
Hourly delay of vasopressor administration	1.07	0.98–1.15	0.113
Timing of vasopressor administration (min)			
>60	Reference		
30–60	0.61	0.24–1.57	0.306
<30	0.33	0.10–1.14	0.079
2 Points			
Hourly delay of vasopressor administration	1.06	1.01–1.11	0.021
Timing of vasopressor administration (min)			
>60	Reference		
30–60	0.71	0.30–1.71	0.451
<30	0.37	0.14–0.94	0.038

OR, odds ratio; CI, confidence interval.
[a]Adjusted variables were age, infection source, initial lactate levels, and Sequential Organ Failure Assessment score.

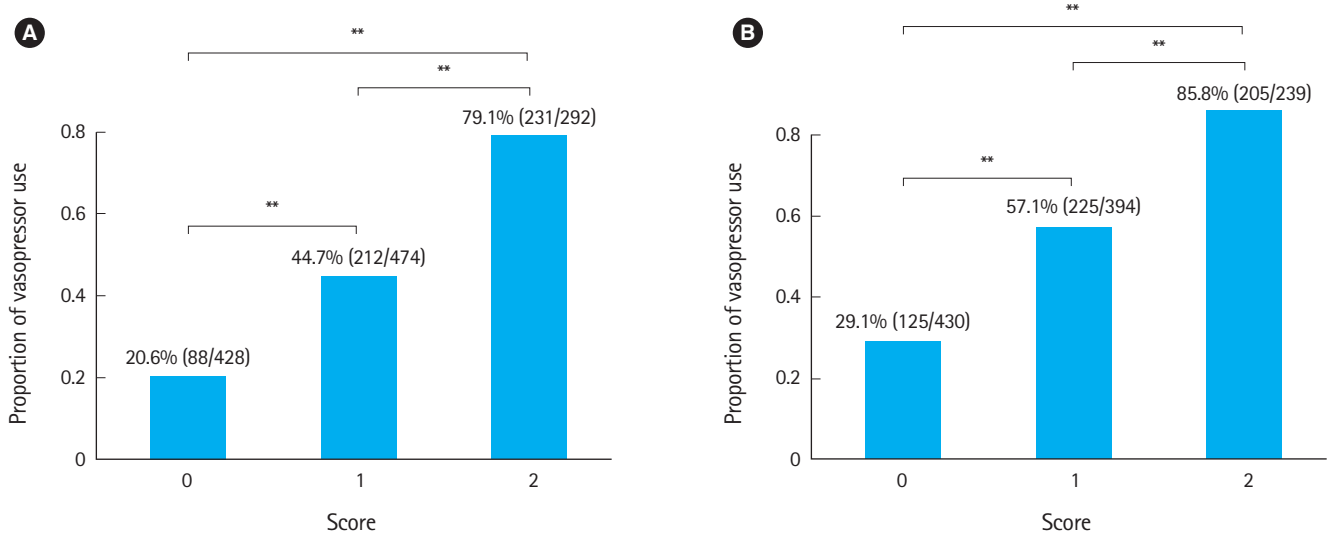

Fig. 3. Vasopressor requirement according to the prediction score using the diastolic shock index and lactate levels (A) at the time of hypotension in the derivation cohort and (B) after fluid challenge in the derivation cohort. **P<0.001.

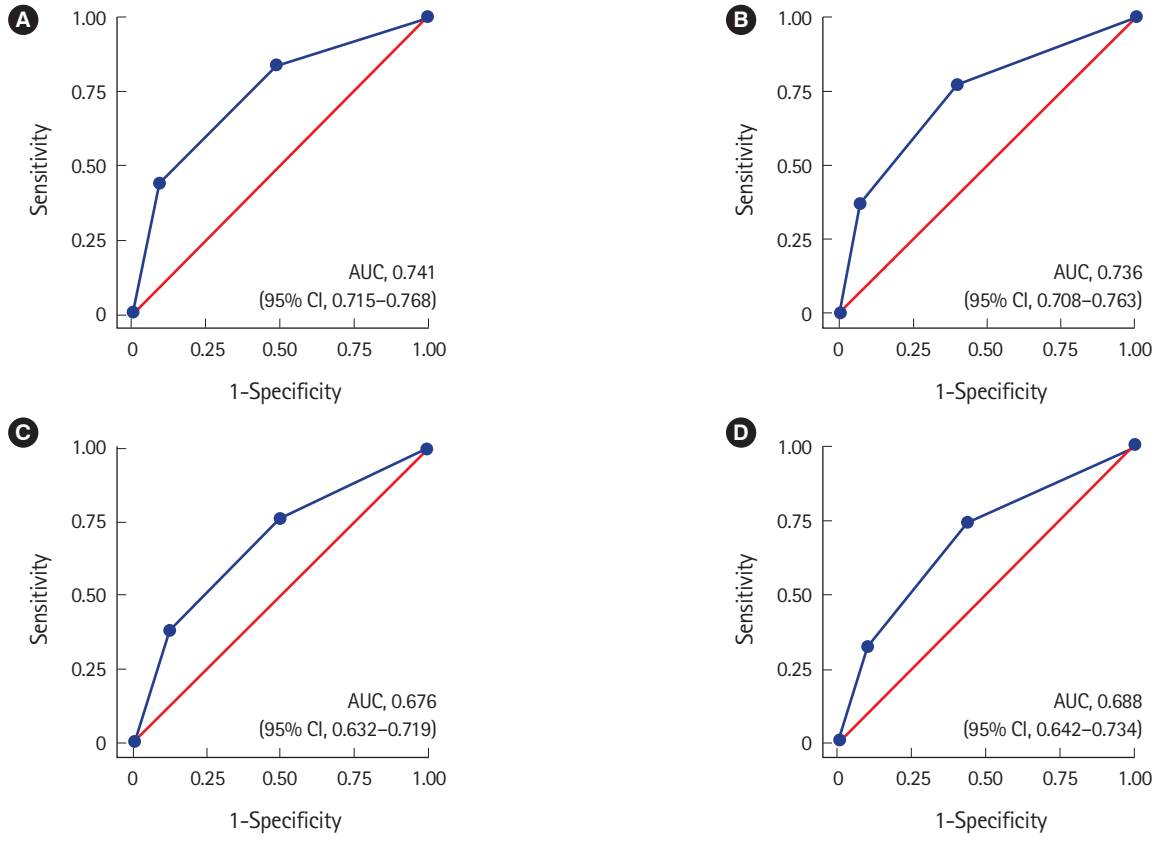

Fig. 4. Area under the receiver operating characteristic curves (AUCs) of the prediction score for vasopressor requirement (A) at the time of hypotension in the derivation cohort, (B) after fluid challenge in the derivation cohort, (C) at the time of hypotension in the validation cohort, and (D) after fluid challenge in the validation cohort. CI, confidence interval.

The prognostic performance of the prediction score was fair, with an AUC of 0.741 (95% CI, 0.715–0.768) at hypotension or 0.736 (95% CI, 0.708–0.763) after fluid challenge in the derivation cohort and 0.679 (95% CI, 0.631–0.719) at hypotension or 0.688 (95% CI, 0.642–0.734) in the validation cohort, respectively, as well as during calibration (Figs. 4, 5).

The 28-day mortality was also increased along with the prediction score both at the time of hypotension (5.1%, 11.8%, and 17.8% for scores of 0, 1, and 2 points, respectively) and after a fluid challenge (5.9%, 16.0%, and 21.8% for scores of 0, 1, and 2 points, respectively) in the derivation and validation cohorts (Supplementary Fig. 2). In the sensitivity analysis using missing value imputation, the prognostic accuracy was similar (Supplementary Fig. 3).

The effect of the timing of vasopressor administration from initial hypotension on 28-day mortality according to the prediction score is shown in Table 3. With a score of 0 points, an hourly delay of vasopressor administration was not associated with 28-day mortality, but an early start of vasopressor administration (<30 minutes or 30–60 minutes) was significantly associated with increased 28-day mortality (aOR, 7.28; 95% CI, 1.43–37.10; P=0.017 or aOR, 4.76; 95% CI, 1.07–21.14; P=0.040). On the contrary, with a score of 2 points, both an hourly delay of vasopressor administration (aOR, 1.06; 95% CI, 1.01–1.11; P=0.021) and early start (<30 minutes) of vasopressor administration (aOR, 0.37; 95% CI, 0.14–0.94; P=0.038) were significantly associated with 28-day mortality.

DISCUSSION

In this study, we demonstrated that the DSI and lactate levels could be used for predicting vasopressor requirement in hypotensive patients with suspected infection. We developed a simple risk assessment model using both values with fair discriminating performance. The prediction model might help to identify patients earlier who are more likely to need vasopressor administration before or during initial fluid resuscitation. Notably, the associations between the timing of vasopressor administration and 28-day mortality were different according to the prediction score. The results suggest that early vasopressor use might show more benefit for improving survival in high-risk patients (DSI ≥2.0 and lactate ≥2.5 mmol/L) than in low-risk patients (DSI <2.0 and

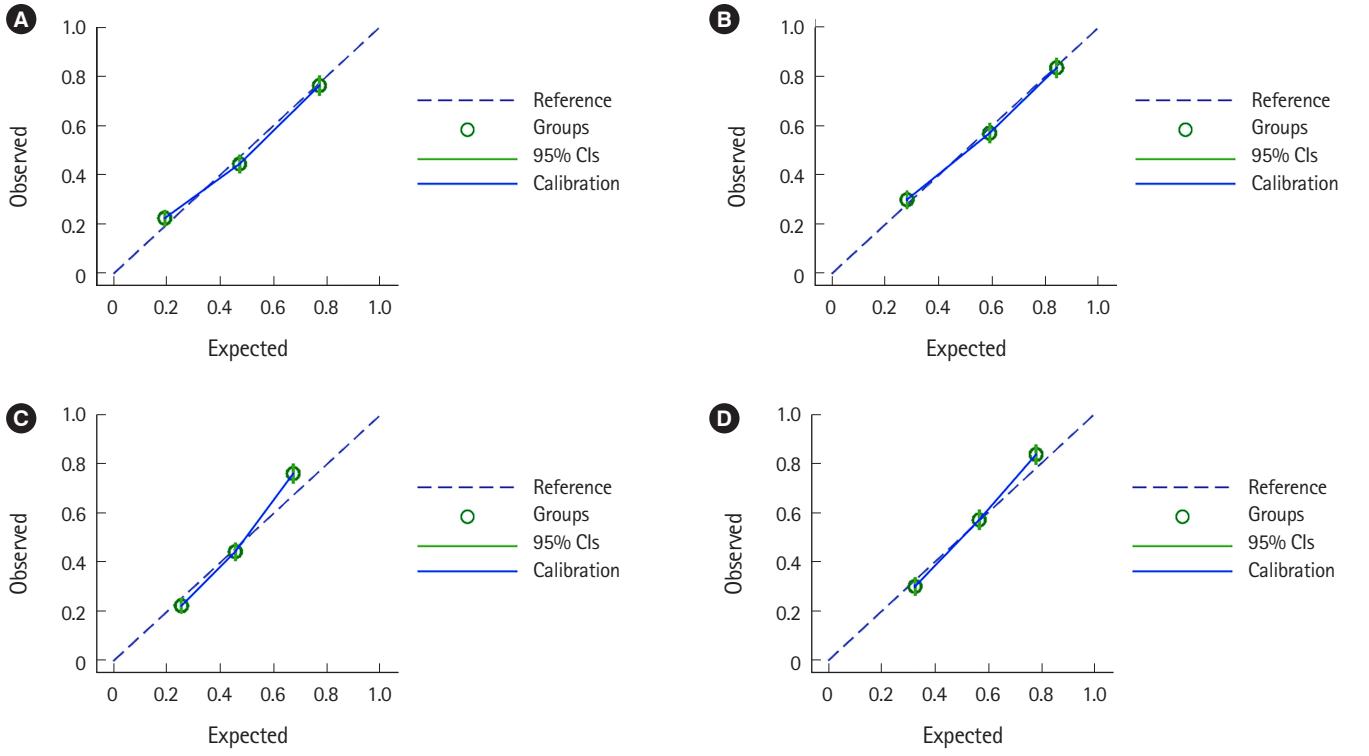

Fig. 5. Calibration plots of the prediction score for vasopressor requirement (A) at the time of hypotension in the derivation cohort, (B) after a fluid challenge in the derivation cohort, (C) at the time of hypotension in the validation cohort, and (D) after a fluid challenge in the validation cohort. CI, confidence interval.

lactate < 2.5 mmol/L).

Sepsis-induced hypotension may be associated with various hemodynamic changes, including severe vasodilatation, decreased preload and cardiac dysfunction.[19] Fluid resuscitation is the initial step of emergency management, but a significant number of hypotensive patients need vasopressor administration to maintain blood pressure.[13,20] Although vasopressor administration is included in the sepsis 1-hour bundle as the first-line intervention,[7,15] vasopressors are commonly used after fluid resuscitation fails, resulting in prolonged duration of hypotension.[17,20,21] Previous studies have suggested the potential benefits of early vasopressor use,[8-12,22,23] but there is no precise index for the timing of vasopressor administration during initial sepsis management. Moreover, we could not conclude that prompt vasopressor use would improve outcomes in all hypotensive patients with suspected sepsis.[14]

The diastolic pressure might be a marker of arterial tone and the perfusion pressure for the left ventricle.[24] The previous 2012 version of the SSC guidelines recommended that administering vasopressors early as an emergency measure in patients with severe shock is often necessary, such as when diastolic blood pressure is too low (e.g., DAP < 40 mmHg).[25] Compared with the systolic or mean arterial pressure, the DAP might remain constant in the peripheral circulation, and differences in invasive and noninvasive measurements of the DAP are usually smaller than those for systolic pressure.[26,27] Despite some advantages of diastolic pressure measurement in septic shock patients, isolated DAP might not be a significant prognostic factor.[17] Rather than a single index, the DSI value could reflect the severity of cardiovascular dysfunction in septic shock, which is a combination of the DAP and HR, because tachycardia might be a compensating or maladaptive process for acute hypotension.

The effect of early vasopressor use on the clinical outcome according to sepsis severity is uncertain and could vary depending on the physiologic status of an individual patient. Unfortunately, we could not clearly explain why an early start of vasopressor therapy was associated with decreased 28-day mortality in high-risk patients and increased mortality in low-risk patients. Theoretically, high-risk patients with higher DSI and lactate levels might have lower vascular tone and more impaired tissue perfusion. Early vasopressor use might allow faster achievement of the mean arterial pressure target. However, there are also traditional concerns regarding the impact of early vasopressor use.[14,28] Vasopressors may have potentially harmful effects in masking inadequate fluid resuscitation, and vasoconstriction may induce tissue hypoperfusion and organ dysfunction.[14] These might be explanations for the

study findings, but further investigation will be needed.

We incorporated lactate values in our predictive scoring. In sepsis, lactate is a strong biomarker for predicting mortality, although it could be increased by various mechanisms such as inadequate oxygen delivery, impaired oxygen extraction, decreased lactate clearance, and glycolytic flux by β_2-stimulation.[29] Our results might be consistent with the prognostic value of lactate and findings of the previous study showing that lactate elevation was a factor in predicting vasopressor use.[18]

There are some limitations to this study. First, this was a single-center study conducted in the ED. External validation studies from multiple centers in different settings will be needed for generalizability. Second, there were some missing lactate level and DSI values, although the proportion of such was not too large. DSI values after a fluid challenge were not available when NE was administered during fluid challenge, and vital signs were not measured. Third, the amounts of fluid were not consistent when the vital signs were followed up on. Due to the study's retrospective nature, we could not control the volume of fluid challenge. However, it is notable that the DSI after fluid challenge was measured before reaching the fluid amount (30 mL/kg of crystalloids) recommended by the SSC guidelines.[7] We used the DSI value after crystalloid administration of about 5 to 15 mL/kg. In a future study, serial DSI values should be tested at fixed doses. Fourth, the AUCs in the validation cohort were relatively lower than those in the derivation cohort. This finding might be due to the smaller sample size of the validation cohort or overfitting in the derivation cohort. Further validation and modification of the model are needed. Fifth, we used only the initial lactate value. However, it would not be practical to wait for repeated values when deciding to administer a vasopressor early since it takes time for the lactate levels to change and to be reported. Sixth, considering the number of variables and incidence of outcome, the sample size might be insufficient in the multivariable models for the subgroups, although the C-statistics of the models were acceptable. The findings should be confirmed in larger cohorts. Seventh, we focused on hypotensive patients with suspected infection, so further study is needed to evaluate whether the score could be used in patients without hypotension for early screening of high-risk sepsis patients.

In conclusion, in this study of a single ED, the DSI and lactate levels showed fair diagnostic accuracy in predicting vasopressor requirement in hypotensive patients with suspected infection. The prediction model using DSI and lactate levels could identify patients who are more likely to need vasopressor administration during initial resuscitation in the ED. External validation and clinical trials for early vasopressor use in high-risk patients are required.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Comparisons by vasopressor requirement in the derivation cohort

Supplementary Table 2. Comparisons by vasopressor requirement in the validation cohort

Supplementary Table 3. Diagnostic performance of the cutoff values of the DSI and lactate levels for predicting vasopressor requirement

Supplementary Table 4. Multivariable linear regression analysis of the DSI and lactate values for vasopressor requirement in the derivation cohort

Supplementary Fig. 1. Vasopressor requirement according to the prediction score using the diastolic shock index and lactate levels (A) at the time of hypotension in the validation cohort and (B) after a fluid challenge in the validation cohort.

Supplementary Fig. 2. 28-Day mortality according to the prediction score for vasopressor requirement using the diastolic shock index and lactate levels (A) at the time of hypotension in the derivation cohort, (B) after a fluid challenge in the derivation cohort, (C) at the time of hypotension in the validation cohort, and (D) after a fluid challenge in the validation cohort.

Supplementary Fig. 3. Sensitivity analysis of area under the receiver operating characteristic curves (AUCs) of the prediction score for vasopressor requirement (A) at the time of hypotension in the derivation cohort, (B) after a fluid challenge in the derivation cohort, (C) at the time of hypotension in the validation cohort, and (D) after a fluid challenge in the validation cohort. CI, confidence interval.

Supplementary materials are available at http://doi.org/10.15441/ceem.22.324.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Comparisons by vasopressor requirement in the derivation cohort

Variable	Vasopressor use (n = 620, 46.2%)	No vasopressor use (n = 722, 53.8%)	P-value
Age (yr)	67 (59–76)	63 (53–72)	< 0.001
Male sex	366 (59.0)	368 (51.0)	0.003
Comorbidity			
Hypertension	220 (35.5)	183 (25.3)	< 0.001
Diabetes	167 (26.9)	140 (19.4)	0.001
Cardiac disease	118 (19.0)	116 (16.1)	0.153
Cerebrovascular disease	76 (12.3)	69 (9.6)	0.112
Chronic lung disease	56 (9.0)	61 (8.4)	0.706
Chronic liver disease	67 (10.8)	68 (9.4)	0.399
Solid cancer	316 (51.0)	384 (53.2)	0.417
Suspected infection source			0.012
Respiratory infection	115 (18.5)	154 (21.3)	< 0.001
Intraabdominal infection	145 (23.4)	212 (29.4)	< 0.001
Urinary tract infection	90 (14.5)	97 (13.4)	< 0.001
Other or unknown	270 (43.5)	259 (35.9)	< 0.001
Blood culture-positive	225 (36.3)	108 (15.0)	< 0.001
Vital sign at the time of hypotension			
Systolic pressure (mmHg)	81 (74–85)	85 (82–88)	< 0.001
Diastolic pressure (mmHg)	49 (43–54)	53 (49–57)	< 0.001
Respiratory rate (/min)	20 (18–23)	18 (18–20)	< 0.001
Heart rate (/min)	109 (93–125)	96 (82–111)	< 0.001
Vital sign after fluid challenge			
Systolic pressure (mmHg)	89 (80–102)	96 (89–105)	< 0.001
Diastolic pressure (mmHg)	51 (44–57)	57 (52–64)	< 0.001
Respiratory rate (/min)	20 (18–25)	19 (17–21)	< 0.001
Heart rate (/min)	104 (91–118)	92 (81–104)	< 0.001
Diastolic shock index			
At the time of hypotension (n = 1,231)	2.2 (1.8–2.6)	1.8 (1.5–2.1)	< 0.001
After fluid challenge (n = 1,081)	2.0 (1.7–2.4)	1.6 (1.4–1.9)	< 0.001
Lactate (mmol/L) (n = 1,304)	3.2 (2.0–4.9)	1.8 (1.3–2.6)	< 0.001
SOFA score on the 1st day	8.0 (7.0–11.0)	3.0 (2.0–5.0)	< 0.001
Mechanical ventilation	131 (21.1)	15 (2.1)	< 0.001
Intensive care unit admission	296 (47.7)	30 (4.2)	< 0.001
28-Day mortality	115 (18.5)	54 (7.5)	< 0.001

Values are presented as median (interquartile range) or number (%).
SOFA, Sequential Organ Failure Assessment.

Supplementary Table 2. Comparisons by vasopressor requirement in the validation cohort

Variable	Vasopressor use (n = 256, 44.5%)	No vasopressor use (n = 319, 55.5%)	P-value
Age (yr)	67 (58.5–75.0)	63 (54.0–71.0)	< 0.003
Male sex	164 (64.1)	154 (48.3)	< 0.001
Comorbidity			
Hypertension	103 (40.2)	75 (23.5)	< 0.001
Diabetes	85 (33.2)	67 (21.0)	0.001
Cardiac disease	56 (21.9)	43 (13.5)	0.008
Cerebrovascular disease	32 (12.5)	20 (6.3)	0.010
Chronic lung disease	27 (10.5)	26 (8.2)	0.324
Chronic liver disease	34 (13.3)	23 (7.2)	0.015
Solid cancer	143 (55.9)	198 (62.1)	0.132
Suspected infection source			0.272
Respiratory infection	52 (20.3)	71 (22.3)	0.966
Intraabdominal infection	71 (27.7)	76 (23.8)	0.831
Urinary tract infection	43 (16.8)	41 (12.9)	0.136
Other or unknown	90 (35.2)	131 (41.1)	0.102
Blood culture-positive	76 (29.7)	33 (10.3)	< 0.001
Vital sign at the time of hypotension			
Systolic pressure (mmHg)	81 (75–85)	85 (81–87)	< 0.001
Diastolic pressure (mmHg)	50 (44–54)	53 (49–58)	< 0.001
Respiratory rate (/min)	20 (18–24)	18 (18–20)	0.001
Heart rate (/min)	104 (89–120)	96 (84–111)	< 0.001
Vital sign after fluid challenge			
Systolic pressure (mmHg)	92 (83–102)	95 (89–105)	0.001
Diastolic pressure (mmHg)	52 (45–59)	57 (52–64)	< 0.001
Respiratory rate (/min)	20 (18–23)	18 (17–21)	0.001
Heart rate (/min)	100 (89–115)	94 (83–109)	0.001
Diastolic shock index			
At the time of hypotension (n = 537)	2.1 (1.8–2.4)	1.8 (1.5–2.1)	< 0.001
After fluid challenge (n = 450)	2.0 (1.6–2.3)	1.6 (1.4–1.9)	< 0.001
Lactate (mmol/L) (n = 561)	2.8 (1.8–5.0)	1.9 (1.3–2.7)	< 0.001
SOFA score on the 1st day	8.0 (6.0–11.0)	3.0 (2.0–5.0)	< 0.001
Mechanical ventilation	52 (20.3)	5 (1.6)	< 0.001
Intensive care unit admission	121 (47.3)	22 (6.9)	< 0.001
28-Day mortality	48 (18.8)	20 (6.3)	< 0.001

Values are presented as median (interquartile range) or number (%).
SOFA, Sequential Organ Failure Assessment.

Supplementary Table 3. Diagnostic performance of the cutoff values of the DSI and lactate levels for predicting vasopressor requirement

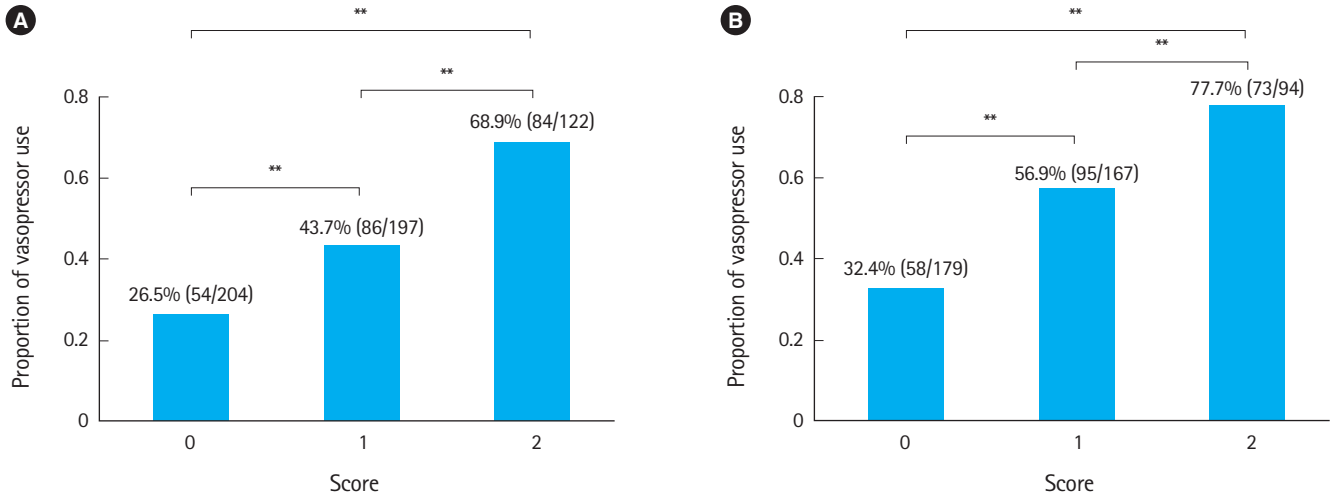
Variable	DSI ≥ 2.0 (initial hypotension)	DSI ≥ 2.0 (after fluid challenge)	Lactate ≥ 2.5 mmol/L
Derivation cohort			
Sensitivity (%)	64.5 (60.3–68.6)	52.1 (47.8–56.3)	63.3 (59.3–67.1)
Specificity (%)	67.8 (64.2–71.2)	83.2 (79.7–86.3)	73.2 (69.7–76.5)
Predictive value			
Positive	60.5 (56.3–64.5)	72.1 (76.7–80.9)	68.0 (64.0–71.8)
Negative	67.8 (71.5–74.9)	58.3 (62.0–65.6)	68.9 (65.4–72.2)
AUC	0.662 (0.635–0.689)	0.676 (0.650–0.703)	0.682 (0.657–0.708)
Validation cohort			
Sensitivity (%)	57.6 (50.8–64.1)	49.6 (42.9–56.3)	56.3 (49.9–62.4)
Specificity (%)	67.1 (61.6–72.3)	79.0 (73.1–84.2)	70.5 (65.0–75.6)
Predictive value			
Positive	55.6 (49.0–62.1)	70.4 (62.7–77.4)	61.5 (55.0–67.8)
Negative	68.9 (63.0–74.0)	55.0 (60.8–66.5)	65.7 (60.3–70.9)
AUC	0.623 (0.582–0.665)	0.643 (0.601–0.685)	0.634 (0.594–0.674)

Values are presented as percentages or AUC (95% confidence interval).
DSI, diastolic shock index; AUC, area under the receiver operating characteristic curve.

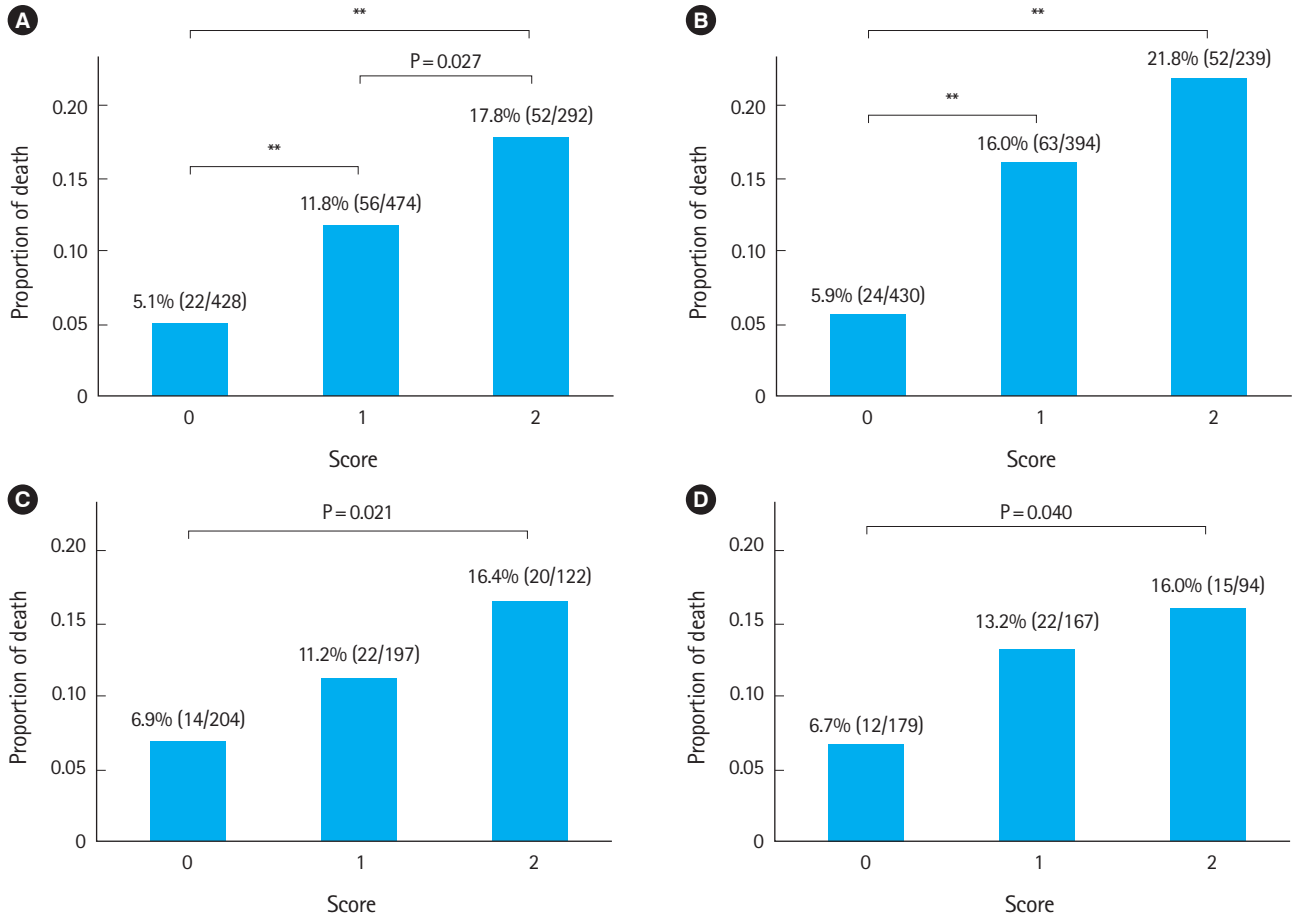
Supplementary Table 4. Multivariable linear regression analysis of the DSI and lactate values for vasopressor requirement in the derivation cohort

Variable	Coefficient (95% CI)	Standard error	P-value
Model 1[a]			
DSI at hypotension	0.300 (0.248 to 0.352)	0.026	<0.001
Lactate	0.264 (0.212 to 0.315)	0.026	<0.001
DSI after fluid	0.243 (0.186 to 0.301)	0.023	<0.001
Lactate	0.323 (0.265 to 0.382)	0.023	<0.001
Model 2[b]			
DSI at hypotension	0.123 (0.087 to 0.160)	0.019	<0.001
Lactate	0.053 (0.015 to 0.092)	0.020	0.006
DSI after fluid	0.140 (0.098 to 0.183)	0.022	<0.001
Lactate	0.039 (-0.043 to 0.082)	0.022	0.078

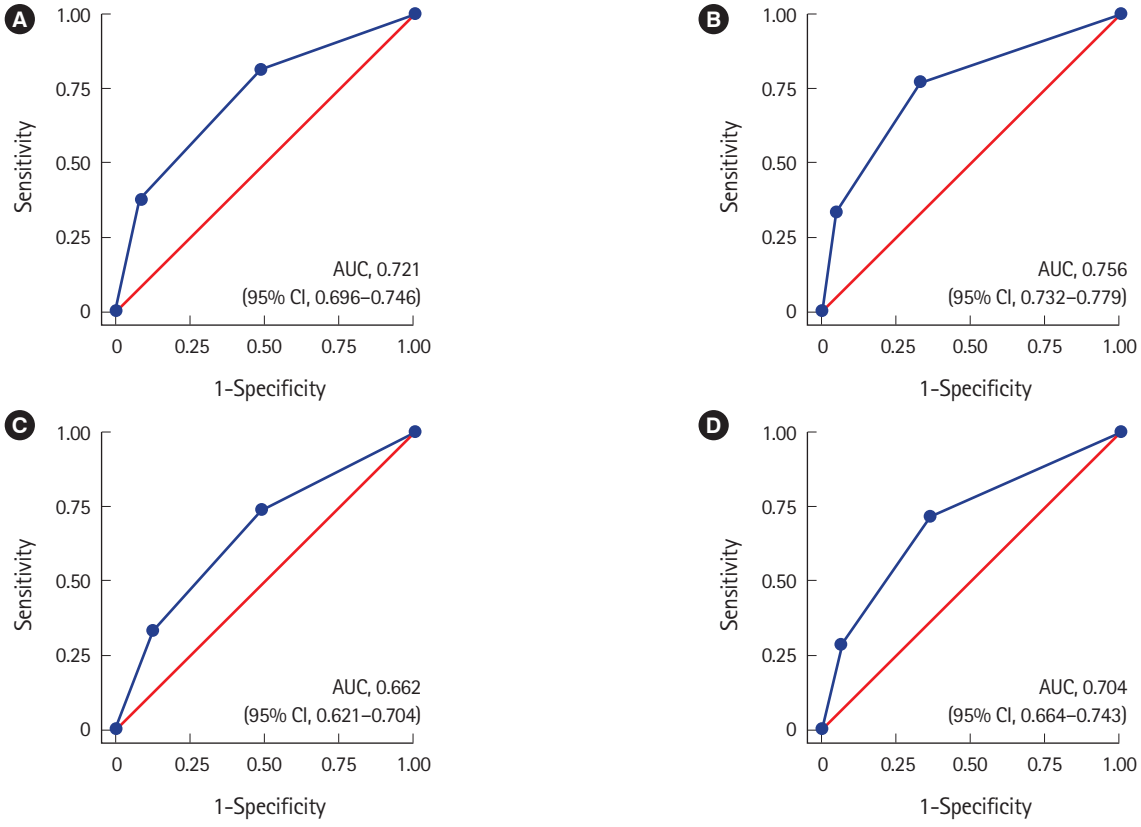
DSI, diastolic shock index; CI, confidence interval.
[a]Model 1 included the DSI and lactate value. [b]Age, sex, hypertension, diabetes, infection focus, bacteremia, Sequential Organ Failure Assessment score, and respiratory rate were adjusted in model 2.



Supplementary Fig. 1. Vasopressor requirement according to the prediction score using the diastolic shock index and lactate levels (A) at the time of hypotension in the validation cohort and (B) after a fluid challenge in the validation cohort. **P<0.001



Supplementary Fig. 2. The 28-day mortality according to the prediction score for vasopressor requirement using the diastolic shock index and lactate levels (A) at the time of hypotension in the derivation cohort, (B) after a fluid challenge in the derivation cohort, (C) at the time of hypotension in the validation cohort, and (D) after a fluid challenge in the validation cohort. **P<0.001



Supplementary Fig. 3. Sensitivity analysis of area under the receiver operating characteristic curves (AUCs) of the prediction score for vasopressor requirement (A) at the time of hypotension in the derivation cohort, (B) after a fluid challenge in the derivation cohort, (C) at the time of hypotension in the validation cohort, and (D) after a fluid challenge in the validation cohort.

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Original Article

Interactive effect of multi-tier response and advanced airway management on clinical outcomes after out-of-hospital cardiac arrest: a nationwide population-based observational study

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Objective We hypothesized that a multi-tier response (MTR) will provide high-quality cardiopulmonary resuscitation including airway management. However, the type of tier response system and airway management will have different interactive effects resulting in varying outcomes following out-of-hospital cardiac arrest (OHCA). This study aimed to determine whether the advanced airway management method has an effect on OHCA outcomes and to compare the size of the effect across MTR types.

Methods This is a retrospective population-based observational study using the Korea OHCA Registry. Airway management methods were categorized into endotracheal intubation (ETI) and supraglottic airway (SGA) groups. The tier system was categorized into single-tier response (STR) or two types of MTR: ambulance-ambulance MTR or fire engine-ambulance MTR.

Results In total, 45,264 patients were analyzed among the 89,087 emergency medical service assessed OHCAs. The SGA group was significantly associated with a lower prehospital return of spontaneous circulation (ROSC) rate compared to the ETI group (adjusted odds ratio [aOR], 0.79; 95% confidence interval [CI], 0.72–0.88). Both MTR with an ambulance or fire engine were significantly associated with higher prehospital ROSC rates compared to STR (STR vs. MTR with an ambulance: aOR, 1.33; 95% CI, 1.21–1.47; STR vs. MTR with a fire engine: aOR, 1.43; 95% CI, 1.20–1.71). Prehospital SGA was significantly associated with poor neurological outcomes in MTR with fire engine (aOR, 0.71; 95% CI, 0.53–0.96).

Conclusion In this nationwide observational study, we observed that MTR was associated with higher prehospital ROSC than STR. Moreover, SGA is associated with a lower prehospital ROSC rate regardless of tier response type compared to ETI.

Keywords Out-of-hospital cardiac arrest; Airway management; Emergency medical services

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Capsule Summary

What is already known

Optimal prehospital airway management during cardiopulmonary resuscitation is debating.

What is new in the current study

This study shows that multi-tier response provides higher prehospital return of spontaneous circulation (ROSC) than single-tier response. Additionally, supraglottic airway management is associated with a lower prehospital ROSC rate regardless of tier response type compared to endotracheal intubation for out-of-hospital cardiac arrest patients.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a major public health burden due to its low survival rate and severe neurological disability.[1] The rate of survival to hospital discharge after OHCA was 10.4% in the US and 0.5% to 8.5% in the Pan-Asian population.[1,2] Primary compositions of high-quality cardiopulmonary resuscitation (CPR) including early defibrillation, uninterrupted chest compression, and optimal airway management are associated with the return of spontaneous circulation (ROSC) and prevention of neurological impairment.[3]

The selection of prehospital optimal airway management is inconclusive. Bag-valve mask (BVM) ventilation is commonly used until advanced airway management such as endotracheal intubation (ETI) or supraglottic airways (SGAs) insertion can be applied. In general, ETI was regarded as the standard airway management during OHCA to provide controlled oxygenation and to protect the lungs from vomitus.[4-6] However, prehospital ETI is a complex task and requires the coordination of multiple actions. Therefore, international recommendations suggest that ETI should be performed by operators with adequate experience and skills.[3,7] Prehospital ETI may worsen patient outcome when associated with delays in basic life support (BLS) procedures, interruptions in chest compressions, or unrecognized esophageal intubation.[8,9]

A recent multicenter trial by Wang et al.[10] showed that initial laryngeal tube insertion was associated with a greater survival rate in OHCA patients compared to initial ETI. However, the AIRWAYS-2 randomized clinical trial, which compared ETI and SGA, reported that SGA did not show favorable functional outcomes.[11] Hence, there is no consensus on the optimal method of initial airway management during OHCA.

A nationwide dispatcher-assisted CPR program and multi-tier response (MTR) service have been implemented in Korea since 2015. Prehospital advanced airway management was more widely applied after the implementation of the MTR system.[12] However, it is uncertain whether the type of tier response and advanced airway method is associated with better outcomes.

We hypothesized that the MTR would provide a higher quality of CPR and airway management. However, the combination of the tier response system and airway management may have different interactive effects resulting in varying outcomes after OHCA. This study aimed to determine whether the airway management method has an effect on outcomes after OHCA and to compare the size of the effect across the types of MTR.

METHODS

Ethics statement

This study was approved by the Institutional Review Board of Seoul National University Hospital (No. 1103-153-357). Informed consent was waived, and patient information was anonymized before analysis. The Korea Centers for Disease Control and Prevention (KCDC) released the national OHCA registry data for public health.[13]

Study design, setting, and data sources

This retrospective study is a population-based observational study using the Korea OHCA Registry (KOHCAR). The KOHCAR has been operated by the KCDC in collaboration with the central fire services since 2006. The Korean emergency medical services (EMSs) system is a government-operated, two-tiered, and dual dispatch system that offers basic to intermediate levels of life support ambulance services from fire stations. According to regional resources, the first response service plus intermediate life service (ILS) or ILS plus ILS models were widely accepted for the MTR (Fig. 1). The fire engine service provides BLS only and the ambulance with a level-1 emergency medical technician (EMT) provides advanced cardiovascular life support. For on-scene CPR protocol, at least 5 minutes of full resuscitative efforts delivered by an EMT is recommended before patient transportation. Prehospital ETI or SGA can be performed only by a level-1 EMT under direct or indirect medical oversight during OHCA. There is no specific protocol for the

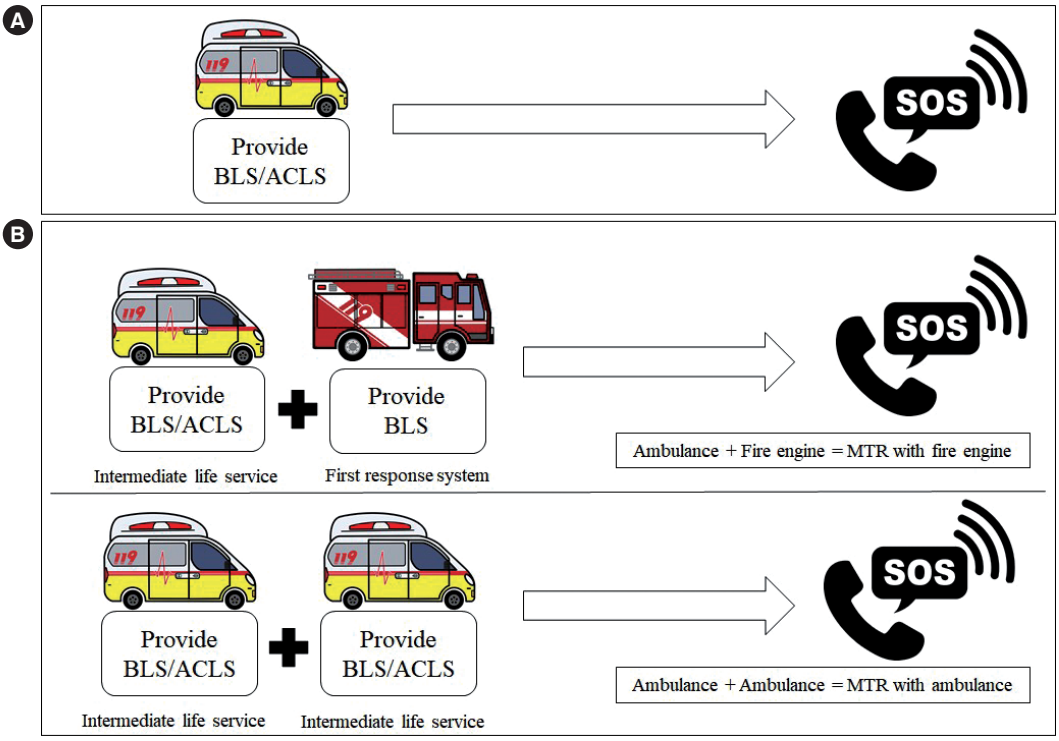

Fig. 1. Tiered emergency medical services response system in Korea. (A) Single-tier response and (B) multi-tier response system (MTR) in Korea. BLS, basic life support; ACLS, advanced cardiovascular life support.

selection of the advanced airway method or cooperation between the two groups of the MTR. Moreover, EMTs are unable to terminate resuscitation attempts in the field unless the OHCA patient shows obvious signs of death such as decapitation, decomposition, or rigor mortis. Thus, nearly all EMS-assessed OHCA patients in Korea are transported to the closest emergency departments (EDs) regardless of prehospital ROSC status.

The dataset was integrated from the following four sources: EMS run sheets for basic ambulance operation information, EMS cardiac arrest registry, dispatcher CPR registry for the Utstein factors, and the national OHCA registry for hospital care and outcomes. The EMS providers recorded the EMS run sheets and cardiac arrest registry for all EMS-assessed OHCA. Medical record reviewers from the KCDC retrieve the recorded clinical information from approximately 700 hospitals.[14,15]

A two-step management of data quality was performed to ensure the quality of the medical record review process. First, the EMTs were educated with EMS data recording through the data dictionary of EMS record variables and education program. Moreover, the EMTs were supervised for each case by EMS medical directors during education. Second, the hospital medical record reviewers were trained on the use of the data dictionary and case review protocols and were dispatched to all hospitals to gather information on hospital care and outcomes. The two-step quality management was supported by the committee members, which consisted of EMS physicians, epidemiology and statistical experts, cardiologists, and medical record review experts. The data quality management reviewed almost all collected data and gave monthly feedback.[16]

Study population

This study included adult EMS-assessed OHCA patients with presumed cardiac etiology, who were not witnessed by EMS providers and/or were defibrillated by a bystander or automated external defibrillation. The study period was from January 2017 to December 2019. Exclusion criteria were age under 18 years, a non-cardiac origin of arrest, resuscitation not attempted in ED, witnessed by EMT, and a BVM or unknown airway management method.

Variables

Airway management methods were categorized into the following two groups: ETI and SGA. The tier system was divided into single-tier response (STR) and two types of MTR: ambulance-ambulance MTR and fire engine-ambulance MTR.[17]

The main exposure was the airway management method and co-exposure was the tier response type. We analyzed the impact of the airway management method and tiered response type on

clinical outcomes.

We assessed all potential confounders including age, sex, residential area, bystander CPR, location of arrest, initial electrocardiogram (ventricular fibrillation, pulseless ventricular tachycardia, pulseless electrical activity, and asystole), place of cardiac arrest, witness status, bystander defibrillation, dispatcher assistance CPR, response time interval, scene time interval, transport time interval, EMS defibrillation attempt, mechanical CPR device, prehospital drugs (epinephrine, amiodarone), level of ED, past medical history, targeted temperature management, reperfusion therapy, and extracorporeal membrane oxygenation.

The primary outcome was the prehospital ROSC rate. The secondary outcomes were survival to discharge and a favorable neurological outcome. Neurological outcome was evaluated according to the cerebral performance categories (CPC) scale of 1 to 5: 1, good cerebral performance (conscious, alert, able to work, and lead a normal life); 2, moderate cerebral disability (conscious and sufficient cerebral function for independent activities of daily life); 3, severe cerebral disability (conscious, dependent on others for daily support); 4, coma or vegetative state; and 5, brain death.[18] CPC 1 and 2 were classified as favorable neurological outcomes and CPC 3, 4, and 5 were categorized as unfavorable outcomes.

Statistical analysis

Categorical variables were analyzed using the chi-square test and continuous variables were analyzed using the Wilcoxon rank-sum test. Continuous variables are presented as median and 25% to 75% interquartile range. The temporal trends by study period interval on the method of airway management and tier type were evaluated by the Cochran-Armitage test.

The unadjusted odds ratio (OR) with 95% confidence interval (CI) were calculated to show the unadjusted association between airway management/tier type and OHCA outcomes. The adjusted OR (aOR) with 95% CI were calculated via multivariable logistic regression analysis to assess the effects of airway management, tier type, and potential confounders such as age, sex, residential area, location of arrest, initial electrocardiogram, place of cardiac arrest, witness status, bystander CPR, bystander defibrillation, dispatcher assistance CPR, response time interval, scene time interval, transport time interval, EMS defibrillation attempt, mechanical CPR device, prehospital epinephrine, level of ED, and past medical history. The aOR with 95% CI were also calculated via multivariable logistic regression analysis to assess the interactive effects of airway management method and tier type. Statistical significance was defined as a P-value less than 0.05. All statistical analyses were performed using the SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Among the 89,087 EMS-assessed OHCAs during the study period, 45,264 patients were analyzed (Fig. 2). The characteristics of OHCA patients by airway management and tier response type are shown in Tables 1 and 2. Of the airway management methods performed, SGA was more preferred than ETI (86.7% vs. 13.3%, $P<0.01$). In tier type, MTR with an ambulance was more prevalent than the STR (74.7% vs. 20.5%, $P<0.01$) or MTR with a fire engine (74.7% vs. 4.9%, $P<0.01$).

Fig. 3 shows trends in the crude incidence rate of airway management method and tier type by year. From 2017 to 2019, MTR with an ambulance was significantly increased from 70.1% to 79.1% ($P_{trend}<0.01$) and prehospital SGA was also significantly increased from 84.7% to 88.4% ($P_{trend}<0.01$) whereas there was a significant decrease in the trend of the STR, MTR with a fire engine, and prehospital ETI ($P_{trend}<0.01$).

Results of multivariable logistic regression models for outcome by airway management method are shown in Table 3. In the case of adjusted analysis, the SGA group was significantly associated with a lower prehospital ROSC rate compared to the ETI group (aOR, 0.79; 95% CI, 0.72–0.88). Table 4 shows multivariable lo-

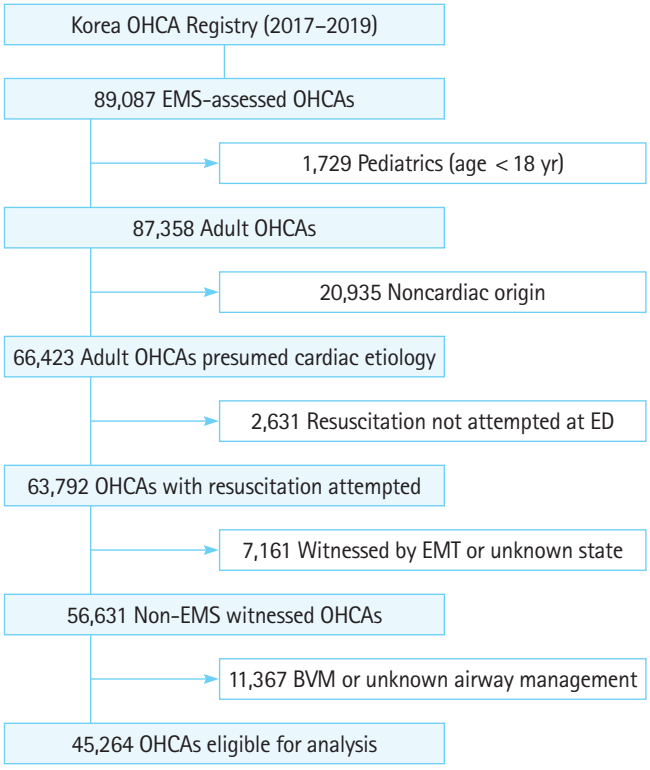

Fig. 2. Study flow chart. OHCA, out-of-hospital cardiac arrest; EMS, emergency medical service; ED, emergency department; EMT, emergency medical technician; BVM, bag-valve mask.

Table 1. Characteristics of out-of-hospital cardiac arrest patients by airway management

Characteristic	All	ETI	SGA	P-value
Total	45,264 (100)	6,020 (100)	39,244 (100)	
Female sex	28,939 (63.9)	3,840 (63.8)	25,099 (64.0)	0.80
Age (yr)				<0.01
18–39	1,649 (3.6)	194 (3.2)	1,455 (3.7)	
40–59	9,083 (20.1)	1,139 (18.9)	7,944 (20.2)	
60–79	19,458 (43.0)	2,605 (43.3)	16,853 (42.9)	
≥80	15,074 (33.3)	2,082 (34.6)	12,992 (33.1)	
Median (IQR)	74 (60–82)	75 (61–82)	74 (60–82)	
Residence of patients (urban)	19,520 (43.1)	3,781 (62.8)	15,739 (40.1)	<0.01
Diabetes mellitus	10,792 (23.8)	1,466 (24.4)	9,326 (23.8)	0.32
Hypertension	16,550 (36.6)	2,252 (37.4)	14,298 (36.4)	0.14
Kidney disease	2,794 (6.2)	383 (6.4)	2,411 (6.1)	0.51
Heart disease	8,637 (19.1)	1,105 (18.4)	7,532 (19.2)	0.12
Stroke	4,349 (9.6)	627 (10.4)	3,722 (9.5)	0.02
Initial ECG				<0.01
VF/VT	7,747 (17.1)	967 (16.1)	6,780 (17.3)	
PEA	8,154 (18.0)	1,195 (19.9)	6,959 (17.7)	
Asystole/unknown	29,363 (64.9)	3,858 (64.1)	25,505 (65.0)	
Place of arrest				<0.01
Public	6,885 (15.2)	854 (14.2)	6,031 (15.4)	
Private	27,987 (61.8)	3,894 (64.7)	24,093 (61.4)	
Others/unknown	10,392 (23.0)	1,272 (21.1)	9,120 (23.2)	
Bystander witness	22,027 (48.7)	3,012 (50.0)	19,015 (48.5)	0.02
Bystander CPR	29,170 (64.4)	3,935 (65.4)	25,235 (64.3)	0.11
Bystander defibrillation	219 (0.5)	32 (0.5)	187 (0.5)	0.57
Dispatch-assisted CPR	26,608 (58.8)	3,576 (59.4)	23,032 (58.7)	0.30
RTI (min)				<0.01
<4	2,176 (4.8)	323 (5.4)	1,853 (4.7)	
4≤ RTI <8	25,131 (55.5)	3,589 (59.6)	21,542 (54.9)	
8≤ RTI <12	12,182 (26.9)	1,460 (24.3)	10,722 (27.3)	
12≤ RTI <16	3,547 (7.8)	379 (6.3)	3,168 (8.1)	
16≤	2,228 (4.9)	269 (4.5)	1,959 (5.0)	
Median (IQR)	7 (5–9)	6 (5–9)	7 (5–9)	
STI (min)				<0.01
<4	374 (0.8)	35 (0.6)	339 (0.9)	
4≤ STI <8	1,987 (4.4)	130 (2.2)	1,857 (4.7)	
8≤ STI <12	9,404 (20.8)	892 (14.8)	8,512 (21.7)	
12≤ STI <16	13,703 (30.3)	1,818 (30.2)	11,885 (30.3)	
16≤	19,796 (43.7)	3,145 (52.2)	16,651 (42.4)	
Median (IQR)	15 (11–19)	16 (12–20)	14 (11–19)	
TTI (min)				0.04
<4	8,540 (18.9)	1,057 (17.6)	7,483 (19.1)	
4≤ TTI <8	19,164 (42.3)	2,604 (43.3)	16,560 (42.2)	
8≤ TTI <12	9,146 (20.2)	1,260 (20.9)	7,886 (20.1)	
12≤ TTI <16	4,008 (8.9)	531 (8.8)	3,477 (8.9)	
16≤	4,406 (9.7)	568 (9.4)	3,838 (9.8)	
Median (IQR)	6 (4–10)	6 (4–10)	6 (4–10)	
EMS defibrillation	10,834 (23.9)	1,399 (23.2)	9,435 (24.0)	0.17
Mechanical CPR device	8,987 (19.9)	2,435 (40.4)	6,552 (16.7)	<0.01
Epinephrine	9,347 (20.6)	1,503 (25.0)	7,844 (20.0)	<0.01

(Continued on the next page)

Table 1. (Continued)

Characteristic	All	ETI	SGA	P-value
Level of ED				<0.01
1	9,885 (21.8)	1,330 (22.1)	8,555 (21.8)	
2	22,076 (48.8)	3,170 (52.7)	18,906 (48.2)	
3	12,028 (26.6)	1,402 (23.3)	10,626 (27.1)	
4	1,275 (2.8)	118 (2.0)	1,157 (2.9)	
Tier response type				<0.01
Single-tier response	9,257 (20.5)	1,058 (17.6)	8,199 (20.9)	
MTR with ambulance	33,809 (74.7)	4,710 (78.2)	29,099 (74.1)	
MTR with fire engine	2,198 (4.9)	252 (4.2)	1,946 (5.0)	
Prehospital ROSC	5,454 (12.0)	751 (12.5)	4,703 (12.0)	0.28
Survival to discharge	4,061 (9.0)	484 (8.0)	3,577 (9.1)	0.01
Favorable neurological outcome	2,655 (5.9)	283 (4.7)	2,372 (6.0)	<0.01

Values are presented as number (%), unless otherwise indicated.
ETI, endotracheal intubation; SGA, supraglottic airway; IQR, interquartile range; ECG, electrocardiogram; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; CPR, cardiopulmonary resuscitation; RTI, response time interval; STI, scene time interval; TTI, transport time interval; EMS, emergency medical services; ED, emergency department; MTR, multi-tier response; ROSC, return of spontaneous circulation.

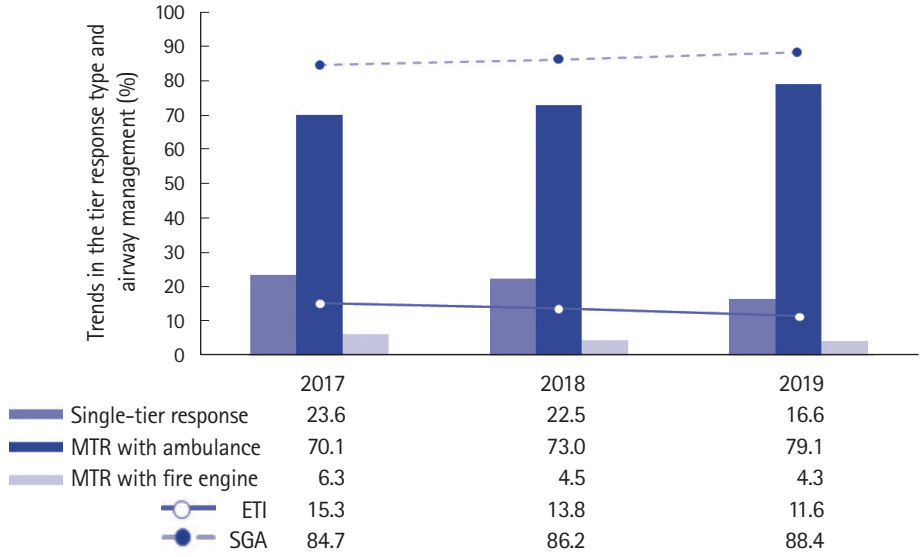

Fig. 3. Trends in the tier response type and airway management of out-of-cardiac arrest. MTR, multi-tier response; ETI, endotracheal intubation; SGA, supraglottic airway.

gistic regression analysis of tier response type and each outcome. Both MTR with an ambulance or with a fire engine were significantly associated with higher prehospital ROSC compared to the STR (STR vs. MTR with an ambulance: aOR, 1.33; 95% CI, 1.21–1.47; STR vs. MTR with a fire engine: aOR, 1.43; 95% CI, 1.20–1.71).

Table 5 shows interaction analysis of tier type response and airway management method on clinical outcomes. Regardless of tier type response, SGA was significantly associated with lower prehospital ROSC than ETI. In the case of MTR with a fire engine, patients who received SGA showed significantly lower favorable neurological outcomes than ETI (aOR, 0.71; 95% CI, 0.53–0.96).

DISCUSSION

In this nationwide population-based observational study, we observed that MTR was associated with higher prehospital ROSC than a STR. Prehospital SGA was associated with a lower prehospital ROSC rate compared to prehospital ETI regardless of the tier response type. In the case of MTR with a fire engine, prehospital ETI was significantly associated with a favorable neurological outcome.

During field resuscitation, an inadequate number of providers may cause low-quality CPR because simultaneous tasks including defibrillation, oxygen supply, airway management, and intravas-

Table 2. Characteristics of out-of-hospital cardiac arrest patients by tier response type

Characteristic	All	Single-tier response	MTR with ambulance	MTR with fire engine	P-value
Total	45,264 (100)	9,257 (100)	33,809 (100)	2,198 (100)	
Female sex	28,939 (63.9)	5,890 (63.6)	21,673 (64.1)	1,376 (62.6)	0.29
Age (yr)					
18–39	1,649 (3.6)	299 (3.2)	1,277 (3.8)	73 (3.3)	< 0.01
40–59	9,083 (20.1)	1,745 (18.9)	6,896 (20.4)	442 (20.1)	
60–79	19,458 (43.0)	3,969 (42.9)	14,558 (43.1)	931 (42.4)	
80 ≤	15,074 (33.3)	3,244 (35.0)	11,078 (32.8)	752 (34.2)	
Median (IQR)	74 (60–82)	75 (61–82)	74 (60–82)	74 (60–82)	
Residence of patients (urban)	19,520 (43.1)	2,002 (21.6)	17,318 (51.2)	200 (9.1)	< 0.01
Diabetes mellitus	10,792 (23.8)	2,033 (22.0)	8,295 (24.5)	464 (21.1)	< 0.01
Hypertension	16,550 (36.6)	3,153 (34.1)	12,653 (37.4)	744 (33.8)	< 0.01
Kidney disease	2,794 (6.2)	466 (5.0)	2,214 (6.5)	114 (5.2)	< 0.01
Heart disease	8,637 (19.1)	1,601 (17.3)	6,672 (19.7)	364 (16.6)	< 0.01
Stroke	4,349 (9.6)	891 (9.6)	3,265 (9.7)	193 (8.8)	0.4
Initial ECG					< 0.01
VF/VT	7,747 (17.1)	1,593 (17.2)	5,763 (17.0)	391 (17.8)	
PEA	8,154 (18.0)	1,764 (19.1)	6,075 (18.0)	315 (14.3)	
Asystole/unknown	29,363 (64.9)	5,900 (63.7)	21,971 (65.0)	1,492 (67.9)	
Place of arrest					< 0.01
Public	6,885 (15.2)	1,562 (16.9)	5,016 (14.8)	307 (14.0)	
Private	27,987 (61.8)	5,514 (59.6)	21,059 (62.3)	1,414 (64.3)	
Others/unknown	10,392 (23.0)	2,181 (23.6)	7,734 (22.9)	477 (21.7)	
Bystander witness (yes)	22,027 (48.7)	4,727 (51.1)	16,338 (48.3)	962 (43.8)	< 0.01
Bystander CPR	29,170 (64.4)	5,236 (56.6)	22,392 (66.2)	1,542 (70.2)	< 0.01
Bystander defibrillation	219 (0.5)	52 (0.6)	157 (0.5)	10 (0.5)	0.48
Dispatch-assisted CPR	26,608 (58.8)	4,412 (47.7)	20,752 (61.4)	1,444 (65.7)	< 0.01
RTI (min)					< 0.01
< 4	2,176 (4.8)	409 (4.4)	1,652 (4.9)	115 (5.2)	
4 ≤ RTI < 8	25,131 (55.5)	4,279 (46.2)	19,783 (58.5)	1,069 (48.6)	
8 ≤ RTI < 12	12,182 (26.9)	2,704 (29.2)	8,851 (26.2)	627 (28.5)	
12 ≤ RTI < 16	3,547 (7.8)	1,077 (11.6)	2,234 (6.6)	236 (10.7)	
≥ 16	2,228 (4.9)	788 (8.5)	1,289 (3.8)	151 (6.9)	
Median (IQR)	7 (5–9)	7 (6–11)	7 (5–9)	7 (5–10)	
STI (min)					< 0.01
< 4	374 (0.8)	192 (2.1)	170 (0.5)	12 (0.5)	
4 ≤ STI < 8	1,987 (4.4)	911 (9.8)	927 (2.7)	149 (6.8)	
8 ≤ STI < 12	9,404 (20.8)	2,732 (29.5)	6,068 (17.9)	604 (27.5)	
12 ≤ STI < 16	13,703 (30.3)	2,667 (28.8)	10,377 (30.7)	659 (30.0)	
≥ 16	19,796 (43.7)	2,755 (29.8)	16,267 (48.1)	774 (35.2)	
Median (IQR)	15 (11–19)	13 (10–16)	15 (12–20)	13 (10–17)	
TTI (min)					< 0.01
< 4	8,540 (18.9)	1,479 (16.0)	6,747 (20.0)	314 (14.3)	
4 ≤ TTI < 8	19,164 (42.3)	3,198 (34.5)	15,244 (45.1)	722 (32.8)	
8 ≤ TTI < 12	9,146 (20.2)	1,884 (20.4)	6,820 (20.2)	442 (20.1)	
12 ≤ TTI < 16	4,008 (8.9)	1,096 (11.8)	2,626 (7.8)	286 (13.0)	
≥ 16	4,406 (9.7)	1,600 (17.3)	2,372 (7.0)	434 (19.7)	
Median (IQR)	6 (4–10)	7 (4–13)	6 (4–9)	8 (5–13)	
EMS defibrillation	10,834 (23.9)	2,387 (25.8)	7,837 (23.2)	610 (27.8)	< 0.01
Mechanical CPR device	8,987 (19.9)	1,200 (13.0)	7,239 (21.4)	548 (24.9)	< 0.01
Epinephrine	9,347 (20.6)	866 (9.4)	8,190 (24.2)	291 (13.2)	< 0.01

(Continued on the next page)

Table 2. (Continued)

Characteristic	All	Single-tier response	MTR with ambulance	MTR with fire engine	P-value
Level of ED					< 0.01
1	9,885 (21.8)	1,592 (17.2)	7,960 (23.5)	333 (15.2)	
2	22,076 (48.8)	3,557 (38.4)	17,537 (51.9)	982 (44.7)	
3	12,028 (26.6)	3,675 (39.7)	7,585 (22.4)	768 (34.9)	
4	1,275 (2.8)	433 (4.7)	727 (2.2)	115 (5.2)	
Airway management					< 0.01
ETI	6,020 (13.3)	1,058 (11.4)	4,710 (13.9)	252 (11.5)	
SGA	39,244 (86.7)	8,199 (88.6)	29,099 (86.1)	1,946 (88.5)	
ROSC	5,454 (12.0)	875 (9.5)	4,327 (12.8)	252 (11.5)	< 0.01
Survival to discharge	4,061 (9.0)	778 (8.4)	3,103 (9.2)	180 (8.2)	0.03
Favorable neurological outcome	2,655 (5.9)	501 (5.4)	2,024 (6.0)	130 (5.9)	0.11

Values are presented as number (%), unless otherwise indicated.
MTR, multi-tier response; IQR, interquartile range; ECG, electrocardiogram; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; CPR, cardiopulmonary resuscitation; RTI, response time interval; STI, scene time interval; TTI, transport time interval; EMS, emergency medical services; ED, emergency department; ETI, endotracheal intubation; SGA, supraglottic airway; ROSC, return of spontaneous circulation.

Table 3. Multivariable logistic regression analysis for out-of-hospital cardiac arrest outcomes by airway management method

Variable	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
Prehospital ROSC				
ETI	1.00		1.00	
SGA	0.96	0.88–1.04	0.79	0.72–0.88
Survival to discharge				
ETI	1.00		1.00	
SGA	1.15	1.04–1.27	0.96	0.85–1.09
Favorable neurological outcomes				
ETI	1.00		1.00	
SGA	1.30	1.15–1.48	1.03	0.88–1.20

OR, odds ratio; CI, confidence interval; ROSC, return of spontaneous circulation; ETI, endotracheal intubation; SGA, supraglottic airway.

Table 4. Multivariable logistic regression analysis for outcomes by tier response type

Variable	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
Prehospital ROSC				
Single-tier response	1.00		1.00	
MTR with ambulance	1.41	1.30–1.52	1.33	1.21–1.47
MTR with fire engine	1.24	1.07–1.44	1.43	1.20–1.71
Survival to discharge				
Single-tier response	1.00		1.00	
MTR with ambulance	1.00	1.01–1.20	1.07	0.97–1.19
MTR with fire engine	0.97	0.82–1.15	1.08	0.88–1.32
Favorable neurological outcome				
Single-tier response	1.00		1.00	
MTR with ambulance	1.11	1.01–1.23	1.13	0.99–1.29
MTR with fire engine	1.10	0.90–1.34	1.27	0.99–1.63

OR, odds ratio; CI, confidence interval; ROSC, return of spontaneous circulation; MTR, multi-tier response.

Table 5. Effects of airway management on clinical outcomes in interaction model with tier response type

Variable	Prehospital ROSC		Survival to discharge		Favorable neurological outcome	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
Single-tier response						
ETI	1.00		1.00		1.00	
SGA	0.88	0.80–0.96	0.94	0.84–1.04	0.96	0.83–1.10
MTR with ambulance						
ETI	1.00		1.00		1.00	
SGA	0.73	0.65–0.82	0.90	0.79–1.03	0.86	0.72–1.02
MTR with fire engine						
ETI	1.00		1.00		1.00	
SGA	0.54	0.44–0.66	0.83	0.65–1.04	0.71	0.53–0.96

ROSC, return of spontaneous circulation; aOR, adjusted odds ratio; CI, confidence interval; ETI, endotracheal intubation; SGA, supraglottic airway; MTR, multi-tier response.

cular access should be provided. It is not easy to manage all tasks on the field with two or three EMT members. MTR is one of the most common methods of providing more manpower for field resuscitation.[19-21] In this study, we showed that the MTR could provide enough manpower to achieve a higher prehospital ROSC rate.

The pros and cons of ETI have been proposed. ETI is a definitive airway management technique that precisely controls gas exchange and protects lungs from vomitus if competency to performance is guaranteed. However, because of its difficulty and complexity, it should be performed by an experienced EMT in cooperation with organized manpower.[3,7-9] ETI showed superiority to SGA in prehospital ROSC regardless of tier type in this study. In Korea, prehospital providers are classified into level-1 EMT (EMT-intermediate in the USA) and level-2 EMT (EMT-basic in the USA).

Prehospital ETI or SGA is performed only by a level-1 EMT, and the selection of the advanced airway management method is dependent on the preference of the EMT. Table 2 shows that prehospital SGA is preferred more than prehospital ETI (86.7% vs.13.3%). In this sense, we expect that ETI was done mostly by skillful and experienced EMTs, which could have affected the results.

We hypothesized that MTR could provide enough manpower. However, the type of tier response provides a different level of service, which could result in different interactive effects with the type of airway management. In the case of MTR with a fire engine, prehospital ETI was associated with favorable neurological outcomes. Table 2 shows that the MTR with a fire engine was more prevalent in rural areas. In rural areas, EMS resources might be insufficient due to a lower population rate resulting in a lack of experience, shortage of eligible hospitals, and shortage of manpower. Due to the shortage of resources, MTR with the fire engine service provides the fire engine team as the first responder, who can only provide BLS. Paradoxically, the divided scope of work between the first responder and the ambulance service may have a positive effect on the prognosis. In rural areas, a team includes a skillful EMT, who can provide advanced cardiovascular life support. Therefore, support members capable of providing BLS might be appropriate in the aspect of resource allocation. The specific protocol of the MTR and the training of the EMT in advanced resuscitation techniques could beneficially affect the clinical outcomes of OHCA patients.

A previous study has shown that the prehospital ROSC rate was significantly associated with survival to discharge and favorable neurological outcomes.[22] In this study population, prehospital ROSC was also associated with survival to discharge (aOR, 27.03; 95% CI, 24.83–29.42) and favorable neurological outcomes (aOR, 59.41; 95% CI, 51.38–68.69). Prehospital ETI was significantly associated with prehospital ROSC. However, it was not associated with survival to discharge or favorable neurological outcomes. There may be two explanations for the study results. First, the prehospital ROSC rate was similar between the ETI and SGA groups (12.5% vs. 12.0%). However, variables related to prehospital outcomes were significantly different. The urban population was more prevalent in the ETI group (62.8% vs. 40.1%), whereas, prehospital epinephrine administration (25% vs. 20%) and mechanical CPR device (40.4% vs. 16.7%) were higher in the ETI group, which could have affected the prehospital ROSC rate more positively. Mechanical device application during ambulance transportation was recommended to provide high-quality CPR.[23,24] Moreover, there was a significant imbalance in the number of included patients between the ETI and SGA groups. We were unable to adjust the confounding conditions completely. Second, failed ETI attempts were reverted to SGA or BVM and these were profound confounding factors. We could not adjust these confounding factors due to the retrospective study design. Further studies using more appropriate statistical analysis to adjust for confounders such as propensity score matching analysis or prospective randomized control study designs are needed to verify prehospital airway management and OHCA outcomes.

This study has several limitations. First, the KOHCAR database was not planned for collecting information on airway management resulting in the lack of details on airway management such as the initial selection of the airway method, number, and duration of initial advanced airway attempts. In addition, there was a lack of information on whether advanced airway management was performed during CPR or after ROSC. We could not adjust the attempts of advanced airway trials. In the Korean EMS system, all EMTs must follow government regulations. The regulation states that one attempt should be performed within a single 30-second duration and up to two attempts of advanced airway management can be made on the scene. Therefore, we could presume that only a small number of cases were reverted to SGA or BVM after prolonged and multiple attempts. Second, this study was conducted in a two-tier, dual dispatch EMS system that provides an intermediate service level, which is different from other countries. Noteworthy differences were also found in the OHCA patient characteristics between the Korea OHCA registry and previously studied registries such as the CARES (Cardiac Arrest Registry to Enhance Survival) registry, ROC (Resuscitation Outcomes Consortium) trial, or the AIRWAYS-2 trial. Field termination of resuscitation comprised a considerable percentage in other registries. However, EMTs in Korea are unable to terminate resuscitation and declare death unless there are signs of irreversible death; therefore, most OHCA cases in Korea are transported to the closest ED. These factors could have influenced study outcomes, limiting the generalizability of the findings in this study. Third, selection bias may exist despite performing multivariable adjustments for potential confounders. We could not exclude the possibility that the preference of ETI over SGA by skillful EMTs resulted in a better patient prognosis. Prehospital ETI is relatively new in Korea. Therefore, organized training and education of airway management are expected to have positive effects on OHCA outcomes. Fourth, there was no information on CPR quality, which is a profound prognostic factor. Korean EMTs, who passed the national level certification, receive annual medical education and clinical training to maintain knowledge and skill performance. Hence, CPR quality management might be well-controlled. Fifth, this was a retrospective registry-based study; thus, there might have

been potential uncontrolled biases.

In conclusion, in this nationwide population-based observational study, we observed that MTR was associated with a higher prehospital ROSC rate compared to a STR. Prehospital SGA was associated with a lower prehospital ROSC rate compared to prehospital ETI, regardless of tier response type. Prehospital ETI was significantly associated with favorable neurological outcomes in MTR with a fire engine.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Original Article

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"Diffusion of innovations": a feasibility study on the pericapsular nerve group block in the emergency department for hip fractures

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Objective Hip fractures are associated with significant morbidity and mortality. Ultrasound-guided peripheral nerve blocks are a safe method to manage pain and decrease opioid usage. The pericapsular nerve group (PENG) block is a novel, potentially superior block because of its motor-sparing effects. Through training, simulation, and supervision, we aim to determine whether it is feasible to perform the PENG block in the emergency department.

Methods Phase 1 consisted of emergency physicians attending a workshop to demonstrate ultrasound proficiency, anatomical understanding, and procedural competency using a low-fidelity model. Phase 2 consisted of a prospective, observational, feasibility study of 10 patients with hip fractures. Pain scores, side effects, and opioid usage data were collected.

Results The median pain score at time 0 (time of block) was 9 (interquartile range [IQR], 6.5–9). The median pain score at 30 minutes was 4 (IQR, 2.0–6.8) and 3.5 (IQR, 1.0–4.8) at 4 hours. All 10 patients required narcotics prior to the initiation of the PENG block with a median dosage of 6.25 morphine milligram equivalents (MME; IQR, 4.25–7.38 MME). After the PENG block, only 30% of the patients required further narcotics with a median dosage of 0 MME (IQR, 0–0.6 MME) until operative fixation.

Conclusion In this feasibility study, PENG blocks were safely administered by trained emergency physicians under supervision. We demonstrated data suggesting a trend of pain relief and decreased opiate requirements, and further investigation is necessary to measure efficacy.

Keywords Nerve block; Hip fractures; Hospital emergency service; Pain management; Interventional ultrasonography

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Capsule Summary

What is already known

The pericapsular nerve group block is a novel nerve block described in the literature in 2018. It has the potential to be superior to the other blocks in emergency department patient with hip fractures because of its "motor-sparing" effects.

What is new in the current study

The pericapsular nerve group block is feasible in the emergency department and has the potential to provide excellent pain relief and decrease the amount of opioid use during the preoperative phase in emergency department patient with hip fractures.

INTRODUCTION

Isolated hip fractures are a common presentation to the emergency department (ED) and are associated with significant morbidity and mortality.[1,2] Regional anesthesia can provide superior pain control when compared to parenteral analgesia and can decrease the need for opioids, avoiding their deleterious side effects of respiratory depression and delirium. Under ultrasound guidance, nerve blocks are a safe, effective method to manage perioperative pain.[3-8] This is a feasibility study of a novel nerve block for hip fractures.

The pericapsular nerve group (PENG) block, described in 2018, is an exciting new analgesic modality that is ideal for the ED management of hip fractures due to its potential for sensory-only nerve blockades.[2,9] Previously established blocks, such as the femoral nerve block, the "3-in-1" block, and the fascia iliaca block, have shown inconsistent or partial analgesia.[4] A possible explanation is demonstrated by both magnetic resonance imaging and cadaveric studies illustrating that the obturator nerve (sensory innervation) is rarely affected by these three blocks.[10]

The PENG block targets the articular branches of the femoral nerve, accessory obturator nerve, and obturator nerve, which provide sensory-only innervation to the hip.[2,9,11,12] The articular branches of these three nerves course between the anterior inferior iliac spine (AIIS) and the iliopubic eminence (IPE). By depositing anesthetic anterior to the IPE, the PENG block is able to provide a sensory-only blockade without causing motor weakness.[2,8,13] The PENG block is potentially more easily adopted than the other blocks because the target for deposition of anesthetic is just anterior to the IPE, which is an easily visualized structure under ultrasound guidance secondary to its density.[14]

In an effort to understand and explain the spread of practices and ideas within a population, Everett Rogers published the book *Diffusion of innovations* in 1962. Rogers described the phases of innovation adoption and named them early, middle, and late adopters.[14] Early and middle adopters are essential to the success of spreading new practice and ideas. This PENG block project involves recruiting early adopters of this procedure to increase the use of this procedure for our patient population.

Wilson et al.[15] recently attempted to implement the fascia iliaca block and observed significant barriers to changing the practice pattern of emergency physicians (EPs) in the ED. While there is evidence on the efficacy of the fascia iliaca block, they discovered that despite training sessions, attending physicians felt uncomfortable performing the block independently without supervision, and consequently the procedure was not widely adopted. They discovered that it was difficult to persuade the entire staff to adopt this practice since it was seen as a great change within the department's current practice patterns.

Prior to this project, our department was not performing peripheral nerve blocks for hip fractures and introducing the PENG block required a dedicated effort from our ultrasound and simulation divisions. We acknowledged the challenges faced by Wilson et al.[15] specific to hip fracture management in the ED as well as the lessons learned in *Diffusion of innovations* regarding the adoption of new technologies and practice patterns. The PENG block has yet to be studied in an ED population in the United States despite case series and reports internationally showing that the PENG block is highly efficacious for pain.[2,8,16] With a dedicated 2-hour workshop, including simulation training on a low-fidelity model and direct supervision, we hypothesized that the PENG block can be successfully taught to EPs and is feasible for administration in the ED for providing pain relief and limiting opiod usage. By training early adopters, this would be the first step in the PENG block "diffusion of innovations."

METHODS

Study design

This was a prospective, observational study to test the feasibility of the PENG block for the management of pain. We enrolled 10 cognitively intact patients with hip fractures, all of whom received a PENG block. The subjects were assessed every 10 minutes for the first 30 minutes, then at the 1-, 2-, 4-, 8-, and 16-hour marks after the PENG block. The trial was approved by the Institutional Review Board of the Albert Einstein College of Medicine (No. 2021-12647). All participants provided written consents prior to participation.

Study setting

This study was performed in an academic, urban ED with an annual adult census of approximately 75,000 patients and a mean incidence of 170 hip fractures per year (2016–2020). The center is an American College of Surgeons Designated Adult Level 1 Trauma Center with a large emergency medicine residency training program and an ultrasound and simulation education fellowship. Pain management of hip fractures prior to this study was almost uniformly parenteral analgesia. The study was conducted between January and September 2021.

Study protocol

Phase 1: simulation training (January to April 2021)

EPs attended a 2-hour workshop of lecture and rapid cycle deliberate practice using a low-fidelity model (Supplementary Materials 1, 2, and Supplementary Figs. 1-4). The EPs were required to complete numerous critical actions at three hands-on stations and score higher than 90% on the postworkshop assessment to pass the workshop.

Phase 2: pilot study of 10 patients (July to September 2021)

This was a pilot study assessing the feasibility of EPs to perform PENG blocks on patients. After an initial clinical working assessment by the EPs, the research team was contacted. The EPs provided the analgesia that they deemed appropriate while radiographs were obtained and consultants were contacted. After radiographic confirmation and patient consent, the PENG block was administered by EPs under direct supervision of the research team. The amount of time from needle entry to final needle exit from the skin was recorded.

Recruitment

Patients were eligible for the study if they were cognitively intact (alert and oriented to person, place, and time), had a radiographically confirmed hip fracture, had a pain score of at least 5 out of 10 at triage or upon EP evaluation, and were able to indicate their pain score on a visual analog pain scale which ranged from 0 (no pain) to 10 (severe pain). Patients were excluded in cases of multitrauma.

Materials and PENG block placement

The 10 PENG blocks were performed under ultrasound guidance with a curvilinear transducer (Sonosite XPorte 5-2 MHz; FUJIFILM SonoSite, Bothell, WA, USA) utilizing a 22-gauge 3.5- or 4-inch PaJunk SonoBlock II (Pajunk Medical Systems, Alpharetta, GA, USA) echogenic needle under sterile techniques. A block kit was developed which contained all the required materials for the procedure (Fig. 1). This kit was prepackaged for convenience and included syringes, sterile gloves, needles, sterile towels, an ultrasound probe cover, and chlorhexidine swabs. Anesthetic was obtained from the ED medication distribution system. The ultrasound machine along with the kit was brought into the room prior to the start of the procedure. The preparation time was typically less than 2 minutes.

Patient positioning is key to ensure a successful block. The physician stood on the ipsilateral side of the hip fracture with the ultrasound machine placed on the opposite side to ensure a direct line of sight of the procedural field and ultrasound screen.

The patient was placed on a cardiac monitor with continuous pulse oximetry. A preprocedural time out was called and vital signs were recorded. A bladder ultrasound was completed, and if gross-

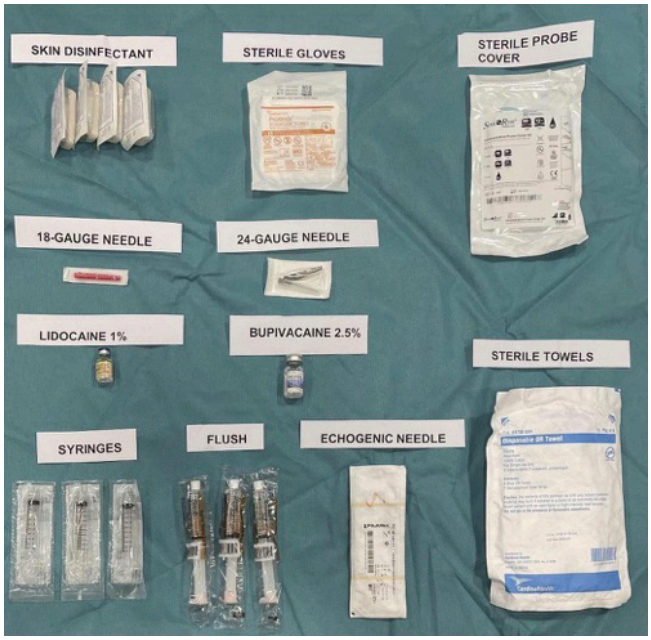

Fig. 1. Block kit materials.

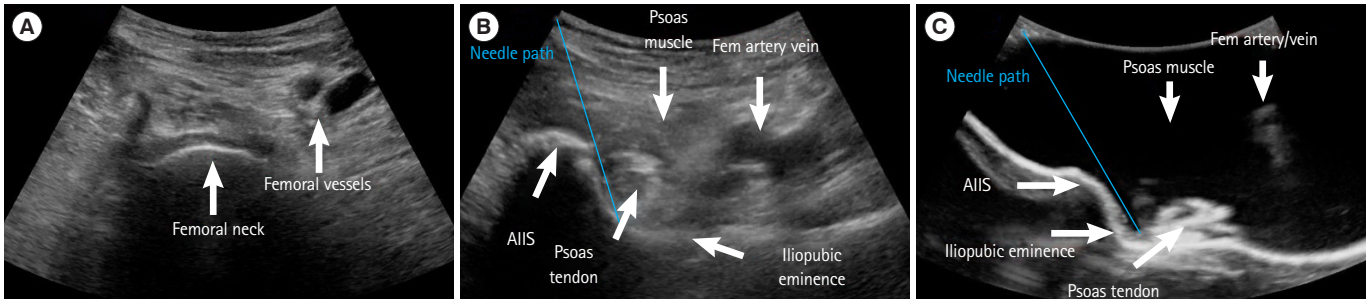

Fig. 2. Patient versus low-fidelity pericapsular nerve group (PENG) block model. (A) Anatomical view in a patient of the characteristic femoral neck (image left is lateral and image right is medial). (B) Anatomical view of the right hip in a patient (image left is lateral and image right is medial). The white arrows illustrate the key anatomical landmarks and the blue line indicates the ideal needle trajectory during a PENG block. (C) Anatomical view of the right hip on our low-fidelity PENG block model (image left is lateral and image right is medial). The white arrows illustrate the key anatomical landmarks and the blue line indicates the ideal needle trajectory during a PENG block. AIIS, anterior inferior iliac spine.

ly distended, a urinary catheter was placed to decompress the bladder. Operator 1 prepped the patient's skin under aseptic technique and a sterile ultrasound cover was placed on the curvilinear transducer. Since the femoral neck has an identifiable semi-circular shape, the transducer was aligned with the inguinal crease searching for this image (Fig. 2). The femoral artery and vein were identified medially and care was taken to avoid these structures. Once this image was obtained, the transducer was moved slightly superiorly to identify the IPE (Fig. 2). The IPE and psoas tendons were identified and a skin wheal was introduced at the needle insertion site. The echogenic nerve block needle was flushed with normal saline. Sterile operator 1 introduced the needle from lateral to medial using an in-plane approach, placing the tip of the needle in the musculofascial plane inferior to the psoas tendon and superior to the IPE. Once the operator contacted the IPE, the needle was rotated to ensure that the fascial layer lying above the bone was pierced. Operator 2 hydrodissected the area with normal saline (injected in 5 mL aliquots) to verify vertical rise of the psoas tendon off of the IPE, ensuring appropriate placement of the needle. Once both operators were satisfied with the needle placement, bupivacaine 0.25% was delivered slowly up to the planned dose of 20 mL. After the administration of bupivacaine, normal saline was once again flushed (3–4 mL) to empty the anesthetic left in the tubing and the needle. Postprocedural vital signs were recorded.

Phase 1 methods

Our ultrasound and simulation fellowship faculty developed a 2-hour workshop, incorporating a preworkshop questionnaire, a brief lecture with key images, three hands-on stations, and concluded with a postassessment questionnaire to assess for knowledge acquisition. To conduct this workshop in an efficient and timely manner, we required four facilitators, a computer, an ultrasound machine, low-fidelity PENG models, echogenic ultrasound needles, and sterile equipment. The questionnaire focused on anatomy, indications, contraindications, terminology, and included questions regarding comfort levels.

The 20-minute lecture at the beginning of the workshop addressed the background regarding the PENG block and described the PENG block as an anatomically derived nerve block targeting the articular branches of the femoral nerve, obturator nerve, and accessory obturator nerve as they course over the IPE and innervate the sensory receptors located in the anterior zone of the hip. It also discussed the indications, contraindications, complications, local anesthetic systemic toxicity treatment, and detailed a step-by-step approach to the PENG block using a two-person technique.

Station 1

The first station focused on informed consent using a standardized patient. A trained facilitator played the role of the patient and ensured that each participant was able to address the following critical actions: confirm the patient's name, date of birth, side of injury, describe the procedure in its entirety to the patient, discuss risk and benefits, search for contraindications, ask the patient if they have questions, and finally determine if the patient is able to provide consent. The facilitator running the station determined the standardized patient's history and ability to consent based on the facilitator's discretion. The participant needed to complete all critical actions to pass this station.

Station 2

The second station focused on visualizing the needle tip in its entirety using an in-plane ultrasound approach. The participants in this station practiced this skill by identifying a target on a low-fidelity model. The critical actions required at this station included:

describing the needle trajectory prior to insertion, identifying the needle tip upon entry into the "skin," readjusting the ultrasound if the needle tip was not identified, demonstrating visualization of the entire shaft of the needle throughout procedure, and accurately reaching an identified target. The participant needed to complete all critical actions to pass this station.

Station 3

The third station focused on the translation of knowledge using hands-on experience on the low-fidelity PENG model through rapid cycle deliberate practice and incorporated technical ultrasound skills, image acquisition, and ability of the operator to follow their needle tip. The participant was tasked with choosing the correct transducer (curvilinear) and adjusting for depth and gain appropriately. The participant needed to correctly match the side of the transducer to the corresponding orientation on the ultrasound screen and identify the AIIS, psoas muscle, psoas tendon, IPE, and femoral neurovascular bundle.

The facilitator verified that the participant was able to track the needle for the entirety of the approach with the in-plane method. The participant needed to avoid hitting the AIIS and avoid going through the psoas tendon. Fig. 2 depicts the ideal path using the blue line. The participant needed to verbalize several key actions at this station: aseptic procedure set-up (hand-washing, sterile gloves, probe cover, drawing up anesthetic, and sterile field placement), lidocaine wheal placement, a description of what a successful block means (psoas tendon rise with the underlying local anesthetic), and anesthetic placement in 5 mL increments. While our model did not support the physical injection of fluids, the participants were advised ahead of time the necessity of verbalizing this step as a part of the critical actions.

Anchoring one's transducer hand on the model is important to ensure the stability of the transducer and desired image. It is also important to anchor the needle hand to help guide it through the desired trajectory. The participants were judged on their overall stability/probe technique during the procedure on a scale from 0 to 2, with the lowest score (0) indicating no stability and the highest score (2) indicating excellent stability.

To pass this station, the participants needed to hit all the critical actions listed above and score a stability score of 1 or higher. The participants were required to repeat each station if they did not pass the first time, but the number of attempts was not recorded.

Measurements

For phase 1, the average scores on the preworkshop and postworkshop assessments were obtained. Comfort levels on a Likert scale were obtained in the preworkshop and postworkshop as well. For phase 2, pain scores were collected at predetermined time intervals: triage, 0, 10, 20, and 30 minutes, 1, 2, 4, 8, and 16 hours. The 0-minute time was immediately before the block was initiated and all the subsequent times were based on the time of completion of the PENG block. The EPs and inpatient physicians all had the option to treat the patient preblock or postblock with their choice of pain regimen if they felt that it was clinically warranted. Side effects and the amount of opioids provided were monitored until the patient went to the operating room. In addition, the time from triage to block and triage to operating room was recorded. Needle entry to exit times were also recorded based on time-stamps obtained during image review.

Data analysis

The sample size was set at 10 patients for a pilot feasibility study. Data was compiled using a standard spreadsheet application (Excel; Microsoft, Redmond, WA, USA) and analyzed using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA). The normality of the data was evaluated using the Kolmogorov-Smirnov test. Normally distributed continuous data were presented as mean and standard deviations, and nonparametric data were presented as a median with interquartile ranges. Categorial data were summarized in cross-tab, expressed as percentages of the group with 95% confidence interval (CI), and analyzed using the chi-square test. For all analyzed data, statistical significance was set at a P-value of < 0.05.

RESULTS

Overall, 21 attending physicians and five residents attended and completed the workshop in phase 1. Identical preworkshop and postworkshop assessments were provided to each participant. The average score on the preworkshop assessment was 61% and the average postworkshop assessment score was 95%, a difference of 34% (95% CI, 11.6–53.4; P = 0.003). Comfort levels before the workshop went from 2.4 out of 5 to 4 out of 5 for a difference of 1.6 (95% CI, 0.3–2.6; P = 0.02) (Fig. 3).

Table 1 illustrates the demographics of the patients enrolled in phase 2 of the study. There were 10 cognitively intact patients, six females and four males. The median age was 80.5 years (interquartile range [IQR], 72.5–84.5 years). Seventy percent of the hip fractures were intertrochanteric, while 30% involved the femoral neck. Three blocks were performed by senior residents, four blocks by nonultrasound fellowship-trained attendings, and three by ultrasound fellowship-trained attendings. Overall, nine different EPs performed the 10 blocks with one person administering two. The mean time from needle entry to final needle exit

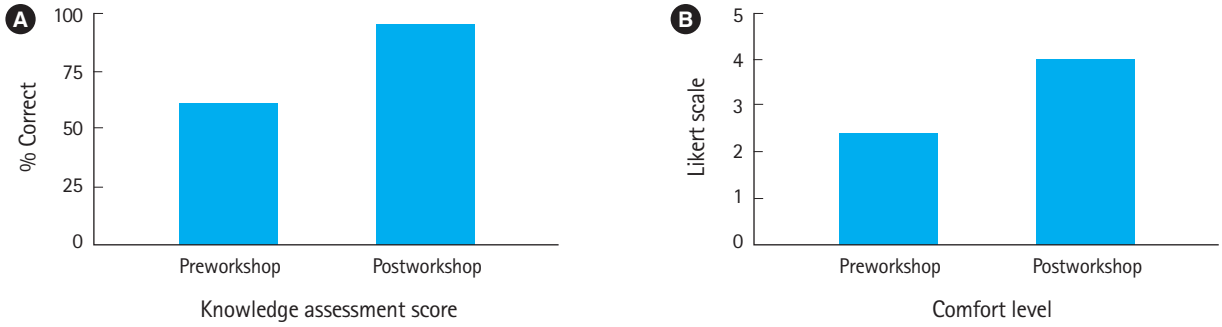

Fig. 3. Average preworkshop and postworkshop (A) assessment scores for all the participants and (B) comfort levels on a Likert scale (1, very uncomfortable; 2, uncomfortable; 3, neutral; 4, comfortable; and 5, very comfortable).

Table 1. Patient demographics and procedural data

Patient no.	Age (yr)	Sex	Fracture type	Preblock MME	Postblock MME	Time to PENG block	Time to OR	Operator	Needle entry to exit
1	101	Female	Left IT	9.0	0	4 hr 10 min	20 hr 44 min	PGY-3	19 min
2	83	Female	Right Fem Neck	11.5	0	3 hr 5 min	20 hr 3 min	PGY-4	36 min
3	59	Female	Left IT	5.0	5.0	1 hr 45 min	27 hr 30 min	Non-US fellowship-trained attending	21 min
4	95	Male	Left Fem Neck	7.0	0	8 hr 11 min	20 hr 1 min	US fellowship-trained attending	15 min
5	74	Female	Left IT	7.5	0	7 hr 28 min	42 hr 30 min	US fellowship-trained attending	20 min
6	63	Male	Left IT	6.5	0	3 hr 40 min	25 hr 44 min	US fellowship-trained attending	16 min
7	94	Male	Right Fem Neck	6.0	0.8	7 hr 41 min	39 hr 9 min	Non-US fellowship-trained attending	17 min
8	83	Female	Right IT	4.0	0	1 hr 55 min	32 hr 15 min	Non-US fellowship-trained attending	12 min
9	78	Male	Left IT	4.0	0	4 hr 45 min	13 hr 57 min	PGY-3	19 min
10	72	Female	Left IT	4.0	4.0	1 hr 27 min	18 hr 17 min	Non-US fellowship-trained attending	15 min

The following conversion scale was used: fentanyl 10 μg = 1 MME, oxycodone 1 mg = 1.5 MME, and hydromorphone 1 mg = 4 MME.
MME, morphine milligram equivalents; PENG, pericapsular nerve group; OR, operating room; IT, intertrochanteric fracture; PGY, postgraduate year; Fem Neck, femoral neck fracture; US, ultrasound.

was 19 minutes. All of the physicians who performed the block had attended the workshop and reported that practicing on the model increased their comfort level prior to performing the block on a live patient.

The median pain score at the time of the patient being triaged was 10 (IQR, 0–10). All 10 patients (100%) required an opioid (oxycodone/acetaminophen, morphine, or fentanyl) prior to the initiation of the PENG block with a median dosage of 6.25 morphine milligram equivalents (MME; IQR, 4.25–7.38 MME). After the PENG block, only 30% of the patients required further narcotic dosing until operative fixation with a median dosage of 0 MME (IQR, 0–0.6 MME).

Fig. 4 illustrates the median pain score of all 10 patients at each time interval. The median door to block time was 3 hours 55 minutes (IQR, 2 hours 13 minutes to 6 hours 47 minutes). The median pain score at time 0 (time of block) was 9 (IQR, 6.5–9.0) out of 10. At 30 minutes, the median pain score was reduced to 4.0 (IQR, 2.0–6.8) with a further reduction to 3.5 (IQR, 1.0–4.8) at the 4-hour mark. Data was not obtained for the 960-minute time

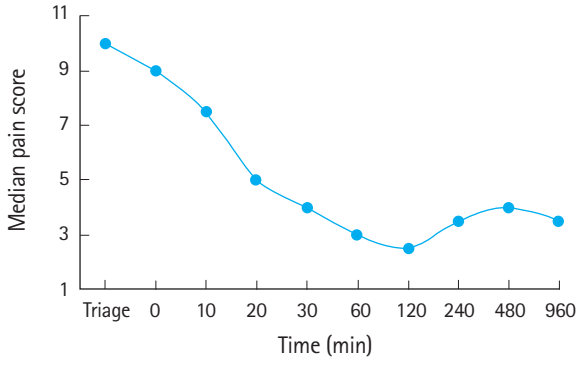

Fig. 4. Pericapsular nerve group block median pain scores. Median pain scores for all participants at the respective time interval.

point in six patients. Seven patients received no opioids after the block was placed, while three required breakthrough opioid analgesia. Fig. 5 illustrates preblock and postblock opioids. One patient received 0.2 mg hydromorphone (5 hours 45 minutes after the block), one patient received 4 mg of morphine (1 hour 25 minutes after the block), and one patient received 50 μg of fentanyl

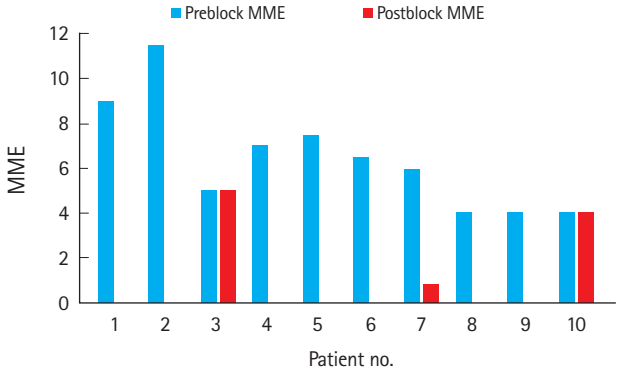

Fig. 5. The prepericapsular and postpericapsular nerve group block morphine milligram equivalents (MME) for all patients. The following conversion scale was used: fentanyl 10 μg = 1 MME, oxycodone 1 mg = 1.5 MME, and hydromorphone 1 mg = 4 MME.

(10 minutes after the block) along with 30 mg methadone, which was the patient's home maintenance dose. Since the patient's methadone was their home dose, it was not included in the postblock MME calculation. The following conversion scale was used: fentanyl 10 μg = 1 MME, oxycodone 1 mg = 1.5 MME, and hydromorphone 1 mg = 4 MME. Overall, minimal opioids were used between the time of the block and the time the patient went to the operating room with a median time of 23 hours 14 minutes (IQR, 20 hours 2 minutes to 31 hours 4 minutes).

There were no procedural complications and no side effects reported from the block. All ultrasound images during the procedure were archived in our institution's image archival system and analyzed for quality assurance.

DISCUSSION

In an ED practice environment where the standard of care is parenteral analgesia for hip fractures, our objective was to determine if we could successfully teach and perform the PENG block through training, simulation, and supervision to a group of early adopters. The PENG block was chosen for three primary reasons: its motor function sparing effects, the simplicity of the anatomical landmarks for the deposition of anesthetic, and the safe distance between the target and the femoral vascular bundle. Our long-term goal is to train middle and late adopters and further study the effectiveness of the PENG block for decreasing pain and reducing opioid usage.

We received overwhelmingly positive feedback regarding our simulation training workshop. The participants enjoyed the template of our workshop, having the opportunity to practice on a model with striking anatomical similarities. We noticed that the EPs who practiced and mastered the in-plane needling technique were quickly able to transfer this technique to live patients. The biggest role of supervision during these 10 live patients was to help with image acquisition. Our experience was that once the EPs could obtain an image similar to the low-fidelity model they trained on, they were comfortable completing the rest of the steps of the procedure. The key factors that influenced how long the procedure took were the time to adequate image acquisition and the skill of the in-plane technique. As an example, in patient 2, it took longer for the proceduralist to complete the block, secondary to issues tracking the needle in-plane that required adjustments.

EPs treated the patient's pain with parenteral or oral analgesics of their choice. For the block, bupivacaine was chosen due to its safety, availability, and long-lasting analgesia. For future studies, we will consider a mixture of lidocaine and bupivacaine so that patients can potentially benefit from the quicker onset of analgesia.

Patient 3 and patient 10 appeared to be outliers as the preblock and postblock morphine equivalents were the same. During quality assurance, we noticed suboptimal images of the needle tip during insertion, but postblock images illustrated an anechoic fluid collection underneath the psoas muscle in both patients. Postblock medications involved fentanyl 50 μg provided 10 minutes after the block for patient 3 and morphine 4 mg administered 1.5 hours after the block for patient 10. The pain scores of patient 3 and patient 10 continued to decrease and required no further opioid use until after surgery. We hypothesize that the patient's block did not necessarily fail, but that its onset was not rapid enough. We theorize that if a mixture of lidocaine and bupivacaine was used, it may have provided quicker onset of pain relief than just bupivacaine alone and suggest that as one future area of further study.

Another challenge in our study had to do with the subjectivity of the pain scores. At the 1-hour mark, six patients had a pain score of less than 4, while four patients reported a score greater than 6. In a few of our patients after the PENG block was administered, we observed that they were seated at a 35° to 40° incline, appeared comfortable as they ate or conversed with family members, and declined additional pain medications, but still reported a pain score greater than 6. While we believe pain scores are helpful, we included postblock opioid consumption data in relation to the time to operative fixation as an objective surrogate measurement to determine if the block was successful or not. Future studies can also look at the amount of additional doses needed as criteria as well.

With proper training, simulation, and supervision, it is feasible for senior residents, ultrasound fellowship-trained faculty, and non-fellowship-trained faculty to perform the PENG block. There

is promising potential to decrease opioid use while providing pain relief in patients with hip fractures. A follow-up with a randomized, controlled study with a larger sample size is potentially needed to confirm the efficacy of the PENG block.

A potentially larger challenge lies ahead in the adoption of a new innovation. It has been 60 years since Everett Rogers first published *Diffusion of innovations* in 1962,[14] and we now have a core group of nearly a dozen early adopter EPs who are able to administer a PENG block. In order to expand the use of the PENG block in our department, we believe that a PENG block on-call team to provide assistance and supervision could be helpful. The on-call team's availability for a year or two would offer a longitudinal program that captures the middle and late adopters, increasing the likelihood of adoption of the PENG block in everyday practice in the ED.

This study is limited by a small sample size and the lack of a control group. It is also a convenience sample given the availability of the research team, which may have introduced selection bias. Pain score collection was a combined effort among the research team and its medical students, but pain scores were sometimes collected by the same person who performed the block, which could potentially add bias. We did not keep records of which person collected the individual scores for each patient. Another limitation was a failure to record the number of attempts required for the needle to reach its target.

The results of this study suggest that it is possible for EPs to safely perform the PENG block in the ED for patients with hip fractures after simulation training and initially under supervision. The PENG block provides pain relief while decreasing the use of opioids for patients with hip fractures in the ED.

SUPPLEMENTARY MATERIAL

Supplementary Material 1. Low-fidelity model

Supplementary Material 2. Pericapsular nerve group (PENG) block knowledge assessment

Supplementary Fig. 1. Plastic pelvis model in 15-L plastic bin, low-fidelity pericapsular nerve group (PENG) simulator.

Supplementary Fig. 2. Foamy layer on top after gelatin mixed, low-fidelity pericapsular nerve group (PENG) simulator.

Supplementary Fig. 3. Yarn and gel filled straws represent tendon and vessels respectively, low-fidelity pericapsular nerve group (PENG) simulator.

Supplementary Fig. 4. Final product low-fidelity pericapsular nerve group (PENG) simulator.

Supplementary materials are available at https://doi.org/10.15441/ceem.22.177.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Supplementary Material 1. Low-fidelity model

As far as we know, there are no commercially available high-fidelity or low-fidelity models for the pericapsular nerve group (PENG) block. Our low-fidelity model underwent multiple iterations. We described our method for creating this model below and hope that it will be useful for others.

Multiple studies describe the effectiveness of low-fidelity models in helping emergency physicians simulate ultrasound guided procedures. Tendons and nerves can be mimicked by yarn soaked in ultrasound gel. Vessels can be mimicked by straws filled with ultrasound gel. Lastly, ballistic gel serves as an excellent medium for ultrasound and has been used to create various different simulators.

To build our low-fidelity PENG simulator, we purchased the following: a plastic skeletal pelvis model (Amazon, Seattle, WA, USA; $35.96) as illustrated in Supplementary Fig. 1, a 15-L clear plastic bin (Home Depot, Atlanta, GA, USA; $4.97), 2 lbs of Knox gelatin powder (Amazon, $20.37), and a Hamilton Beach 6-Speed open handle hand mixer (Target, Minnealopis, MN, USA; $27.26).

The goal was to encapsulate the pelvis in gelatin while simultaneously ensuring the yarn and straws are suspended in the appropriate anatomical locations. We proceeded with a two-layer technique. We used tape to secure the pelvis to the bottom of the bin. We mixed 9 L of boiling hot water with 24 ounces of Knox gelatin to create the first layer. We used multiple pots and a water kettle to bring tap water to a boil and pour it into the bin. We introduced 2.6 ounces of gelatin for every liter of water utilizing the hand mixer to reduce clumping. It is important to make sure there is immediate mixing of the gelatin powder to avoid clumping. We recommend an electronic hand mixer to ensure the gelatin is equally mixed throughout the bin. Once all 9 L are in, there will be a foamy layer on top illustrated in Supplementary Fig. 2. We used a spoon to slowly scoop out the foam and any remaining clumps. The model needs to be left in the refrigerator for a minimum of 6 to 8 hours but we opted to leave it in the refrigerator overnight.

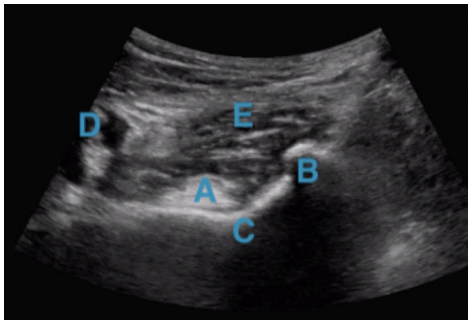
Once sufficient time has passed, the gelatin will harden and you may notice air bubbles at the top. You can use a spoon or a knife to remove any air bubbles that may have risen to the surface. With a knife, make an incision over the iliopublic eminence, cut a small piece of yarn soaked in ultrasound gel and place it on both sides. Use plastic straws filled with ultrasound gel and place just lateral to the pubic symphysis. Ensure that there is no air inside the straw and cut the straw if needed to the desired length. At this point, you may use the space around the pelvis and place small pieces of yarn to serve as target practice for the in-plane approach. Supplementary Fig. 3 illustrates the yarn and straws in their appropriate places.

Lastly, boil 3 to 4 L of water and mix in Knox gelatin powder using the electronic hand mixer in a separate pot. Slowly introduce the premixed solution into the bin so as to not disturb the yarn and straws until the entire pelvis is covered. Place it back in the fridge for 4 to 6 hours and the model is ready for use. Please note that in this initial model, we did not place pieces of yarn around the pelvis to serve as target practice, but after an iterative feedback process, we did for the second model we made. Supplementary Fig. 4 demonstrates the final product.

We added a thin layer of water on top of the model to prevent ultrasound gel requirement during the training session. We found that the thin water layer greatly diminished the artifacts left over by the needle in between learners as an added benefit.

Once the model was used for a session, we were able to refrigerate the model for several weeks. Prior to the next session, only the top layer was cut out and a new layer was added and the model was ready to be reused. Roughly 1 L of water and 3 ounces of gelatin were used to replace the top layer. This model lasted through multiple sessions over 10 weeks. At each session, the model underwent well over 100 needle sticks without leaving any significant leftover artifact.

Supplementary Material 2. Pericapsular nerve group (PENG) block knowledge assessment



1. Match the following anatomical landmarks on the figure with the appropriate letter (each one point)
   1) Iliopsoas muscle
   2) Psoas minor tendon
   3) IPE (iliopubic eminence)
   4) Femoral neurovascular bundle
   5) AIIS (anterior inferior iliac spine)

2. Which of the following is true about the PENG block?
   1) Provides a sensory only blockade
   2) Described in 2018
   3) Deposits anesthetic superior to the iliopubic eminence
   4) Both A and C
   5) All of the above

3. What complications do patients with hip fractures face?
   1) Untreated pain
   2) Pneumonia
   3) Delirium
   4) All of the above
   5) None of the above

4. Which part of the hip joint provides the most sensory information to the brain (i.e., pain)?
   1) Anterior
   2) Posterior
   3) Medial
   4) Lateral

5. Which of the following nerves provide the majority of pain sensation from the hip joint?
   1) Sciatica nerve
   2) Femoral nerve
   3) Obturator nerve
   4) All of the above
   5) B and C only

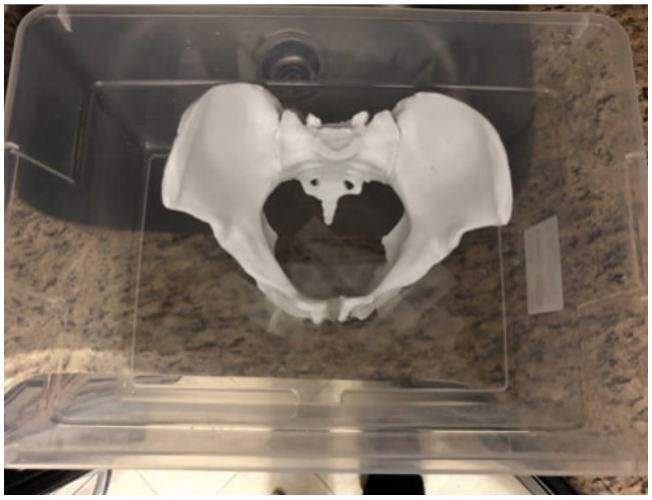
6. What landmark should you palpate to help aid image acquisition?
   1) Anterior superior iliac spine
   2) Anterior inferior iliac spine
   3) Pubic symphysis
   4) Greater trochanter

7. What indicates a successful PENG block?
   1) Lateral displacement of psoas tendon on the ultrasound screen
   2) Medial displacement of psoas tendon on the ultrasound screen
   3) Anterior/superior displacement of psoas tendon on the ultrasound screen

8. Where is intralipid located in the ED (emergency department)?
   1) Resus bay Pyxis
   2) Pharmacy
   3) Above the lidocaine inside medication room
   4) North side of ED

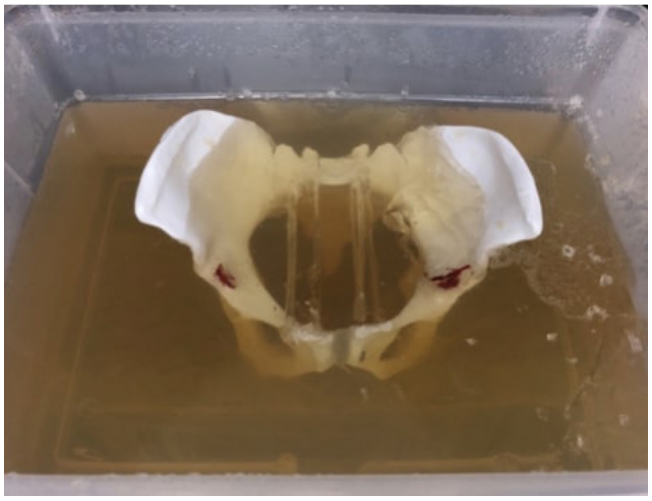
9. What are the first signs and symptoms of LAST (local anesthetic systemic toxicity)?
   1) Tongue/lip paresthesias
   2) Tinnitus
   3) Coma
   4) Only A and B
   5) All of the above

10. What are contraindications to the PENG block?
   1) Patient refusal
   2) Allergy to anesthetic
   3) Infection over injection site
   4) Multi-system trauma
   5) All of the above



Supplementary Fig. 1. Plastic pelvis model in 15-L plastic bin, low-fidelity pericapsular nerve group (PENG) simulator.

Supplementary Fig. 2. Foamy layer on top after gelatin mixed, low-fidelity pericapsular nerve group (PENG) simulator.



Supplementary Fig. 3. Yarn and gel filled straws represent tendon and vessels respectively, low-fidelity pericapsular nerve group (PENG) simulator.

Supplementary Fig. 4. Final product low-fidelity pericapsular nerve group (PENG) simulator.

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Original Article

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Neurologic outcomes of prehospital mechanical chest compression device use during transportation of out-of-hospital cardiac arrest patients: a multicenter observational study

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Objective High-quality cardiopulmonary resuscitation with chest compression is important for good neurologic outcomes during out-of-hospital cardiac arrest (OHCA). Several types of mechanical chest compression devices have recently been implemented in Korean emergency medical services. This study aimed to identify the effect of prehospital mechanical chest compression device use on the outcomes of OHCA patients.

Methods We retrospectively analyzed data drawn from the regional cardiac arrest registry in Daegu, Korea. This registry prospectively collected data from January 2017 to December 2020. Patients aged 18 years or older who experienced cardiac arrest presumed to have a medical etiology were included. The exposure variable was the use of a prehospital mechanical device during transportation by emergency medical technicians. The outcomes measured were neurologic outcomes and survival to discharge. Logistic regression analysis was used.

Results Among 3,230 OHCA patients, 1,111 (34.4%) and 2,119 (65.6%) were managed with manual chest compression and with a mechanical chest compression device, respectively. The mechanical chest compression group showed poorer neurologic outcomes than the manual chest compression group (adjusted odds ratio, 0.12; 95% confidence interval, 0.04–0.33) and decreased survival to discharge (adjusted odds ratio, 0.39; 95% confidence interval, 0.19–0.82) after adjustment for confounding variables.

Conclusion Prehospital mechanical chest compression device use in OHCA was associated with poorer neurologic outcomes and survival to discharge compared to manual chest compression.

Keywords Cardiopulmonary resuscitation; Out-of-hospital cardiac arrest; Emergency medical services

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Capsule Summary

What is already known

Although prehospital use of mechanical chest compression devices has no benefit in the survival and neurologic outcomes of out-of-hospital cardiac arrest patients, their use can be considered in special situations, such as in an ambulance, during coronary angiography, during extracorporeal cardiopulmonary resuscitation, or when there is a risk of exposure to an infectious disease.

What is new in the current study

With the introduction of mechanical chest compression devices in prehospital emergency medical services, their use during prehospital transport has increased annually in Korea. The use of mechanical compression devices during transport is associated with worse neurologic outcomes and survival to discharge than is manual compression.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a global health issue; approximately 347,000 adult OHCA patients are assessed by emergency medical services (EMSs) each year in the United States, and approximately 30,000 cases of OHCA occur annually in Korea.[1-3] High-quality cardiopulmonary resuscitation (CPR) (i.e., chest compression with adequate depth, rate, chest recoil, and minimal hands-off time) is an important factor for return of spontaneous circulation and favorable neurologic outcomes.[4-7] In previous randomized controlled trials or meta-analysis studies, the use of mechanical chest compression was not shown to improve neurologic outcomes compared to manual chest compression in OHCA.[8-11]

Although prehospital use of mechanical chest compression devices has no benefit in the outcomes of OHCA patients, their use can be considered in special situations, such as in an ambulance, during coronary angiography, during extracorporeal CPR, or when there is a risk of exposure to an infectious disease such as COVID-19.[12,13] In addition, rescuer fatigue might lead to inadequate chest compression rates and depth.[14,15] Thus, mechanical chest compression devices can have the advantage of providing continuous, high-quality chest compression during transportation, characterized by minimal compression hands-off time and constant depth of compression and relaxation. This has led to introduction of these devices to prehospital EMS in Korea. Several types of mechanical chest compression devices have been introduced to prehospital EMS, but only a limited number of studies has assessed their effectiveness.

In this study, we aimed to identify trends in the frequency of use and outcomes of mechanical chest compression devices in EMS and to compare the outcomes of OHCA patients managed with prehospital mechanical chest compression devices to those managed with manual chest compression.

METHODS

Study design and participants

This is a retrospective observational study that used data from the regional cardiac arrest registry in Daegu. We included patients aged 18 years or older who experienced cardiac arrest that was presumed to have a medical etiology in Daegu from January 2017 to December 2020. The exclusion criteria used for patients further screened were no attempt at resuscitation (n = 64), younger than 18 years (n = 85), the arrest had a noncardiac etiology (n = 967), OHCA occurred in the ambulance during transport (n = 295), prehospital return of spontaneous circulation occurred at the scene (n = 348), insufficient information of prehospital variables was available (n = 9), mechanical compression devices of unknown origin were used (n = 84), and other devices were used (n = 11) (Fig. 1). This study was approved by the Institutional Review Board of Kyungpook National University Hospital (No.2016-03-027). The Institutional Review Board waived the need for written informed consent.

Study setting

Daegu has a population of 2.4 million and an area of 883.51 km^2. The Korean prehospital EMS is operated by a single provincial fire department supported by eight local EMS agencies with 50 ambulance stations and a single unified dispatch center.[16] Mechanical chest compression devices were first introduced in November 2016, and there are currently a total of 55 devices being used in Daegu EMS: 34 from Easy Pulse (Schiller, Baar, Switzerland) and 21 from LUCAS-2 (Jolife AB, Lund, Sweden).

Each prehospital EMS team is comprised of two to three emergency medical technicians (EMTs), including a level 1 EMT (similar to intermediate level EMTs in the EMS of the United States) as the top-level ambulance crew, a level 2 EMT (similar to basic level EMTs), and a driver.[16-18] For both EMTs, the scope of practice is limited to the basic level of life support; for some EMTs who com-

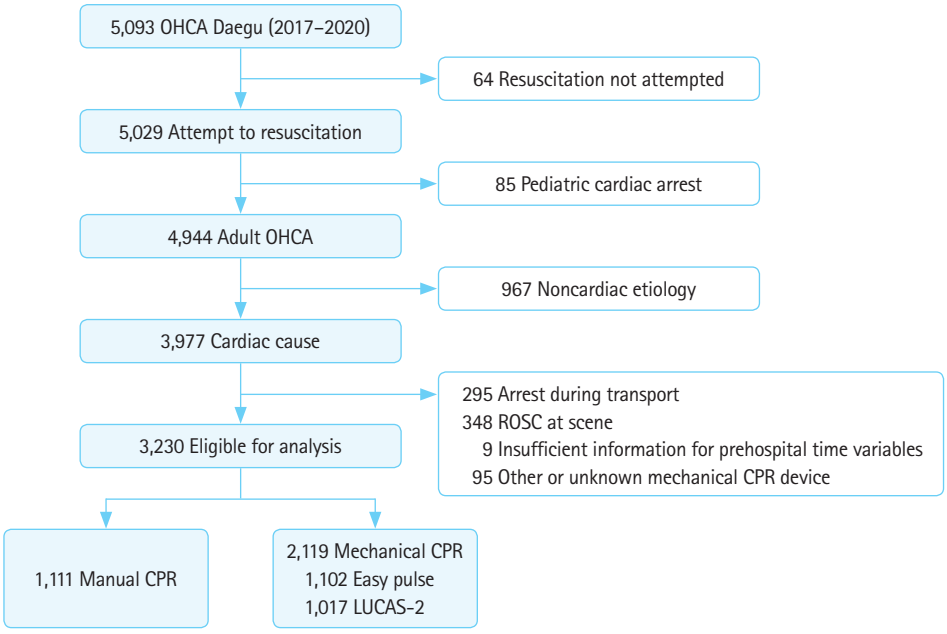

Fig. 1. Study population. OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation.

pleted an advanced training course after September 2019, the scope of practice can be expanded to include intravenous epinephrine administration during CPR under medical oversight. In March 2015, the dual-dispatch system was initiated in Daegu EMS to reduce response time and increase the number of EMTs responding to OHCA cases.[17] Since March 2017, EMS medical directors have regularly facilitated team CPR training programs to enable a well-coordinated team approach with predefined roles for each EMT.[16] This team CPR program includes training with equipment to provide high-quality CPR (i.e., end-tidal CO_2 equipment, CPR feedback device, video-laryngoscopy, and mechanical compression device) as well as scenario-based dual-dispatch CPR training. In the team program, CPR was practiced by applying a mechanical chest compression device before scene departure to provide high-quality CPR during transport in cases of dual dispatch. CPR was performed according to the Korean fire department EMS protocol and the team CPR protocol, and a mechanical chest compression device was applied immediately before transportation. The mechanical chest compression device was applied to the patient by EMTs according to availability of the chest compression device in the ambulance, field situation, and team CPR protocol.

Data source and variables

We used the regional OHCA registry, which includes all OHCA cases of level 1 and 2 hospitals in Daegu.[16-19] Data were retrieved from the EMS run sheets for basic ambulance operational information, the EMS CPR registry, the dispatcher CPR registry, and the hospital OHCA registry for hospital care and outcomes.

We analyzed the following data: demographic information (i.e., age, sex, and past medical history); community factors (i.e., presence of a witness, CPR by a bystander, location of the arrest, and primary electrocardiogram rhythm at the scene); EMS factors (i.e., activation of the dual-dispatch system, details of EMS resuscitation including defibrillation and epinephrine administration, and prehospital advanced airway management by EMTs); time variables (i.e., response time interval, scene time interval, transport time interval, duration between collapse and initiation of CPR, and duration between initiation of CPR and end of resuscitation efforts); and hospital treatments (i.e., target temperature management [TTM], percutaneous coronary intervention [PCI], and extracorporeal membrane oxygenation [ECMO]).

Outcome measures

The primary outcome measured was neurologic outcome. "Good" outcome was defined as cerebral performance category 1 (alert, conscious, able to work, and possibly having a mild neurologic or psychological deficit) or cerebral performance category 2 (conscious, sufficient cerebral function for independent activities of daily life, and able to work in a sheltered environment). The secondary outcome was survival to discharge. Each outcome was reviewed based on hospital records.

Statistical analysis

Demographics and outcomes of the study population were compared. These were also analyzed among subgroups of types of mechanical chest compression devices used. Descriptive statistics are presented as medians with interquartile ranges (25th and 75th percentiles), while categorical variables are presented as counts and percentages. The significance of the differences between the two groups was analyzed using the Mann-Whitney U-

Table 1. General characteristics of the study population

Characteristic	Total	Manual compression	Mechanical compression	P-value
All	3,230 (100)	1,111 (100)	2,119 (100)	
Sex				0.039
Male	2,049 (63.4)	678 (61.0)	1,371 (64.7)	
Female	1,181 (36.6)	433 (39.0)	748 (35.3)	
Age (yr)	75 (62–82)	75 (62–83)	75 (63–81)	0.430
≥ 65	2,302 (71.3)	782 (70.4)	1,520 (71.7)	0.422
< 65	928 (28.7)	329 (29.6)	599 (28.3)	0.422
Year[a)]				< 0.001
2017	811 (100)	637 (78.5)	174 (21.5)	
2018	827 (100)	276 (33.4)	551 (66.6)	
2019	759 (100)	127 (16.7)	632 (83.3)	
2020	833 (100)	71 (8.5)	762 (91.5)	
Comorbidity				
Hypertension	1,227 (38.0)	397 (35.7)	830 (39.2)	0.056
Diabetes mellitus	909 (28.1)	274 (24.7)	635 (30.0)	0.001
Cerebrovascular accident	414 (12.8)	135 (12.2)	279 (13.2)	0.412
Heart disease	342 (10.6)	116 (10.4)	226 (10.7)	0.844
Place				0.262
Nonpublic	2,727 (84.4)	927 (83.4)	1,800 (84.9)	
Public	503 (15.6)	184 (16.6)	319 (15.1)	
Witnessed arrest	1,508 (46.7)	557 (50.1)	951 (44.9)	0.005
Performed bystander CPR	1,824 (56.5)	584 (52.6)	1,240 (58.5)	0.001
Initial electrocardiogram rhythm				0.037
Shockable	342 (10.6)	135 (12.2)	207 (9.8)	
Nonshockable	2,888 (89.4)	976 (87.8)	1,912 (90.2)	
Time from collapse to initiation of CPR (min)	9 (3–22)	7 (3–17)	10 (4–25)	< 0.001
Time from start of CPR to the end of resuscitation efforts (min)	47 (37–57)	43 (33–53)	49 (40–58)	< 0.001
Emergency medical technician defibrillation	523 (16.2)	184 (16.6)	339 (16.0)	0.680
Dual-dispatch	2,995 (92.7)	941 (84.7)	2,054 (96.9)	< 0.001
Prehospital airway management				< 0.001
Bag-valve mask	191 (5.9)	127 (11.4)	64 (3.0)	
Subglottic airway	1,830 (56.7)	632 (56.9)	1,198 (56.5)	
Endotracheal intubation	1,209 (37.4)	352 (31.7)	857 (40.4)	
Prehospital epinephrine administration	1,128 (34.9)	148 (13.3)	980 (46.2)	< 0.001
Response time interval (min)	8 (6–10)	7 (6–9)	8 (6–10)	< 0.001
Scene time interval (min)	16 (13–19)	14 (11–17)	17 (14–20)	< 0.001
Transport time interval (min)	6 (4–10)	6 (4–9)	7 (4–10)	0.007
Treatment at hospital				
Targeted temperature management	69 (2.1)	22 (2.0)	47 (2.2)	0.657
Percutaneous coronary intervention	92 (2.8)	42 (3.8)	50 (2.4)	0.021
Extracorporeal membrane oxygenation	25 (0.8)	7 (0.6)	18 (0.8)	0.499
Survival to discharge	78 (2.4)	47 (4.2)	31 (1.5)	< 0.001
Good neurologic outcome	49 (1.5)	38 (3.4)	11 (0.5)	< 0.001

Values are presented as number (%) or median (interquartile range).
CPR, cardiopulmonary resuscitation.
[a)]The year-wise percentage shows the ratio of manual compression and mechanical compression each year.

test for continuous variables and the chi-square test for categorical variables. All trends were tested by the Cochran-Armitage test.

Associations between the study groups and outcomes were assessed using logistic regression analysis. We included potential confounding variables of demographic factors (i.e., sex, age, and presence of comorbidities); arrest characteristics (i.e., witness status, primary electrocardiogram rhythm, and location of arrest); prehospital time variables (i.e., response time interval, scene time interval, and transport time interval); EMS resuscitation procedures (i.e., prehospital airway management, prehospital epinephrine administration, and dual dispatch); and postresuscitation hospital management (i.e., PCI, TTM, and ECMO). Logistic regression analysis was performed to analyze associations between study groups and outcomes according to initial electrocardiogram rhythm, as shown in Supplementary Table 1. The results are expressed as adjusted odds ratios (AORs) and 95% confidence intervals (CIs). All statistical analyses were performed with SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA). Based on a two-sided test, $P<0.05$ was considered statistically significant.

RESULTS

Demographic analysis

Among 3,230 patients eligible for analysis, 1,111 and 2,119 were managed with manual compression and mechanical compression, respectively (Fig. 1 and Table 1). The demographic analyses of each study group are shown in Table 1. The mechanical compression group had smaller proportions of witnessed arrest and prehospital bag-valve mask ventilation but a larger proportion of dual-dispatch and prehospital epinephrine administration than did the manual compression group. Scene time interval, time from arrival to departure from the scene, was also longer in the mechanical compression group. Overall, 3.4% and 0.5% of patients in the manual compression and mechanical compression groups, respectively, had good neurologic outcomes.

Trend analysis

The rate of mechanical chest compressions during transport in OHCA patients tends to increase every year ($P<0.001$). Annually, the proportion of patients with good neurologic outcomes showed an increasing trend for the manual chest compression group ($P=0.002$), but a plateau was observed in the mechanical compression group ($P=0.598$) (Fig. 2A). Similarly, the rate of survival to discharge in the manual compression group showed an increasing trend over time, but no significant trend was seen in the mechanical compression group (Fig. 2B).

Subgroup analysis

The subgroup analysis according to the type of mechanical compression device used is shown in Table 2. Among 2,119 patients in the mechanical chest compression group, Easy Pulse and LUCAS-2 were used in 1,102 and 1,017 patients, respectively. The proportions of patients with good neurologic outcome in the Easy Pulse and LUCAS-2 groups were 0.5% and 0.6%, respectively ($P=0.663$).

Main analysis

Overall, patients treated with mechanical chest compression devices had worse neurologic outcomes (AOR, 0.12; 95% CI, 0.04–

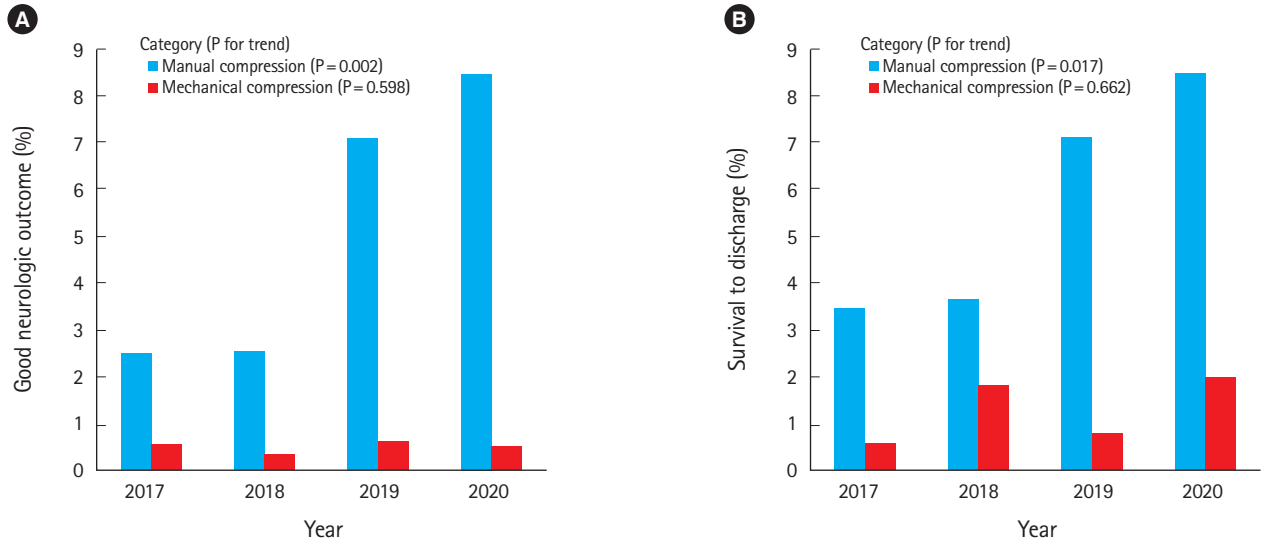

Fig. 2. Trend of (A) good neurologic outcomes and (B) survival to discharge with out-of-hospital cardiac arrest according to chest compression method.

Table 2. Comparison of the study population according to mechanical chest compression device

Variable	Easy Pulse	LUCAS-2	P-value
All	1,102 (100)	1,017 (100)	
Sex			0.413
Male	704 (63.9)	710 (69.8)	
Female	398 (36.1)	307 (30.2)	
Age (yr)	76 (63–82)	74 (62–81)	0.009
≥ 65	810 (73.5)	710 (69.8)	0.060
< 65	292 (26.5)	307 (30.2)	0.060
Year			< 0.001
2017	11 (1.0)	163 (16.0)	
2018	233 (21.1)	318 (31.3)	
2019	371 (33.7)	261 (25.7)	
2020	487 (44.2)	275 (27.0)	
Comorbidity			
Hypertension	427 (38.7)	403 (39.6)	0.679
Diabetes mellitus	328 (29.8)	307 (30.2)	0.832
Cerebrovascular accident	153 (13.9)	126 (12.4)	0.309
Heart disease	130 (11.8)	96 (9.4)	0.079
Place			0.022
Nonpublic	955 (86.7)	845 (83.1)	
Public	147 (13.3)	172 (16.9)	
Witnessed arrest	517 (46.9)	434 (42.7)	0.050
Performed bystander CPR	652 (59.2)	588 (57.8)	0.529
Initial electrocardiogram rhythm			0.330
Shockable	101 (9.2)	106 (10.4)	
Nonshockable	1,001 (90.8)	911 (89.6)	
Time from collapse to initiation of CPR (min)	10 (3–28)	10 (4–23)	0.926
Time from start of CPR to the end of resuscitation efforts (min)	49 (40–58)	49 (39–58)	0.253
EMT defibrillation	167 (15.2)	172 (16.9)	0.270
Dual-dispatch	1,082 (98.2)	972 (95.6)	0.001
Prehospital airway management			0.317
Bag-valve mask	31 (2.8)	33 (3.2)	
Subglottic airway	640 (58.1)	558 (54.9)	
Endotracheal intubation	431 (39.1)	426 (41.9)	
Prehospital epinephrine administration	609 (55.3)	371 (36.5)	< 0.001
Response time interval (min)	8 (6–10)	8 (6–10)	0.804
Scene time interval (min)	18 (15–21)	16 (14–19)	< 0.001
Transport time interval (min)	7 (5–10)	6 (4–10)	0.046
Survival to discharge	13 (1.2)	18 (1.8)	0.258
Good neurologic outcome	5 (0.5)	6 (0.6)	0.663

Values are presented as number (%) or median (interquartile range).
CPR, cardiopulmonary resuscitation; EMT, emergency medical technician.

0.33) than patients with manual compressions. There was also a lower survival to discharge ratio in the mechanical chest compression group (AOR, 0.39; 95% CI, 0.19–0.82) compared to the manual chest compression group after adjusting for confounders (Table 3).

DISCUSSION

We evaluated the types and trends of mechanical chest compression device use during OHCA in patients and analyzed its association with neurologic outcomes and survival. With the introduction of mechanical chest compression devices, such as Easy Pulse and LUCAS-2, in prehospital ambulances, their use during transport has been increasing. However, use of a mechanical chest compression device during transport was associated with poorer neurological prognosis (AOR, 0.12; 95% CI, 0.04–0.33) and survival (AOR, 0.39; 95% CI, 0.19–0.82) compared to manual chest compression.

The 2020 American Heart Association CPR guidelines and the Korean CPR guidelines suggest that mechanical chest compression be considered in special situations, such as having a small number of staff who can perform CPR, being in an ambulance, during coronary angiography, during extracorporeal CPR, or when there is a risk of exposure to infectious diseases such as COVID-19.[12,13,20] The guidelines emphasize that interruption of chest compressions could be minimized with use of a mechanical chest compression device.[12] However, few studies have analyzed neurologic and survival outcomes related to the use of a mechanical chest compression device in OHCA patients immediately prior to transfer and departure from the scene. In this study, a team CPR training program for EMTs was conducted every year on proper use of the mechanical chest compression device of the local ambulance. Based on dual-dispatch, CPR was performed at the scene according to the fire department EMS protocol of Korea and applied during the transfer process immediately prior to departure. This study was conducted based on regional cardiac arrest registry data reflecting the actual use of the EMS mechanical chest compression devices in the region. Therefore, our study is meaningful because the comparison of outcomes between mechanical chest compression devices and manual chest compressions was contextualized according to a regional prehospital protocol for OHCA patients. In addition, this study might assist in the establishment of an EMS strategy in the region.

In this study, use of a mechanical chest compression device during transport of OHCA patients was associated with poor neurological prognosis. Despite differences in the type and application protocol of chest compression devices, the AutoPulse Assisted Prehospital International Resuscitation Trial reported favorable neurological prognosis at hospital discharge in 3.1% and 7.5% of patients managed with the automated load distributing band (LDB) chest compression device and manual CPR, respectively. In that study, the LDB-CPR group reported poorer neurological prognosis than manual CPR patients, similar to the results of our study.[21]

Table 3. Multivariable logistic regression analysis of the effect of mechanical cardiopulmonary resuscitation on out-of-hospital cardiac arrest outcome

Variable	Good neurologic outcome				Survival to discharge			
	OR	95% CI	AOR[a)]	95% CI	OR	95% CI	AOR[a)]	95% CI
Manual compression	1.00		1.00		1.00		1.00	
Mechanical compression	0.15	0.08–0.29	0.12	0.04–0.33	0.34	0.21–0.53	0.39	0.19–0.82

OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio.
[a)]Adjusted for year, sex, age, presence of comorbidity (hypertension, diabetes mellitus, cerebrovascular accident, heart disease), response time interval, scene time interval, transport time interval, location of cardiac arrest, initial electrocardiogram rhythm, witnessed arrest, bystander cardiopulmonary resuscitation, prehospital airway management, prehospital epinephrine administration, dual-dispatch, and hospital treatment (targeted temperature management, extracorporeal membrane oxygenation, percutaneous coronary intervention).

Hallstrom et al.[21] reported that the poor neurological prognosis of the LDB-CPR group could be a result of the Hawthorne effect, in which the quality of manual CPR was higher than average and because the mechanical device takes longer to set up. In a video-recording and time-motion study performed during resuscitation in the emergency department, an average of 122.6 seconds was required to apply the mechanical chest compression device, and approximately 72.7% of the time elapsed was reported as no-flow time.[22] Thus, in this study, application of a mechanical chest compression device in the field was possibly associated with increased no-flow time. Considering that the median transport time interval was 6 minutes in an EMS in a large city with a relatively shorter transport time than in a rural area, application of mechanical chest compression devices during transport might not have benefited the chest compression fraction.

Another possible explanation is that the mechanical chest compression device was displaced from the proper position during transport. A randomized crossover manikin study by Blomberg et al. reported that, during CPR, the rate of compressions with sufficient depth among total chest compressions was lower with the mechanical chest compression device than with manual CPR (58% vs. 88%). It is suggested that the mechanical chest compression device may have been affected by changes from the proper position of chest compression during application.[23] Our study showed that the rates of favorable neurological prognosis and survival at discharge have been increasing yearly in the manual chest compression group, but these rates remained constant in the mechanical chest compression device group. Each year, paramedics are periodically educated regarding OHCA, proper application of mechanical chest compression devices, and team CPR; but the effectiveness of this training might not have been sufficient. The training process should further emphasize the importance of reducing no-flow time and maintaining appropriate chest compression position during application. Also, assessment and feedback regarding EMT proficiency are necessary.

This study has several limitations. First, as a retrospective observational study, selection and information biases might have occurred. Second, there might have been differences in chest compression quality and team CPR performance depending on the individual capabilities of the EMT and paramedics; additional information to evaluate the quality of CPR (e.g., chest compression fraction) was not provided. Third, although team CPR training was conducted every year, there was no assessment of EMT proficiency before and after training or annually. It also is possible that the effectiveness of the training in mechanical device use for EMTs was insufficient. Fourth, there can be differences between hospitals in quality of CPR and in postcardiac arrest treatment capacity (i.e., TTM, ECMO, and PCI). These factors can influence the patient's neurological prognosis. Last, there are inherent differences between EMS, out-of-hospital CPR protocols, and EMTs; therefore, consideration of these is necessary before generalizing and applying these findings to other regions or countries.

In conclusion, use of mechanical chest compression devices during transport of OHCA patients was associated with poorer neurological and survival outcomes at discharge compared to manual chest compressions. When applying a mechanical chest compression device during transport, paramedics should be trained to minimize interruption of chest compressions and to maintain the device at an appropriate position.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Effect of mechanical cardiopulmonary resuscitation on out-of-hospital cardiac arrest outcomes according to initial electrocardiogram rhythm
Supplementary material is available at https://doi.org/10.15441/ceem.21.142.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Effect of mechanical cardiopulmonary resuscitation on out-of-hospital cardiac arrest outcomes according to initial electrocardiogram rhythm

	Good neurologic outcome						Survival to discharge					
	No. (%)	Total	OR	95% CI	AOR[a]	95% CI	No. (%)	Total	OR	95% CI	AOR[a]	95% CI
Shockable rhythm	37 (10.8)	342					46 (13.5)	342				
Manual compression	29 (21.5)	135	1.00		1.00		29 (21.5)	135	1.00		1.00	
Mechanical compression	8 (3.9)	207	0.15	0.07–0.33	0.06	0.01–0.26	17 (8.2)	207	0.34	0.17–0.62	0.24	0.08–0.78
Nonshockable rhythm	12 (0.4)	2,888					32 (1.1)	2,888				
Manual compression	9 (0.9)	976	1.00		1.00		18 (1.8)	976	1.00		1.00	
Mechanical compression	3 (0.2)	1,912	0.17	0.05–0.63	0.13	0.02–0.87	14 (0.7)	1,912	0.39	0.19–0.79	0.58	0.20–1.70

OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio.

[a]Adjusted for year, sex, age, comorbidity (hypertension, diabetes mellitus, cerebrovascular accident, heart disease), response time interval, scene time interval, transport time interval, place of cardiac arrest occurred, witnessed arrest, bystander cardiopulmonary resuscitation, prehospital airway management, prehospital epinephrine administration, dual-dispatch, and hospital treatment (targeted temperature management, extracorporeal membrane oxygenation, percutaneous coronary intervention).

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Original Article

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Clinical study on ureteritis observed in contrast-enhanced computed tomography in the emergency department

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Objective We aimed to investigate the causes and clinical and laboratory features of patients with ureteritis observed on intravenous contrast-enhanced abdominopelvic computed tomography (APCT) conducted in the emergency department (ED).

Methods All APCTs conducted in the ED from November 2017 to November 2020 were investigated for the presence of ureteritis. The incidence of ureteritis, presumed cause of ureteritis, and clinical as well as laboratory features of patients with ureteritis were retrospectively analyzed.

Results Ureteritis was observed in 422 out of 7,386 patients (5.7%) who underwent APCTs. The two main reasons for undergoing APCT in the ED were abdominal pain (49%) and infection focus workup (33%). The first major cause of ureteritis was urinary tract infection (UTI) (351 of 422, 83%). Most patients (85%) were febrile, but 208 (59%) exhibited no urinary symptoms such as dysuria, increased frequency, or residual urine sense. The second major cause of ureteritis was ureteral stones (42 of 422, 10%). Thirty-two of 42 patients (76%) had simple obstructive uropathy, while 24% of patients had a combined infection along with an obstruction. Other rare causes were malignancy and the spread of adjacent inflammation.

Conclusion Ureteritis was a common finding observed in 5.7% of patients who underwent APCTs at the ED, and most of them were secondary to UTIs and ureteral stones. UTIs can cause ureteritis even without typical symptoms or signs suggestive of UTI, and diagnosis without an APCT can be difficult. More liberal use of APCTs should be considered when the cause of fever is difficult to diagnose.

Keywords Ureteral diseases; Computed tomography; Urinary tract infections; Ureteral calculi

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Capsule Summary

What is already known

The causes, frequency and clinical characteristics of ureteritis among emergency department patients are not well investigated.

What is new in the current study

Ureteritis was a common finding observed in 5.7% of patients who underwent contrast-enhanced abdominal computed tomography in the emergency department, and most of them were secondary to urinary tract infection (UTI) and ureteral stones. UTI can cause ureteritis even without typical symptoms or signs suggestive of UTI. Ureteral stones can cause ureteritis either by obstruction or combined infectious inflammation.

INTRODUCTION

The ureter is a tubular structure approximately 20 to 30 cm in length, connecting the kidneys to the bladder. The ureter is histologically composed of three layers (the mucosa consists of transitional epithelium, submucosal connective tissue, and lamina propria), but the histological layered structure cannot be distinguished on computed tomography (CT). Generally, the wall thickness of the ureter in an average adult does not exceed 1 mm, and there is no contrast-enhancement.[1] However, in the presence of ureteritis, the ureter wall thickens to 1 mm or more, and contrast of the ureter wall is enhanced if an intravenous agent is used.

Intravenous contrast-enhanced abdominopelvic CT (APCT) is an essential imaging test frequently conducted in the emergency department (ED) for various reasons, including abdominal pain, fever, and trauma. However, the authors experienced a relatively low interest in the ureter compared to the major abdominal organs. For this reason, we inferred that there might be cases where ureteritis on APCTs was overlooked.

The known causes of ureter abnormalities observed on CT are ureteral malignant neoplasms,[2,3] metastasis of other malignant neoplasms,[2-4] fibroepithelial polyps,[5] ureteritis Cystica,[6] tuberculosis,[7] amyloidosis,[8] inflammation due to urinary tract infections (UTIs),[1,9] non-infectious inflammation caused by indwelling ureteral stents or radiation,[1,10] the spread of peripheral inflammation such as pancreatitis or enteritis,[1] urinary tract obstruction due to ureteral stones or neoplasia,[1] and retroperitoneal fibrosis.[9] However, little is known about the clinical characteristics of patients with ureteritis observed in APCTs performed in the ED. Therefore, this study investigated the causes of ureteritis observed in APCTs conducted in the emergency room and examined the clinical and laboratory (blood and urine tests) characteristics of ureteritis patients.

METHODS

Ethics statement

After obtaining approval from the Institutional Review Board of Kangbuk Samsung Hospital (No. 2021-05-032), a retrospective cross-sectional study was conducted. The Institutional Review Board exempted written informed consent due to the retrospective nature of the study. To ensure anonymity, personal information such as patient name, date of birth, and social indentification number were deleted after assigning research subject numbers. This study was conducted in compliance with the World Medical Association Declaration of Helsinki.[11]

Study subjects

We investigated the results of every APCT conducted in the ED of our hospital for 3 years from November 2017 to November 2020. In repeated APCT scans due to revisits of the same patient, only the first APCT was included for analysis. Results of scans of the same patient performed at more than one time during the study period were excluded. Furthermore, patients with missing blood

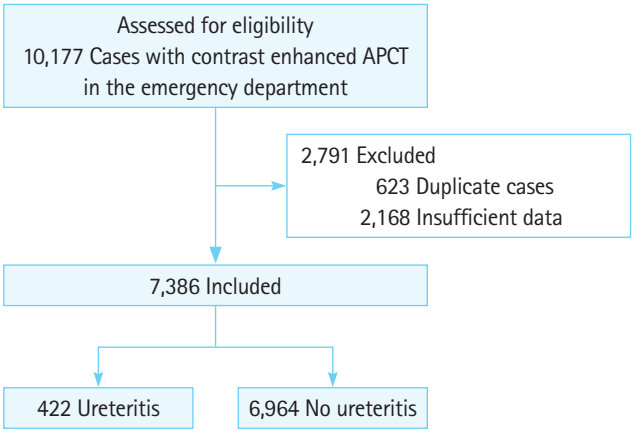

Fig. 1. Flow diagram of the study. APCT, abdominopelvic computed tomography.

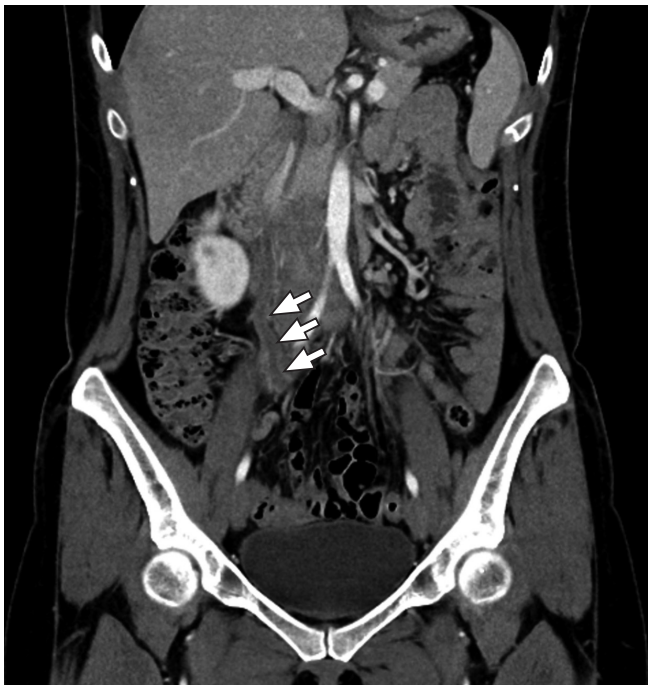

Fig. 2. A case of ureteritis due to urinary tract infection. The patient was a 38-year-old female with right lower quadrant area pain and fever. Diffuse urothelial wall thickening and urothelial enhancement are observed in the right ureter (arrows).

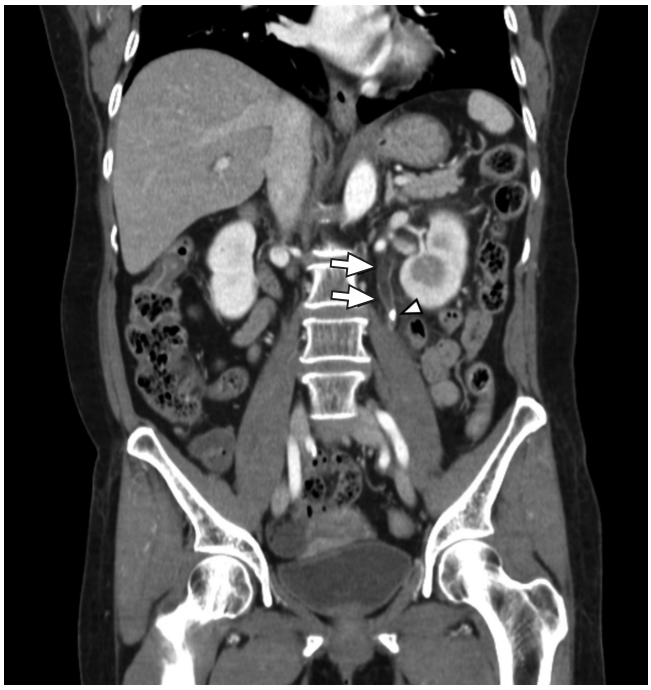

Fig. 3. A case of ureteritis associated with urinary tract stones. The patient was a 68-year-old female with abdominal pain and a ureter stone (arrowhead). The resulting obstructive uropathy are observed. Mild wall thickening of the left upper ureter (arrows) suggests combined inflammation.

or urine tests or missing clinical data were excluded. Lastly, patients were analyzed retrospectively for the presence or absence of ureteritis on APCTs, and patients with ureteritis were selected as the final study subjects (Fig. 1). The presence or absence of ureteritis was judged based on the radiologist's formal report.

Outcome measures

The cause of ureteritis and the clinical and laboratory characteristics of patients with ureteritis were analyzed. Ureteritis was defined as a diffuse circumferential urothelial wall thickening greater than 1 mm and contrast-enhancement (± periureteral fat stranding) on APCTs. The cause of ureteritis was presumed to be a UTI if the patient exhibited a fever (or history of fever)+serum infection marker (C-reactive protein [CRP] or procalcitonin [PCT]) elevation +no cause of infection other than acute pyelonephritis (APN) or cystitis (Fig. 2). Ureteral stones were presumed to be the cause of ureteritis if diffuse, circumferential urothelial wall thickening of more than 1 mm and contrast-enhancement was observed in the ureter proximal to the ureteral stone (Fig. 3). Ureteritis caused by ureteral stones was considered to be due to simple obstructive uropathy if there was no pyuria and serum infection marker elevation. On the other hand, if there was pyuria or a positive urine culture and serum infection marker elevation, ureteritis was considered due to a combined infection rather than a simple obstructive uropathy. Additionally, the characteristics of patients with only ureteritis on APCTs (no APN nor cystitis on APCTs) were also analyzed.

Statistical analysis

A descriptive analysis was conducted to show the clinical and laboratory characteristics of ureteritis. Graphical methods and Shapiro-Wilk tests were conducted to determine the normality of the continuous variables, but most of the continuous variables did not satisfy normality. Therefore, the Mann-Whitney U-test was used to compare continuous variables. Categorical variables were compared using chi-square or Fisher exact test according to the expected frequency. Continuous variables were expressed as the median (interquartile range), while nominal variables were expressed as frequency (%), and statistical significance was considered with P-values less than 0.05. The statistical analyses were conducted using Stata ver. 15.0 (StataCorp, College Station, TX, USA).

RESULTS

We investigated the results of 10,177 cases of APCTs conducted in the ED of our hospital over 3 years from November 2017 to

Table 1. Primary reason for contrast-enhanced abdominal computed tomography (n=7,386)

Reason for computed tomography	Frequency	Cases with ureteritis
Abdominal pain	3,585 (48.5)	62/3,585 (1.7)
Fever or infection source work up	2,425 (32.8)	321/2,425 (13.2)
Trauma	405 (5.5)	4/405 (1.0)
Flank or back pain	327 (4.4)	22/327 (6.7)
Gastrointestinal symptoms other than abdominal pain[a]	291 (3.9)	7/291 (2.4)
Alleged malignancy	85 (1.2)	0/85 (0)
Perineal and inguinal problems	45 (0.6)	1/45 (2.2)
Hematuria	32 (0.4)	2/32 (6.3)
Laboratory abnormality[b]	24 (0.3)	0/24 (0)
Others[c]	167 (2.3)	3/167 (1.8)

Values are presented as number (%).
[a]Anorexia, nausea, vomiting, constipation, diarrhea, hiccups, melena, hematochezia, abdominal distension, and palpable mass. [b]Abnormal liver function test, pancreatic enzyme elevation, etc. [c]Altered mental status, shock, anemia, etc.

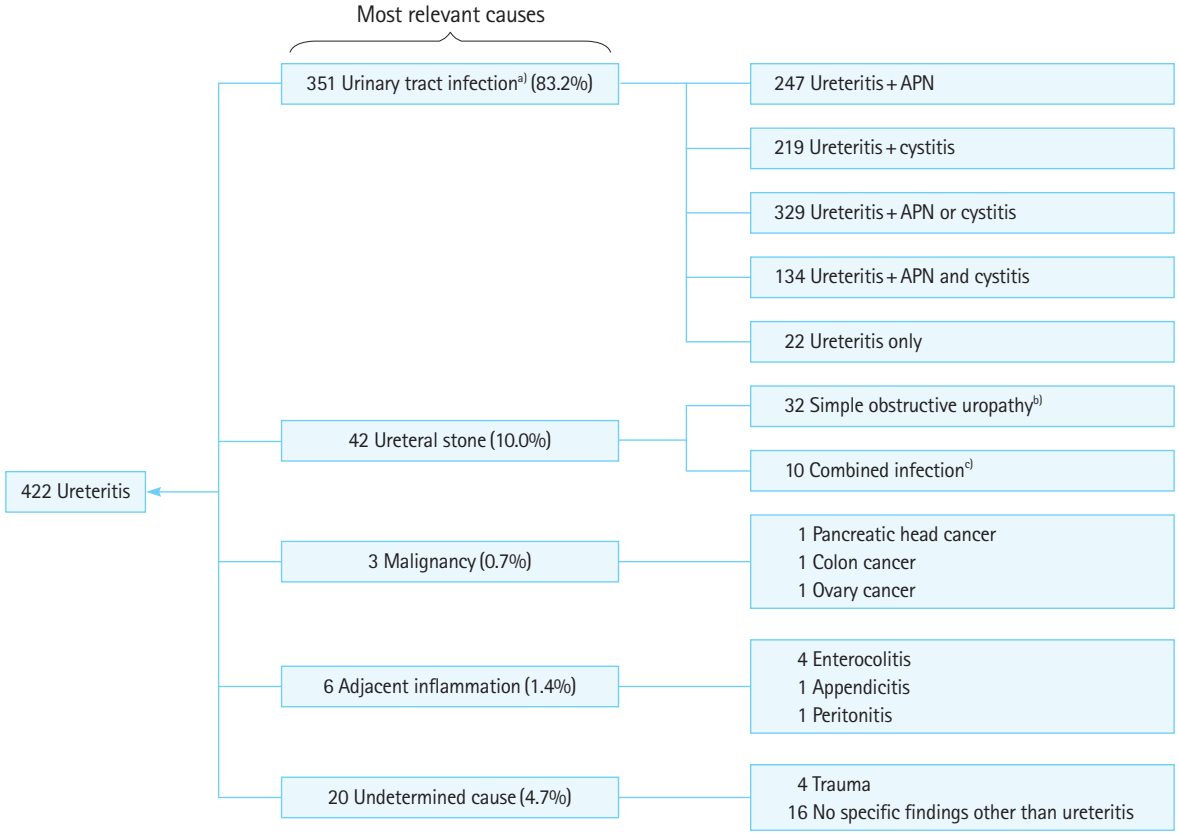

Fig. 4. Classification by etiology in 422 cases with ureteritis confirmed on intravenous contrast-enhanced abdominopelvic computed tomography. [a]Ureteritis+no cause of infection other than pyelonephritis or cystitis on abdominopelvic computed tomography+fever (or history of fever)+serum infection marker (C-reactive protein or procalcitonin) elevation. [b]Ureteritis+ureteric stone+no pyuria+no serum infection marker elevation. [c]Ureteritis+ureteric stone+pyuria or positive urine culture+serum infection marker elevation. APN, acute pyelonephritis.

November 2020. The results of 623 APCT scans on the same patients, performed more than once during the study period, were excluded. Furthermore, 2,103 patients with missing blood or urine tests and 65 patients with missing clinical data were excluded. A final total of 7,386 patients were retrospectively analyzed for the presence or absence of ureteritis on APCTs, and 422 patients (5.7%) with ureteritis were selected as the final study subjects (Fig. 1).

The main reason for undergoing APCT in the ED was differential diagnosis of abdominal pain, followed by fever workup (fever

Table 2. Clinical and laboratory characteristics of 351 patients with ureteritis caused by UTI

Characteristic	Ureteritis caused by UTI (n = 351)
Age (yr)	63.0 (47.0–76.0)
Sex	
Female	307 (87.5)
Male	44 (12.5)
Time interval between symptom onset and ED visit (hr)	31 (10–72)
Signs and symptoms	
Fever, chill	299 (85.2)
Flank pain, back pain	114 (32.5)
Costovertebral angle tenderness	130 (37.0)
Urinary symptoms (dysuria, frequency, RU sense)	143 (40.7)
Voiding difficulty	2 (0.6)
Gross hematuria	25 (7.1)
Abdominal pain	85 (24.2)
Other gastrointestinal symptoms	49 (14.0)
Systolic blood pressure (mmHg)	128.0 (114.0–142.0)
Diastolic blood pressure (mmHg)	70.0 (61.0–80.0)
Heart rate	100.0 (88.0–111.0)
Body temperature (°C)	38.5 (37.6–39.3)
Laboratory	
White blood cell ($\times 10^3/\mu L$)	11.14 (8.71–13.95)
Neutrophil (%)	84.2 (77.3–88.8)
Hemoglobin (g/dL)	12.2 (11.4–13.2)
C-reactive protein (mg/dL)	8.18 (3.52–15.11)
Procalcitonin (ng/mlL)	0.654 (0.21–3.01)
Pyuria (white blood cell > 5)	300 (85.5)
Positive urine culture (n = 106)	77 (72.6)
Hematuria (red blood cell > 5)	111 (31.6)
Glucosuria	45 (12.8)
Proteinuria	214 (61.0)

Values are presented as median (interquartile range) or number (%).
UTI, urinary tract infection; ED, emergency department; RU, residual urine.

Table 3. Clinical and laboratory characteristics of 22 patients who had ureteritis caused by urinary tract infection but showed only ureteritis on abdominopelvic computed tomography

Characteristic	Ureteritis only (n = 22)
Age (yr)	58.5 (48.0–76.0)
Sex	
Female	19 (86.4)
Male	3 (13.6)
Signs and symptoms	
Fever, chill	22 (100)
Flank pain, back pain	9 (40.9)
Costovertebral angle tenderness	8 (36.4)
Urinary symptoms (dysuria, frequency, RU sense)	8 (36.4)
Voiding difficulty	0 (0)
Gross hematuria	0 (0)
Abdominal pain	6 (27.3)
Other gastrointestinal symptoms	2 (9.1)
Systolic blood pressure (mmHg)	124.5 (113.0–134.0)
Diastolic blood pressure (mmHg)	71.5 (61.0–76.0)
Heart rate	97.5 (86.0–112.0)
Body temperature (°C)	38.6 (37.8–39.7)
Laboratory	
White blood cell ($\times 10^3/\mu L$)	9.785 (8.42–12.08)
Neutrophil (%)	87.55 (75.5–91.0)
Hemoglobin (g/dL)	12 (10.6–13.4)
C-reactive protein (mg/dL)	4.63 (2.16–5.59)
Procalcitonin (ng/mlL)	0.493 (0.218–1.340)
Urine pH	5.75 (5–7)
Glucosuria	1 (4.6)
Proteinuria	9 (40.9)
Nitrite in urine	8 (36.4)
Leukocyte esterase in urine	17 (77.3)
Pyuria (white blood cell > 5)	17 (77.3)
Hematuria (red blood cell > 5)	4 (18.2)
Bacteriuria	17 (77.3)
Urine culture positive (n = 4)	3 (75.0)

Values are presented as median (interquartile range) or number (%).
RU, residual urine.

source investigation and differential diagnosis of infectious disease) and trauma (Table 1). Particularly, of the 2,425 patients who underwent APCT for fever workups, ureteritis was observed in 321 (13%) (Table 1).

Among the 422 patients who had ureteritis on APCT during this study period, the cause of ureteritis in 351 cases was UTIs, accounting for 83% of the cases. Additionally, of the 351 patients with ureteritis due to UTIs, 329 (93.7%) had ureteritis and APN or cystitis simultaneously, while 22 patients (6.3%) had only ureteritis without APN or cystitis. The cause of sole ureteritis on APCTs could be assumed to be UTIs because the 22 patients had fever (or history of fever), pyuria or positive urine culture, elevated serum infection marker (CRP or PCT), and no other findings that could be the cause of fever or infection rather than ureteritis (Fig. 4).

The second most common cause of ureteritis observed on APCT was ureteral stone, which accounted for up to 10% of 422 ureteritis patients. Among the 42 cases of ureteritis caused by ureteral stones, 32 (76%) were presumed to be due to simple obstructive uropathy (no pyuria and no serum infection marker elevation). Additionally, 10 cases (24%) had combined UTIs (pyuria or positive urine culture and the serum infection marker elevation) along with obstruction (Fig. 4).

UTIs and ureteral stones accounted for 93% of ureteritis on APCTs conducted in the ED. Other rare causes of ureteritis were the spread of malignant tumors or nearby inflammation (Fig. 4).

Table 2 shows the clinical features and laboratory test results of 351 patients with ureteritis caused by UTIs. The median age of

Table 4. Clinical and laboratory characteristics of 42 patients with ureteritis caused by ureteral stone

Characteristic	Ureteritis caused by ureteral stone (n = 42)
Age (yr)	55.0 (42.0–68.0)
Sex	
Female	28 (66.7)
Male	14 (33.3)
Time interval between symptom onset and ED visit (hr)	3.5 (1–10)
Signs and symptoms	
Fever, chill	5 (11.9)
Flank pain, back pain	23 (54.8)
Costovertebral angle tenderness	4 (9.5)
Urinary symptoms (dysuria, frequency, RU sense)	3 (7.1)
Voiding difficulty	0 (0)
Gross hematuria	5 (11.9)
Abdominal pain	29 (69.1)
Other gastrointestinal symptoms	7 (16.7)
Systolic blood pressure (mmHg)	149.5 (135.0–170.0)
Diastolic blood pressure (mmHg)	83.0 (74.0–97.0)
Heart rate	75.5 (69.0–84.0)
Body temperature (°C)	36.7 (36.3–37.2)
Laboratory	
White blood cell ($\times 10^3/\mu L$)	9.52 (7.49–11.47)
Neutrophil (%)	72.4 (61.6–82.2)
Hemoglobin (g/dL)	13.9 (12.6–14.6)
C-reactive protein (mg/dL)	0.175 (0.04–0.90)
Procalcitonin (ng/mL)	0.061 (0.020–0.677)
Pyuria (white blood cell > 5)	6 (14.3)
Positive urine culture (n = 6)	3 (50.0)
Hematuria (red blood cell > 5)	23 (54.8)
Glucosuria	4 (9.52)
Proteinuria	7 (16.7)

Values are presented as median (interquartile range) or number (%).
ED, emergency department; RU, residual urine.

patients was 63 years, and more than 85% had fevers or chills. Infection markers (CRP and PCT) were elevated, and pyuria was present in more than 85% of patients (Table 2).

Table 3 shows the characteristics of 22 patients who had ureteritis caused by UTIs, but exhibited only ureteritis on the APCT (no accompanied findings of APN nor cystitis on APCTs). Of the 22 patients with only ureteritis on the APCTs, all (100%) exhibited fevers and chills at the time of their visit to the ED. However, only 36.4% had costovertebral angle tenderness and less than 50% of the patients complained of upper UTI symptoms such as flank pain and lower UTI symptoms such as dysuria, frequency, or residual urine sense.

Table 4 shows the clinical features and laboratory test results of 42 patients with ureteritis caused by ureteral stones. The median age of the patients was 55 years, and approximately 55% exhibited flank pain. Infection markers (CRP and PCT) were not elevated, and hematuria was present in about 55% of the patients.

DISCUSSION

This is the first report on the causes and clinical features of ureteritis observed on APCTs conducted in the ED. Ureteritis was observed in approximately 6% of the 7,500 APCTs conducted in the ED during the study period. The most common cause of ureteritis was UTI, resulting in 83% of ureteritis cases. This result agrees with a previous report in which cases of ureteritis were caused by ascending infections of cystitis or descending infections of pyelonephritis by UTI causing bacteria (*Escherichia coli, Staphylococci, Streptococci, Enterococci*, and *Proteus*) rather than a primary lesion of the ureter.[12] Bacterial endotoxins cause functional changes such as decreased muscle tone and abnormal peristalsis of the ureter, and size changes such as swelling of the mucosal and submucosal layers.[1,9]

The result that drew attention in this study was a small group of patients where only ureteritis was observed without pyelonephritis or cystitis. An interesting feature is that 100% of the patients had fevers upon visiting the ED, but less than 40% had presumptive symptoms or signs of UTI, while one-quarter of the patients had no pyuria. In patients with only ureteritis, it can be difficult to suspect a UTI as the cause of the fever during the initial evaluation of the patient in the ED. Therefore, for patients whose cause of fever is unclear, APCTs should actively be considered. It is necessary to examine the presence of ureteritis in APCTs carefully. In fact, the trigger for initiating this study was experience with patients with UTIs who had ureteritis without pyelonephritis or cystitis on APCTs that were conducted in search of the fever source.

The difference between this study's results and those of previous studies is that ureteral stones were the second most common cause of ureteritis in ED patients. To the best of our knowledge, considering the absence of previous ED-based studies, we believe that this is the first study to report that ureteral stones are the cause of ureteritis in approximately 10% of APCTs performed in the ED. However, the mechanism of ureteritis caused by ureteral stones remains unclear. There is no study suggesting its pathophysiology and the mechanism of ureteritis may be the result of simple edema due to obstruction or inflammation caused by combined UTIs and obstruction. In this study, one-fourth of patients with ureteral stones and ureteritis exhibited positive pyuria or urine cultures, and infection-related markers increased in blood tests, suggesting that combined UTIs, as well as simple obstruc-

tion, may cause ureteritis. Alternatively, the remaining three quarters of the patients did not exhibit pyuria, positive urine cultures, and blood infection-related marker elevations. Therefore, ureteral edema due to simple obstruction could be the main cause of ureteritis. However, when ureteritis is observed in patients with ureteral stones, the possibility of subclinical infectious ureteritis cannot be excluded.

Among the APCT findings that occur in the ureter related to ureteral stones, soft-tissue rim signs (rim signs) or ureteral wall thickness should be distinguished from ureteritis.[13-15] The rim sign is an edema of the short segment ureter surrounding the ureteral stone, which is observed as a soft-tissue density on APCTs and can be used to distinguish a ureteral stone from a phlebolith.[13,14] Ureteral wall thickness is caused by localized short segment ureteral wall edema around an impacted ureteral stone. It has been reported that if the thickness of the ureteral wall surrounding the ureteral stone is 2.7 mm or greater, the possibility of spontaneous passage of the ureteral stone is very low.[15] Alternatively, ureteritis is not a local edema of the short segment ureter, but APCT findings revealed that the ureteral wall thickens by 1 mm or more, and the contrast of the ureter wall is increased over the long segment of the ureter. However, the results of this study suggest that not only infectious inflammation, but also ureteral wall edema due to obstruction can be a major cause of ureteritis. Further research is required to determine the mechanism of ureteritis, observed only in some patients with ureteral stones, and its clinical significance.

This study's limitations are as follows. First, there is a high possibility that selection bias occurred as study subjects were recruited only among patients who underwent APCTs in a single-center ED. CT is not a gold standard for the diagnosis of UTIs, and there is a report that approximately 12.9% of APN patients exhibited normal CT findings.[16] However, since ureteritis is a finding that cannot be confirmed without APCT, it is inevitable to recruit ureteritis patient only from those who have undergone APCT. Second, there is a limit to the reliability of the data because the clinical parameters used are obtained through medical record research, an unavoidable fundamental limitation of retrospective research. Third, we could not explain whether the ureteritis mechanism caused by ureteral stones is due to ureteral wall edema caused by obstruction or infectious inflammation by accompanying UTIs. Lastly, we could not explain why some trauma patients exhibited ureteritis on APCTs.

In conclusion, ureteritis was a common finding observed in 6% of patients who underwent APCTs in the ED. The most common cause of ureteritis was UTI. Ureteritis can be an infection source even without symptoms or signs suggestive of UTIs. For patients whose cause of fever is unclear, APCTs should be actively considered, and it is necessary to carefully examine the presence of ureteritis in APCTs. The second major cause of ureteritis was ureteral stones that can cause ureteritis either by obstruction or combined infectious inflammation.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Original Article

Pediatric triage modifications based on vital signs: a nationwide study

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Objective To analyze the clinical significance of a heart rate (HR) or respiratory rate (RR) higher or lower than the normal in pediatric triage.

Methods A retrospective observational study was conducted with data from the Korean National Emergency Department Information System. The subjects were children < 15 years of age in 2016. Reported HRs and RRs were divided into seven groups: grade -3 (3 or more standard deviations [SDs] < normal), grade -2 (2 SDs < normal), grade -1 (1 SD < normal), grade 0 (normal), grade 1 (1 SD > normal), grade 2 (2 SDs > normal), and grade 3 (3 or more SDs > normal). The main outcomes were hospitalization and intensive care unit (ICU) admission rates. Logistic regression analysis was used to analyze the relationship of the outcomes according to grade in each group.

Results Data for 981,297 patients were analyzed. Hospitalization and ICU admission rates increased significantly in the higher HR group (grades 1 to 3; odds ratio [OR], 1.353; P < 0.001; OR, 1.747; P < 0.001; respectively) and in the higher RR group (OR, 1.144; P < 0.001; OR, 1.396; P < 0.001; respectively), compared with grade 0 group. In the lower HR group (grades -1 to -3), the hospitalization rate decreased (OR, 0.928; P < 0.001), whereas the ICU admission rate increased (OR, 1.207; P = 0.001). Although the hospitalization rate increased. In the lower RR group (OR, 1.016; P = 0.008), the ICU admission rate did not increase (OR, 0.973; P = 0.338).

Conclusion Deviations in HR and RR above normal are related to increased risks of hospitalization and ICU admission. However, this association may not apply to deviations below normal.

Keywords Child; Emergency hospital service; Triage; Vital signs

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Capsule Summary

What is already known

In the Pediatric Korean Triage and Acuity Scale, abnormal vital signs are supposed to raise the triage level in 1 standard deviation increments as they deviate from the center. Regardless of whether it is higher or lower than normal, if the degree of deviation from normal is the same, it is treated the same. However, there is no medical evidence for this.

What is new in the current study

In this study, effects of higher or lower heart rate and respiratory rate on the emergency department disposition were investigated, and only higher heart rate or respiratory rate were associated with hospitalization/intensive care unit admission rate.

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INTRODUCTION

The Canadian Triage and Acuity Scale (CTAS) is widely used around the world,[1] and the pediatric CTAS (PedCTAS) was developed specifically for pediatric populations.[2] In the 2008 revision, the PedCTAS introduced the concept of triage modification for specific chief complaints, and the modifiers included heart rate (HR) and respiratory rate (RR).[3]

Triage modification is applicable only when it corresponds to at least one of the chief complaints specified in the PedCTAS guidelines, and the following criteria are used to determine whether to adjust the triage acuity level: HR and RR within the normal range for age indicate PedCTAS level 4 or 5; HR and RR 1 standard deviation (SD) outside the normal range indicate PedCTAS level 3; and HR and RR 2 SDs and 3 SDs outside the normal range indicate PedCTAS levels 2 and 1, respectively.[1,4] There is evidence to support varying the acuity level according to the degree that HR or RR deviates from the normal ranges. However, even if the degree of deviation is identical, the clinical significance may differ according to whether the values are above or below normal. It is therefore necessary to verify the current scale, which assumes that triage acuity is uniformly affected by the degree of deviation and not the direction of deviation. A few studies provide data regarding this issue. This study was conducted to determine whether the clinical significance and outcome of emergency department (ED) visits differ according to the direction that HR or RR deviates from normal, even if the degree of deviation is the same.

METHODS

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (No. H-2012-114-1183). Informed consent was waived due to the retrospective nature of the study and because the analysis used anonymous clinical data.

Data source and collection

This retrospective observational study was conducted with data provided by the National Emergency Department Information System (NEDIS), a national database in Korea that receives real-time information on patients visiting EDs at medical institutions nationwide. Data collected from all regional and local emergency medical centers from January to December 2016 were accessed, and patients younger than 15 years of age were enrolled in this study. Patients with a chief complaint for which triage modification was not applicable and patients missing data for both HR and RR were excluded. Data including demographics, HR, RR, and ED disposition were collected. Because NEDIS data are anonymized, it is impossible to know which patient cases were collected from which center, and it is not possible to determine how HR and RR were measured. However, when measuring initial vital signs in the ED in Korea, HR is usually recorded by a noninvasive blood-pressure measuring device or pulse oximetry, and RR is measured primarily by a visual count for 1 minute.

Data preprocessing

The triage system used in this study, Pediatric Korean Triage and Acuity Scale (PedKTAS), is based on PedCTAS and developed in collaboration with the CTAS National Working Group. By 2016, all EDs in Korea utilized PedKTAS. At that time, PedCTAS was adopted and applied with minimal modification, other than Korean translation. The main symptoms indicating a need for triage modification, modification criteria, and normal ranges for HR and RR by age were the same as those in PedCTAS.[5]

According to the PedCTAS participant manual, HR and RR by age are divided into four groups: "normal range," "1 SD from (> or <) normal range," "2 SDs from (> or <) normal range," and "3 or more SDs from (> or <) normal range."[4] However, in this study, both the degree of deviation from normal and the direction of deviation were analyzed. Depending on whether the HR and RR values were above or below the normal range, patients were assigned to the "higher" or "lower" group, respectively. The grades were then reclassified for each group. For example, grade 1 in the higher group was "1 SD > normal range" and grade 1 in the lower group was "1 SD < normal range."

Age groups were divided according to US criteria as follows: infancy was defined as between birth and 2 years of age, childhood was from 2 to 12 years of age, and adolescence was from 12 to 15 years of age. Although the latter definition in the cited reference is from 12 to 21 years old; in this study, children younger than 15 years of age were targeted, and the definition was changed to 12 to 15 years old.[6]

Hospitalizations included patients admitted directly to the operating room, general ward, or intensive care unit (ICU) and those transferred to another hospital for admission. Admissions to ICUs included all admissions directly from the ED, admissions after passing through the operating room, and transfer to another hospital for ICU admission.

Outcomes

The outcomes of this study were change in hospitalization rate and ICU admission rate according to HR and RR grades. The outcomes in the higher and lower group were compared with each

other. In addition to the classification of the higher or lower groups, subgroup analysis was performed to determine how the above outcomes changed by age group or trauma.

Statistical analysis

Continuous variables were described as mean ± standard deviation if they followed a normal distribution, and as median (interquartile range [IQR]) if they did not. Categorical variables were described as number (%). Logistic regression analysis was used to analyze the relationship of the outcomes according to grade in each group. P-values less than 0.05 were considered statistically significant, and R ver. 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

RESULTS

Records for 1,448,466 patients were reviewed and, after applying the exclusion criteria, data from 981,297 patients were used in the final analyses (Fig. 1). The median (IQR) age was 3 (1–6) years, and 43% were girls. Table 1 provides the baseline characteristics of the study population.

In the higher group, both the hospitalization rate and the ICU admission rate increased significantly with higher HR grade (odds ratio [OR], 1.353; 95% confidence interval [CI], 1.345–1.361; P < 0.001; OR, 1.747; 95% CI, 1.704–1.791; P < 0.001; respectively) and higher RR (OR, 1.144; 95% CI, 1.133–1.156; P < 0.001; OR, 1.396; 95% CI, 1.340–1.455; P < 0.001; respectively). In the lower group, the ICU admission rate increased with lower HR grade, and the hospitalization rate increased with lower RR grade (OR, 1.207; 95% CI, 1.084–1.345; P = 0.001; OR, 1.016; 95% CI, 1.004–1.028; P = 0.008; respectively). However, the change in the ICU admission rate according to the increase in RR grade was not statistically significant (OR, 0.973; 95% CI, 0.920–1.029; P = 0.338), and the hospitalization rate significantly decreased as the HR

Table 1. Baseline characteristics of the study population (n=981,297)

Variable	Value
Age (yr)	3.0 (1.0–6.0)
Female sex	421,894 (43.0)
Heart rate (beats/min)	120.0 (100.0–134.0)
Respiratory rate (breaths/min)	24.0 (20.0–28.0)
Body temperature (°C)	37.0 (36.6–38.2)
ED length of stay (min)	88.0 (44.0–170.0)
ED disposition	
Discharge	853,794 (87.0)
Admission to general ward	120,773 (12.3)
Admission to intensive care unit	5,068 (0.5)
Mortality	28 (0)
Unknown	1,634 (0.2)
Grade[a] of heart rate by age	
Grade -3	1,864 (0.2)
Grade -2	8,075 (0.8)
Grade -1	50,107 (5.1)
Grade 0	524,337 (53.4)
Grade 1	216,254 (22.0)
Grade 2	105,051 (10.7)
Grade 3	64,059 (6.5)
Unknown	11,550 (1.2)
Grade[a] of respiratory rate by age	
Grade -3	712 (0.1)
Grade -2	37,957 (3.9)
Grade -1	266,209 (27.1)
Grade 0	403,705 (41.1)
Grade 1	224,083 (22.8)
Grade 2	21,027 (2.1)
Grade 3	15,688 (1.6)
Unknown	11,916 (1.2)

Values are presented as number (%) or median (interquartile range).
ED, emergency department; SD, standard deviation.
[a]Grade -3, 3 or more SDs < normal range; grade -2, 2 SDs < normal range; grade -1, 1 SD < normal range; grade 0, normal range; grade 1, 1 SD > normal range; grade 2, 2 SDs > normal range; grade 3, 3 or more SDs > normal range.

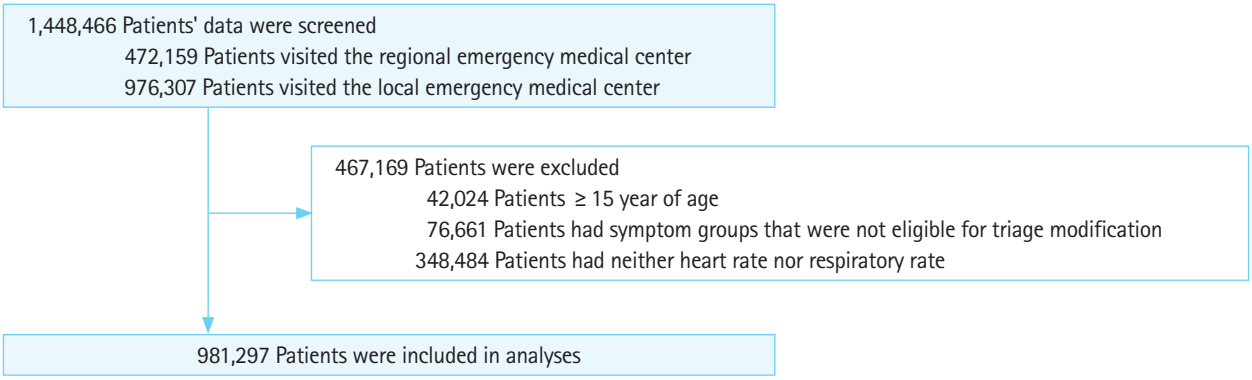

Fig. 1. Participant flow chart.

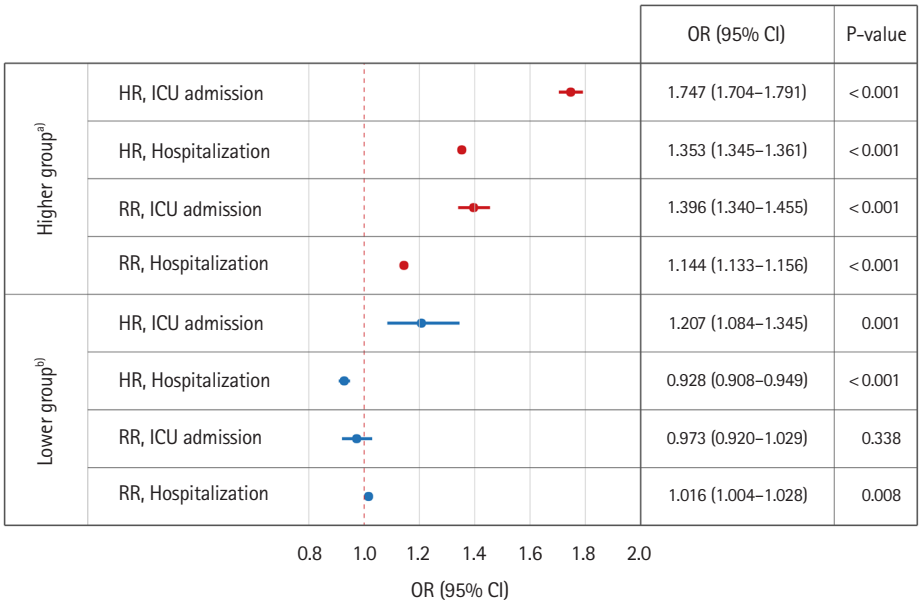

Fig. 2. Emergency department disposition according to grade of age-specific heart rate (HR) and respiratory rate (RR). Logistic regression analysis results of each outcome as each vital sign deviated from the normal range. OR, odds ratio; CI, confidence interval; ICU, intensive care unit. [a]Above or equal to the normal range. [b]Below or equal to the normal range.

Table 2. Outcomes according to grade of vital signs by age

Variable	Grade[a] of vital sign by age							
	-3	-2	-1	0	1	2	3	Unknown
Heart rate								
Total patients for each grade	1,864	8,075	50,107	524,337	216,254	105,051	64,059	11,550
Hospitalization	195 (10.5)	778 (9.6)	4,726 (9.4)	55,053 (10.5)	30,395 (14.1)	19,237 (18.3)	14,042 (21.9)	1,415 (12.3)
ICU admission	19 (1.0)	44 (0.5)	108 (0.2)	1,447 (0.3)	1,386 (0.6)	1,103 (1.0)	899 (1.4)	62 (0.5)
Respiratory rate								
Total patients for each grade	712	37,957	266,209	403,705	224,083	21,027	15,688	11,916
Hospitalization	80 (11.2)	5,198 (13.7)	32,978 (12.4)	50,600 (12.5)	28,720 (12.8)	3,416 (16.2)	3,267 (20.8)	1,582 (13.3)
ICU admission	15 (2.1)	243 (0.6)	1,120 (0.4)	2,090 (0.5)	903 (0.4)	243 (1.2)	307 (2.0)	147 (1.2)

Values are presented as number or number (%).
ICU, intensive care unit; SD, standard deviation.
[a]Grade -3, 3 or more SDs < normal range; grade -2, 2 SDs < normal range; grade -1, 1 SD < normal range; grade 0, normal range; grade 1, 1 SD > normal range; grade 2, 2 SDs > normal range; grade 3, 3 or more SDs > normal range.

grade increased (OR, 0.928; 95% CI, 0.908–0.949; P < 0.001) (Fig. 2 and Table 2).

Demographic data for subgroups according to age group and trauma are shown in Supplementary Table 1. Hospitalization and ICU admission rates by age group are presented in Supplementary Table 2, and outcomes according to trauma are indicated in Supplementary Table 3. Although there were some numerical differences by subgroup, the degree of deviation and outcomes were generally related in the higher group. No consistent correlation was evident in the lower group.

DISCUSSION

This study found that, even if HR or RR deviated by the same degree from normal, the clinical significance differed depending on whether the deviation was above or below the normal range. In general, common sense suggests that abnormal vital signs indicate a deterioration in a patient's condition; the more vital signs deviate from normal, the more abnormal they are and the greater the degree of deterioration. The results of this study provide objective evidence to support this assumption.

In the higher group, the hospitalization and ICU admission rates increased as both the HR and RR deviated from the normal

range, whereas the same results were not observed in the lower group. When the HR or RR was above normal, the deviation was significantly associated with deterioration of the patient's condition; however, when the deviation was below normal, the relationship disappeared. In a case-controlled study of adult patients admitted to the ED, an increased RR was a predictor of early clinical deterioration.[7] Another retrospective study on the clinical significance of RR in patients with community-acquired pneumonia found that an increased RR was an important factor associated with increased in-hospital mortality.[8] These two studies showed that an increase in RR is associated with patient deterioration, which agrees with the results of this study. With regard to HR, a retrospective study of children showed that bradycardia alone was a poor predictor of severe worsening of the condition of a patient.[9] That study did not directly compare tachycardia and bradycardia, and caution should be used when interpreting the results. However, the results suggest a need to reconsider the idea that bradycardia is directly related to patient deterioration.

The results of additional analysis to determine whether there would be different results depending on the child's age or presence of trauma were also slightly different for each subgroup but not significantly different from the overall analysis results. In the higher group, increases in severity were proportional to the degree of deviation, but the lower group did not show a consistent trend. It is beyond the scope of this study to determine the cause of these different characteristics in higher and lower groups due in part to the anonymized public dataset. However, a few causes are worth considering. First, one of the most common chief complaints among children visiting an ED is fever,[10] which can increase HR and RR.[11-15] Hospitalization for the treatment of febrile disease or even ICU admission in case of severe disease such as septic shock can therefore be expected. However, bradycardia or bradypnea may appear in a stable situation in which the parasympathetic nervous system is stimulated, rather than in a pathological or stressful situation in which the sympathetic nervous system is hyperactive.[16] Assessing the worsening of a patient's condition using only the above signs may therefore be inadequate. In one pediatric bradycardia study, bradycardia in the absence of a cardiac anomaly or decreased cardiac function had little predictive power to predict patient exacerbation.[9] Separate analysis of patients with and without cardiac disease may have resulted in a significant finding that bradycardia in patients with cardiac disease is more likely to result in hospitalization or admission to an ICU. However, because this is beyond the scope of this study, it would be good to conduct it in a subsequent study.

This study has several limitations. First, it focused on the effects of the HR or RR grade on the hospitalization rate or ICU admission rate; other factors that can affect hospitalization were not investigated. However, data from this study were obtained from a public database in which patients were anonymized, which is a limitation inherent in such research. To minimize the influence of factors other than HR and RR, we narrowed the analytical targets to patients with chief complaints indicative of a need for triage modification according to HR and RR. Second, the effect of abnormal vital signs on ED disposition differed according to whether the deviations were above or below the normal range, and no detailed analysis was conducted on the adjustment of the weight for each deviation. Third, whether the measurement methods of HR and RR were uniformly used is not known. Human error can be minimized because conventional HR measurement employs a noninvasive blood-pressure measurement device or a pulse oximetry. However, because RR was measured primarily by a subjective visual count rather than objective measurement through an end-tidal carbon dioxide monitoring device, the accuracy may be limited. Because neither PedCTAS nor PedKTAS provides a specific method for measuring HR or RR, we assumed that there would be no difficulty in deriving the result even if the measurement method was slightly different for each institution. Fourth, in the process of excluding cases in which both HR and RR were missing, a significant portion of cases were excluded. This was an essential process in this study to analyze the effect of HR or RR among cases where triage modification is possible, but it contains the possibility of selection bias. Lastly, it is difficult to completely rule out the possibility that the higher and lower groups have an imbalance in sample size, etc., which may have affected the result derivation.

In conclusion, deviations in both HR and RR above the normal range were related to increased risks of hospitalization and ICU admission. However, these associations may not be apply when the deviations were below the normal range. These findings strongly suggest that the assumptions underlying current triage modifications based on HR and RR should be modified to include the direction of the deviation.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Baseline characteristics for each subgroup
Supplementary Table 2. Comparison of emergency department disposition of higher and lower groups according to age group
Supplementary Table 3. Comparison of emergency department disposition of higher and lower groups according to the presence of trauma
Supplementary materials are available at https://doi.org/10.15441/

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Baseline characteristics for each subgroup

Variable	Age group[a]			Trauma		
	Infancy (n = 315,799)	Childhood (n = 584,550)	Adolescence (n = 80,948)	Trauma (n = 250,707)	Non-trauma (n = 730,362)	NA (n = 228)
Age (yr)	1.0 (0.6–1.0)	4.0 (3.0–7.0)	13.0 (12.0–14.0)	4.0 (2.0–8.0)	3.0 (1.0–6.0)	3.0 (1.0–6.0)
Female sex	141,097 (44.7)	248,311 (42.5)	32,486 (40.1)	94,689 (37.8)	327,103 (44.8)	102 (44.7)
Heart rate (beats/min)	134.0 (123.0–150.0)	112.0 (100.0–126.0)	89.0 (80.0–100.0)	108.0 (96.0–122.0)	122.0 (104.0–138.0)	110.0 (100.0–131.0)
Respiratory rate (breaths/min)	28.0 (24.0–32.0)	24.0 (20.0–26.0)	20.0 (20.0–20.0)	22.0 (20.0–26.0)	24.0 (22.0–28.0)	22.0 (20.0–27.0)
Body temperature (°C)	37.4 (36.7–38.5)	37.0 (36.5–38.1)	36.7 (36.5–37.3)	36.6 (36.4–36.8)	37.5 (36.7–38.5)	36.9 (36.5–37.9)
ED length of stay (min)	94.0 (45.0–191.0)	84.0 (42.0–160.0)	98.0 (51.0–169.0)	61.0 (32.0–115.0)	101.0 (50.0–190.0)	83.5 (38.0–152.0)
ED disposition						
Discharge	261,319 (82.7)	522,610 (89.4)	69,865 (86.3)	239,610 (95.6)	614,106 (84.1)	78 (34.2)
Admission to GW	50,214 (15.9)	59,902 (10.2)	10,657 (13.2)	9,984 (4.0)	110,782 (15.2)	7 (3.1)
Admission to ICU	3,733 (1.2)	1,022 (0.2)	313 (0.4)	707 (0.3)	4,360 (0.6)	1 (0.4)
Mortality	15 (0.0)	11 (0.0)	2 (0.0)	7 (0.0)	21 (0.0)	0 (0.0)
Unknown	518 (0.2)	1,005 (0.2)	111 (0.1)	399 (0.2)	1,093 (0.1)	142 (62.3)
Grade[b] of heart rate by age						
Grade -3	1,274 (0.4)	535 (0.1)	55 (0.1)	684 (0.3)	1,180 (0.2)	0 (0.0)
Grade -2	6,170 (2.0)	1,866 (0.3)	39 (0.0)	3,070 (1.2)	4,995 (0.7)	10 (4.4)
Grade -1	29,592 (9.4)	18,478 (3.2)	2,037 (2.5)	18,196 (7.3)	31,890 (4.4)	21 (9.2)
Grade 0	175,654 (55.6)	303,882 (52.0)	44,801 (55.3)	160,913 (64.2)	363,315 (49.7)	109 (47.8)
Grade 1	49,750 (15.8)	148,704 (25.4)	17,800 (22.0)	47,070 (18.8)	169,142 (23.2)	42 (18.4)
Grade 2	30,027 (9.5)	65,393 (11.2)	9,631 (11.9)	14,314 (5.7)	90,716 (12.4)	21 (9.2)
Grade 3	18,518 (5.9)	39,296 (6.7)	6,245 (7.7)	3,934 (1.6)	60,103 (8.2)	22 (9.6)
Unknown	4,814 (1.5)	6,396 (1.1)	340 (0.4)	2,526 (1.0)	9,021 (1.2)	3 (1.3)
Grade[b] of respiratory rate by age						
Grade -3	133 (0.0)	567 (0.1)	12 (0.0)	263 (0.1)	449 (0.1)	0 (0.0)
Grade -2	32,083 (10.2)	5,753 (1.0)	121 (0.1)	11,530 (4.6)	26,399 (3.6)	28 (12.3)
Grade -1	162,604 (51.5)	102,815 (17.6)	790 (1.0)	68,038 (27.1)	198,107 (27.1)	64 (28.1)
Grade 0	107,878 (34.2)	282,938 (48.4)	12,889 (15.9)	99,000 (39.5)	304,621 (41.7)	84 (36.8)
Grade 1	4,309 (1.4)	159,239 (27.2)	60,535 (74.8)	63,561 (25.4)	160,481 (22.0)	41 (18.0)
Grade 2	907 (0.3)	15,359 (2.6)	4,761 (5.9)	4,094 (1.6)	16,927 (2.3)	6 (2.6)
Grade 3	625 (0.2)	13,385 (2.3)	1,678 (2.1)	2,670 (1.1)	13,013 (1.8)	5 (2.2)
Unknown	7,260 (2.3)	4,494 (0.8)	162 (0.2)	1,551 (0.6)	10,365 (1.4)	0 (0.0)

The continuous variables are presented as median (interquartile range).

NA, not available; ED, emergency department; GW, general ward; ICU, intensive care unit; SD, standard deviation.

[a]Age groups were divided as follows: infancy, between birth and 2 years of age; childhood, from 2 to 12 years of age; and adolescence, from 12 to 15 years of age.[6] [b]Grade -3, 3 or more SDs < normal range; grade -2, 2 SDs < normal range; grade -1, 1 SD < normal range; grade 0, normal range; grade 1, 1 SD > normal range; grade 2, 2 SDs > normal range; grade 3, 3 or more SDs > normal range.

Supplementary Table 2. Comparison of emergency department disposition of higher and lower groups according to age group

Age group	Odds ratio (95% confidence interval)	P-value
Infancy		
Higher group		
Heart rate		
ICU admission	1.804 (1.754–1.855)	<0.001
Hospitalization	1.448 (1.434–1.462)	<0.001
Respiratory rate		
ICU admission	3.073 (2.925–3.228)	<0.001
Hospitalization	2.125 (2.048–2.204)	<0.001
Lower group		
Heart rate		
ICU admission	0.693 (0.599–0.802)	<0.001
Hospitalization	0.794 (0.772–0.816)	<0.001
Respiratory rate		
ICU admission	0.504 (0.474–0.537)	<0.001
Hospitalization	0.786 (0.774–0.799)	<0.001
Childhood		
Higher group		
Heart rate		
ICU admission	1.849 (1.748–1.955)	<0.001
Hospitalization	1.343 (1.332–1.354)	<0.001
Respiratory rate		
ICU admission	1.993 (1.863–2.133)	<0.001
Hospitalization	1.265 (1.250–1.281)	<0.001
Lower group		
Heart rate		
ICU admission	2.290 (1.923–2.728)	<0.001
Hospitalization	0.937 (0.897–0.978)	0.003
Respiratory rate		
ICU admission	1.334 (1.131–1.574)	0.001
Hospitalization	0.859 (0.840–0.879)	<0.001
Adolescence		
Higher group		
Heart rate		
ICU admission	1.616 (1.465–1.782)	<0.001
Hospitalization	1.283 (1.259–1.309)	<0.001
Respiratory rate		
ICU admission	2.157 (1.840–2.530)	<0.001
Hospitalization	1.223 (1.180–1.268)	<0.001
Lower group		
Heart rate		
ICU admission	1.895 (1.188–3.023)	0.007
Hospitalization	1.034 (0.918–1.164)	0.584
Respiratory rate		
ICU admission	0.612 (0.167–2.241)	0.459
Hospitalization	0.813 (0.677–0.975)	0.025

ICU, intensive care unit.

Supplementary Table 3. Comparison of emergency department disposition of higher and lower groups according to the presence of trauma

Variable	Odds ratio (95% confidence interval)	P-value
Trauma		
Higher group		
Heart rate		
ICU admission	2.101 (1.947–2.267)	<0.001
Hospitalization	1.502 (1.467–1.538)	<0.001
Respiratory rate		
ICU admission	1.912 (1.729–2.115)	<0.001
Hospitalization	1.516 (1.472–1.562)	<0.001
Lower group		
Heart rate		
ICU admission	1.265 (1.026–1.559)	0.028
Hospitalization	0.769 (0.717–0.824)	<0.001
Respiratory rate		
ICU admission	0.961 (0.816–1.132)	0.636
Hospitalization	0.693 (0.662–0.726)	<0.001
Nontrauma		
Higher group		
Heart rate		
ICU admission	1.649 (1.606–1.693)	<0.001
Hospitalization	1.242 (1.234–1.250)	<0.001
Respiratory rate		
ICU admission	1.316 (1.259–1.376)	<0.001
Hospitalization	1.106 (1.094–1.118)	<0.001
Lower group		
Heart rate		
ICU admission	1.219 (1.075–1.383)	0.002
Hospitalization	1.006 (0.982–1.030)	0.625
Respiratory rate		
ICU admission	0.992 (0.934–1.053)	0.787
Hospitalization	1.074 (1.061–1.088)	<0.001

ICU, intensive care unit.

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Original Article

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Prognostic value of the myeloperoxidase index for early prediction of neurologic outcome in acute carbon monoxide poisoning

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Objective Carbon monoxide (CO) activates intravascular neutrophils through platelet-neutrophil aggregates, which cause neutrophil degranulation. This process causes the release of myeloperoxidase (MPO), proteases, and reactive oxygen species. The MPO index (MPXI) is a newly reported inflammatory marker that reflects the MPO level within neutrophils. The MPXI in conditions associated with neutrophil activation depends on the net effect of azurophil degranulation. This study aimed to determine whether the MPXI can predict neurocognitive prognosis 1 month after acute CO poisoning.

Methods We included patients aged ≥ 16 years with acute CO poisoning from a cohort at a single tertiary academic hospital in Wonju, Korea, between January 2010 and May 2021. Data from 699 patients were analyzed. The neurocognitive outcome was assessed using Global Deterioration Scale scores and classified as favorable (score, 1–3 points) or poor (score, 4–7 points). The MPXI was determined within 1 hour of arrival to the emergency department.

Results Among the 699 patients, 52 (7.4%) showed poor outcomes. The median MPXI of the patients in the poor outcome group was higher than that of the favorable outcome group (0.85 vs. 0.2, P = 0.189). However, a significant difference was not found between the favorable and poor outcome groups, and MPXI was not a significant variable in multivariate logistic regression.

Conclusion The MPXI evaluated in the emergency department did not differ based on neurocognitive outcome at 1 month after acute CO poisoning.

Keywords Carbon monoxide poisoning; Prognosis; Cognitive dysfunction; Biomarkers

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CEEM

Capsule Summary

What is already known

Carbon monoxide (CO) causes the release of myeloperoxidase (MPO) and MPO plays an important role in CO toxicity. The MPO index (MPXI) is a newly reported inflammatory marker that reflects the MPO level within neutrophil. The MPXI in conditions associated with neutrophil activation may be dependent on the net effect of azurophil degranulation.

What is new in the current study

We aimed to determine whether the MPXI can predict the patients' neurocognitive prognosis 1 month after CO poisoning. The MPXI evaluated in the emergency department did not differ according to the neurocognitive outcome at 1 month after acute CO poisoning.

INTRODUCTION

Acute carbon monoxide (CO) poisoning can exhibit many symptoms and neurocognitive sequelae, including mental deterioration, cognitive dysfunction, amnesia, gait disturbance, mutism, urinary or fecal incontinence, psychosis, depression, and parkinsonism.[1-3] CO poisoning causes tissue hypoxia resulting from the high affinity of hemoglobin for CO and direct inflammatory damage to tissues through various mechanisms. CO competitively binds to heme-containing proteins (e.g., hemoglobin and myoglobin) and mitochondrial cytochrome c oxidase (complex IV), causing tissue hypoxia.[4] CO activates intravascular neutrophils through platelet-neutrophil aggregates, subsequently causing neutrophil degranulation.[5] This process causes the release of myeloperoxidase (MPO), proteases, and reactive oxygen species,[5] leading to oxidative stress, transformation of xanthine dehydrogenase to xanthine oxidase in endothelial cells, lipid peroxidation, and apoptosis.[5,6] Furthermore, CO poisoning causes adduct formation between myelin basic protein and a reactive product of lipid peroxidation (i.e., malondialdehyde). Chemical modification of myelin basic protein is associated with an adaptive immunologic response that causes CO-mediated neurocognitive sequelae.[7]

MPO plays an important role in this process. Exposure to CO triggers intravascular platelet-neutrophil interactions that lead to neutrophil degranulation, as observed in both experimental animals and human patients with acute CO poisoning.[5] In an animal model, CO poisoning reportedly increases the MPO level in the brain along the vascular lining and appears to cause vascular oxidative stress based on its colocalization with nitrotyrosine.[5] MPO can catalyze the reaction between nitrite and H_2O_2 to form nitrogen dioxide, which causes nitration of local protein tyrosine residues, induces lipid peroxidation, and stimulates expression of endothelial adhesion molecule.[8-11] MPO and nitrotyrosine have been shown to colocalize with each other along the subendothelial lining of human tissues of patients with inflammatory disease.[12] In a study by Thom et al.[5] platelet-neutrophil aggregates were detected in blood samples obtained from 50 consecutive patients, and the plasma MPO level was significantly elevated in patients with confirmed CO poisoning. Thom et al.[5] examined knockout mice lacking MPO and responses and showed a direct link between alterations in myelin basic protein and MPO. The MPO index (MPXI) is a newly reported marker for inflammation that reflects the MPO level within neutrophils.[13] In conditions associated with neutrophil activation, the MPXI might depend on the net effect of azurophil degranulation, which decreases the MPXI, and the stimulated synthesis of MPO in response to inflammation which increases the MPXI. Therefore, the MPXI can show specific patterns (attenuation, no change, or elevation) distinct from the plasma level of MPO or other biomarkers of inflammation, and further investigations on the association of MPXI with specific pathologic conditions might yield interesting findings.[14]

Because the plasma MPO level is significantly elevated due to degranulation of neutrophils in patients with confirmed CO poisoning,[5] we hypothesized the MPXI would be low in these patients. Therefore, we determined whether the MPXI can predict the neurocognitive prognosis of patients 1 month after CO poisoning.

METHODS

Ethics statement

The study was approved by the Institutional Review Board of Wonju Severance Christian Hospital (No. CR321138) and complied with the ethical guidelines of the Declaration of Helsinki. Informed consent was obtained and the patient data were anonymized before the analysis.

Study design and setting

The data used in this study were derived from a cohort at a single tertiary academic hospital in Wonju, Korea. The CO poisoning registry was established in January 2006 to prospectively collect data from consecutive patients at the hospital. Data from January 2010 to July 2020 were obtained from the existing prospective registry, and data from August 2020 to May 2021 were prospectively collected with informed consent (ClinicalTrials.gov identifier: NCT04490317).

The exclusion criteria were as follows: (1) age < 16 years, (2) no acute CO poisoning, (3) history of a previous CO poisoning or a previous neurocognitive disease (e.g., stroke, dementia, or Parkinson disease) before acute CO poisoning, (4) any serious illness that could affect the outcome, (5) specific additive treatment such as therapeutic hypothermia or steroid, (6) cardiac arrest before emergency department (ED) arrival or at the ED, (7) failure to attend the follow-up examinations for neurocognitive status after discharge, (8) no available MPXI value determined within 24 hours after ED arrival, (9) hematologic disease and use of anticancer chemotherapy (which can influence the MPXI level or other important variables), (10) infections such as aspiration pneumonia diagnosed based on clinical symptoms, chest radiography findings, and sputum culture results (which can increase MPXI level), and (11) fire as the CO source.

At our institution, acute CO poisoning is diagnosed based on the patient's medical history and a carboxyhemoglobin (COHb) level > 5% (> 10% for smokers). Patients with CO poisoning were treated with 100% oxygen therapy through a face mask with a reservoir bag. Patients with any loss of consciousness, any neurocognitive symptoms and signs, cardiovascular dysfunction, elevated levels of cardiac enzymes, ischemic electrocardiogram changes, severe acidosis, or COHb ≥ 25% were treated with hyperbaric oxygen (HBO_2) therapy.[15]

Study variables and definitions

Variables that can affect the prognosis of patients with acute CO poisoning were investigated, including age, sex, intentionality, CO sources, CO exposure time, initial Glasgow Coma Scale (GCS) score, comorbidities (diabetes mellitus, hypertension, and psychiatric diseases), current smoking, symptoms and signs (loss of consciousness, shock, and seizure), and use of HBO_2. Shock was defined as need for a vasopressor and lactate level > 2 mmol/L.[16] The investigated laboratory parameters were initial MPXI value and COHb, bicarbonate, lactate, creatinine, creatine kinase, and troponin I levels measured within 1 hour of ED arrival. At our institution, serum MPXI measurement is performed as a routine laboratory test using ADVIA 120/2120 (Siemens, Tarrytown, NY, USA).

The neurocognitive outcome was assessed using the Global Deterioration Scale (GDS).[17] The scores GDS range from 1 to 7, and higher scores indicate a more severe condition. The GDS score was assessed during an outpatient rehabilitation visit. For patients in poor condition who could not attend outpatient rehabilitation, their caregivers were interviewed. The neurocognitive outcome was classified as favorable (GDS score, 1–3 points) or poor (GDS score, 4–7 points). If a patient died of CO poisoning (CO-related death) within 1 month, the outcome was expressed as a GDS score of 7. In addition, GDS was assessed at 6 months, and the changes between GDS values at 1 and 6 months were investigated.

Study outcome

The primary outcome in the present study was whether the MPXI measured at the ED was associated with the GDS score 1 month after CO poisoning.

Statistical analysis

The normality of data distribution was determined using the Shapiro-Wilk normality test. Continuous variables with a normal distribution were expressed as mean (standard deviation) and compared using Student t-test. Continuous variables with a non-normal distribution were presented as median (interquartile range). Differences between the two groups were assessed using the independent t-test or Mann-Whitney U-test for continuous variables and the chi-square test or Fisher exact test for categorical variables. One-way analysis of variance was performed to compare the difference of MPXI based on time quartile from rescue to HBO_2 therapy. Multivariable logistic regression was used to assess the independent association between MPXI and poor neurocognitive outcome after adjusting for continuous and categorical variables. Two adjusted models were constructed: model 1 was a minimally adjusted model, and model 2 included statistically significant baseline characteristics of age, CO exposure time, GCS, hypertension, smoking, loss of consciousness, shock, bicarbonate (mmol/L), lactate (mmol/L), creatinine (mg/dL), creatine kinase (U/L), and troponin I (ng/mL). All statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA), and all graphics were produced using R ver. 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P < 0.05$.

RESULTS

A total of 1,601 patients with acute CO poisoning visited the ED during the study period, and 699 were included in the present study (Fig. 1). Based on the 1-month GDS scores, the patients

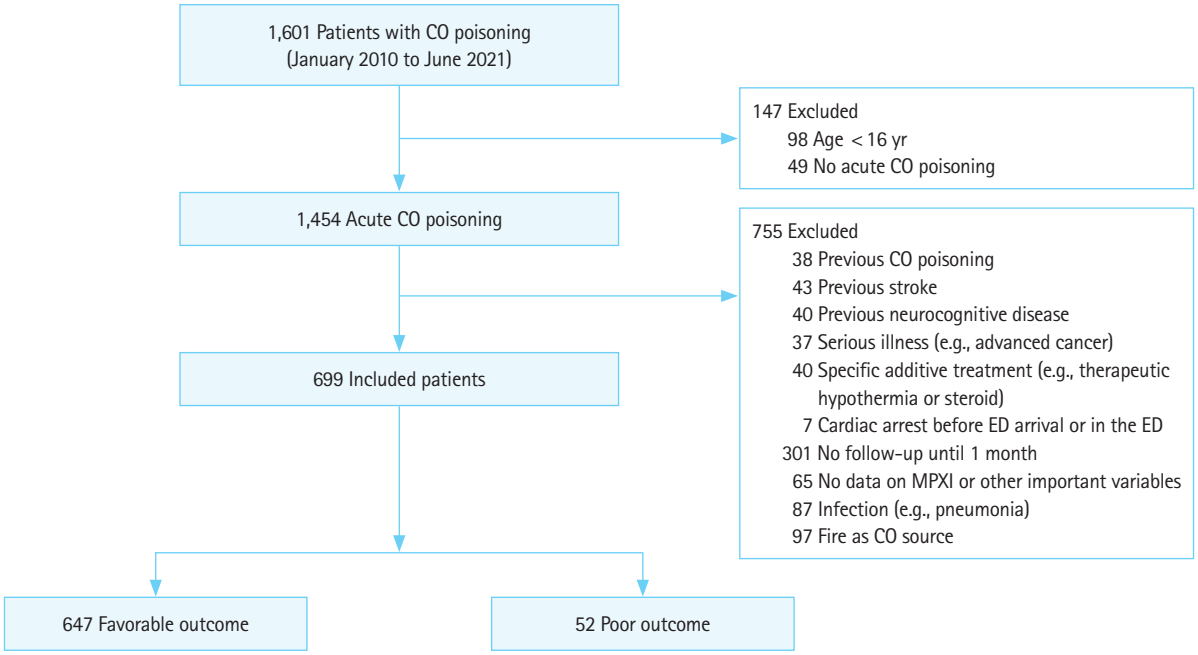

Fig. 1. Flowchart of patient inclusion. CO, carbon monoxide; ED, emergency department; MPXI, myeloperoxidase index.

Table 1. Baseline characteristics of the patients

Characteristic	Total (n = 699)	Favorable outcome (n = 647, 92.6%)	Poor outcome (n = 52, 7.4%)	P-value
Age (yr)	47.0 (35.0 to 59.0)	45.0 (35.0 to 58.0)	62.5 (53.0 to 74.0)	< 0.001
Male sex	439 (62.8)	411 (63.5)	28 (53.9)	0.165
Intentional poisoning	291 (41.6)	269 (41.6)	22 (42.3)	0.918
CO source				0.092
Charcoal	421 (60.2)	387 (59.8)	34 (65.4)	-
Gas or oil	278 (16.8)	260 (40.2)	18 (34.6)	-
CO exposure time (hr)	4 (1.5 to 8.0)	3.6 (1.2 to 8.0)	8.0 (2.5 to 13.3)	< 0.001
Glasgow Coma Scale score	15.0 (12.0 to 15.0)	15.0 (12.0 to 15.0)	12.0 (8.0 to 12.0)	< 0.001
Comorbidities				
Diabetes mellitus	73 (10.4)	64 (9.9)	9 (17.3)	0.093
Hypertension	129 (18.5)	111 (17.2)	18 (34.6)	0.002
Psychiatric disease	84 (12.0)	75 (11.6)	9 (17.3)	0.223
Current smoking	287 (41.1)	277 (42.8)	10 (19.2)	0.001
Symptoms and signs in the ED				
Loss of consciousness	394 (56.4)	349 (53.9)	45 (86.5)	< 0.001
Shock	13 (1.9)	8 (1.2)	5 (9.6)	0.002
Seizure	4 (0.6)	4 (0.6)	0 (0)	> 0.999
Use of HBO_2 therapy	653 (93.4)	605 (93.5)	48 (92.3)	0.769
Laboratory findings				
Myeloperoxidase index	0.2 (-2.0 to 2.7)	0.2 (-2.1 to 2.6)	0.85 (-1.6 to 3.85)	0.189
Carboxyhemoglobin (%)	21.1 (9.6 to 31.1)	21.1 (9.6 to 30.8)	20.9 (10.7 to 33.0)	0.624
Bicarbonate (mmol/L)	21.5 (19.1 to 23.3)	21.5 (19.3 to 23.3)	19.6 (18.3 to 23.0)	0.020
Lactate (mmol/L)	2.1 (1.4 to 3.3)	2.0 (1.3 to 3.3)	2.5 (1.8 to 3.6)	0.026
Creatinine (mg/dL)	0.81 (0.66 to 0.99)	0.80 (0.66 to 0.97)	1.00 (0.75 to 1.22)	< 0.001
Creatine kinase (U/L)	129.0 (86.0 to 233.0)	125.0 (85.0 to 219.0)	457.5 (123.5 to 3,153.5)	< 0.001
Troponin I (ng/mL)	0.02 (0.02 to 0.12)	0.02 (0.02 to 0.08)	0.21 (0.05 to 1.63)	< 0.001

Values are presented as median (interquartile range) or number (%).
CO, carbon monoxide; GCS, Glasgow Coma Scale; ED, emergency department; HBO_2, hyperbaric oxygen.

Table 2. Multivariate logistic regression of myeloperoxidase index

Variable	Univariate odds ratio	P-value	Multivariate odds ratio			
			Model 1[a]	P-value	Model 2[b]	P-value
Myeloperoxidase index	1.07 (0.98–1.16)	0.125	1.07 (0.98–1.16)	0.126	1.05 (0.96–1.16)	0.263

[a]Adjusted for age and sex. [b]Adjusted for statistically significant variables (age, carbon monoxide exposure time, Glasgow Coma Scale, hypertension, smoking, loss of consciousness, shock, bicarbonate (mmol/L), lactate (mmol/L), creatinine (mg/dL), creatine kinase (U/L), and troponin I (ng/mL).

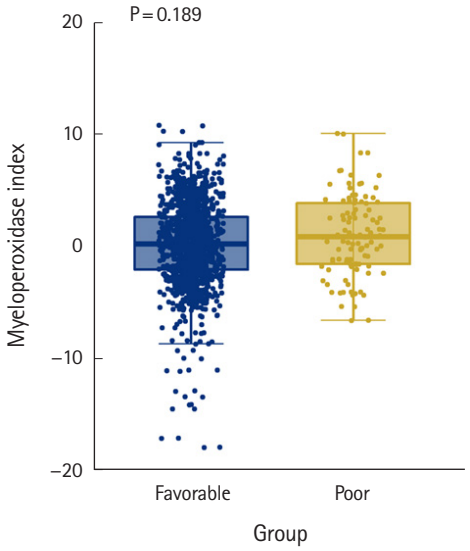

Fig. 2. Comparison of myeloperoxidase index between the favorable and poor outcome groups.

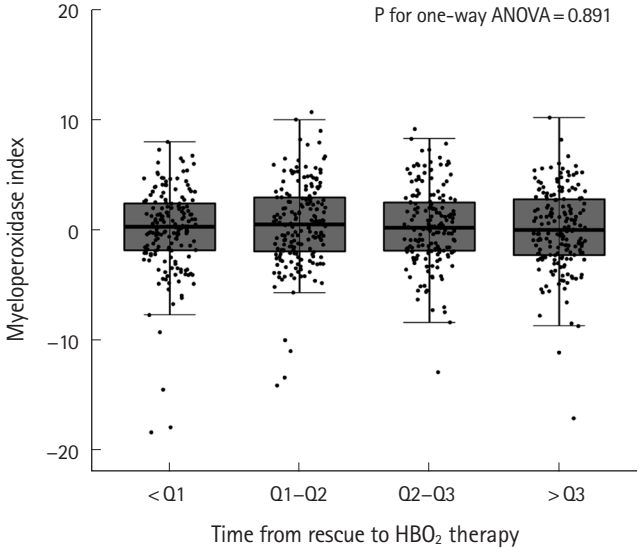

Fig. 3. Comparison of myeloperoxidase index based on time from rescue to hyperbaric oxygen (HBO_2) therapy between favorable and poor outcome groups. ANOVA, analysis of variance; Q, quartile.

were divided into favorable and poor outcome groups. The favorable outcome group included 647 patients (92.6%) and the poor outcome group 52 patients (7.4%).

The baseline characteristics of the study patients are shown in Table 1. The median age was 47 years, and 439 patients (62.8%) were male patients. The CO originated from a nonfire source of charcoal (421 patients, 60.2%) and gas or oil combustion (278 patients, 16.8%), and 36.9% of the patients had intentional poisoning. Loss of consciousness occurred in 394 patients (56.4%), and 653 patients (93.4%) were treated with HBO_2. The baseline characteristics of the patients divided based on the neurocognitive outcome are shown in Table 1. Patients in the poor outcome group were older than patients in the favorable outcome group ($P < 0.001$). In addition, patients in the poor outcome group had longer CO exposure times ($P < 0.001$), lower proportion of current smokers ($P = 0.001$), and lower GCS score ($P < 0.001$) compared with the favorable outcome group. Patients in the poor outcome group experienced hypertension, loss of consciousness, and shock more frequently ($P < 0.001$) than patients in the favorable outcome group.

The results of laboratory tests are also shown in Table 1. Patients in the poor outcome group had higher levels of lactate, creatinine, creatine kinase, and troponin I than patients in the favorable outcome group. Serum bicarbonate level was higher in patients in the favorable outcome group than in the poor outcome group. MPXI level was not significantly different between the favorable and poor outcome groups. Contrary to our hypothesis, the MPXI level in the poor outcome group was higher than that of the favorable outcome group. Fig. 2 shows the MPXI values based on neurocognitive outcome. MPXI was not a significant variable in multivariate logistic regression (Table 2). In addition, when MPXI level was analyzed based on time from rescue to HBO_2 therapy between favorable and poor outcome groups, significant difference was not observed (Fig. 3).

The 6-month GDS score was obtained for 648 (92.7%) of the 699 patients: 586 subjects (90.4%) had no interval change in GDS score, 52 patients (8.0%) had a worse score, and 10 patients (1.6%) had improved GDS score (Table 3).

DISCUSSION

Because MPO is released from neutrophils in the initial inflam-

Table 3. Change between GDS scores from 1 to 6 months

Difference in GDS at 1 month from GDS at 6 months (n = 648)	No. (%)
Improvement	
-3 points	1 (0.2)
-2 points	6 (0.9)
-1 point	3 (0.5)
No interval change	586 (90.4)
Worsening	
1 point	42 (6.5)
2 points	8 (1.2)
3 points	2 (0.3)

GDS, Global Deterioration Scale.

matory reaction process after CO poisoning, severe cases are expected to have higher MPO level. Therefore, we hypothesized the MPXI would be lower in the poor outcome group. However, the poor outcome group had higher MPXI levels than the favorable outcome group, contrary to our hypothesis. This finding can be attributed to several factors. First, the pathophysiology of acute CO poisoning includes hypoxia and inflammatory reactions such as platelet-neutrophil activation, oxidative stress, and cell apoptosis.[2,4] The increase in MPXI might have been due to inflammatory reactions. We postulate the MPXI would be lower if MPO was secreted from neutrophils through an inflammatory reaction. However, the change caused by the inflammatory reaction resulting from CO poisoning might have been stronger than expected leading to a further increase in the MPXI in the poor outcome group. Second, Thom et al.[5] and Thom et al.[18] reported the mean plasma MPO level to be five-fold higher in patients with CO poisoning (75.7 ng/mL) than in subjects without CO poisoning (control group, 15.0 ng/mL). However, the MPXI is analyzed differently from plasma MPO level. Plasma MPO level is directly measured in blood, whereas the MPXI reflects the MPO content in neutrophils and is a calculated, not a directly measured, value. The plasma MPO level increases in parallel with coronary atherosclerosis, and high plasma MPO level is associated with both severity of coronary lesions and prognosis of patients.[19] However, Yonezawa et al.[14] provided evidence that MPXI is not correlated with ischemic heart disease. They reported the MPXI is elevated in cases of milder arteriosclerosis obliterans but not in severe cases, and that the MPXI dramatically decreases when ischemic heart disease develops in patients with arteriosclerosis obliterans. Third, the MPXI might not be a sensitive tool because its value is derived through calculation, whereas the actual MPO level is directly measured in blood.[14] Cha et al.[20] reported the MPXI cannot differentiate sepsis from non-infectious systemic inflammatory response syndrome in patients diagnosed with systemic inflammatory response syndrome in the ED. Fourth, the time from the occurrence of CO poisoning to the blood test in the hospital differed among patients and might have affected the relationship between the MPO level released from neutrophils and the MPXI value in the present study. In addition, in patients with a relatively short CO exposure time, a significant MPXI decrease might not be reflected.

The present study had several limitations. First, this was an observational, nonrandomized study that involved only one hospital ED. Consequently, not all relevant parameters could be assessed. Second, several neurocognitive tests (approximately six), usually equivalent to CO batteries, were conducted in a few randomized controlled trials.[21,22] Conversely, in the present study, the outcome was only evaluated using the GDS score. In our institution, GDS scores are used to evaluate neurocognitive prognosis in patients with CO poisoning because neurocognitive functions, such as memory and concentration, as well as activities of daily living, are evaluated through interviews. We have previously reported the GDS score as a measure of neurocognitive outcome associated with CO poisoning.[23-25] Third, the MPXI was not continuously measured. The relationship between the MPXI and poor neurologic outcome over time after CO poisoning was not investigated. Fourth, accurately investigating the CO exposure time was sometimes challenging and especially difficult in unconscious patients. Because only patients with acute CO poisoning were included and subjects with chronic intermittent exposure were excluded, the CO exposure time was shorter than in a previous study.[21] Fifth, the predictive value of MPXI and other serum markers, including serum neuronal-specific enolase or S100β, was not compared.[26,27] Last, many patients were lost to follow-up due to their condition, a long distance from their residence to the hospital, or poor compliance.

In summary, the MPXI evaluated at the ED did not differ based on the neurocognitive outcome at 1 month after acute CO poisoning in the present study.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Original Article

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Experience of emergency medical services provider training using online training of trainers during COVID-19: official development assistance project in Tashkent, Uzbekistan

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Objective Since onsite education is difficult due to the COVID-19 pandemic, official development assistance (ODA) projects have implemented online training of trainers (ToT) for emergency medical experts and staff. This study aims to share and discuss the ToT experience and its results in Uzbekistan.

Methods We trained emergency medical advanced course instructors through online ToT among emergency medical service experts in Uzbekistan as a part of an ODA project. After the ToT, instructors were selected based on written tests, video monitoring of practice, and simulation performance. They operated the emergency medical course including lectures, practices, and simulations for 5 days. We tested the trainees through written tests before and after the course. They were surveyed regarding the course contents, its relevance, and their satisfaction with the course.

Results Six instructors were selected after the online ToT program. They educated 68 emergency medical workers through the three training courses. The total score of the pretest was 129.2±34.8, and the posttest score was 170.8±31.2, which was significantly higher ($P<0.05$). The satisfaction calculated by adding the values of survey items for this curriculum was 28.0 (interquartile range, 26.0–30.0), and there was no statistical difference regarding trainee satisfaction between the three courses ($P=0.148$).

Conclusion Instructors trained by online ToT programs could provide an in-person emergency medical advanced course.

Keywords Official development assistance; Uzbekistan; Teacher training; Simulation training

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CEEM

Capsule Summary

What is already known

The official development assistance projects for the health care sector of the underdeveloped countries have largely begun to shift their focus to improving the emergency medical system for life-threatening diseases and injuries by educating the emergency medical services providers on first aid. However, onsite education has proved to be difficult due to COVID-19.

What is new in the current study

We conducted online training of trainers to tutor instructors of emergency medical advanced courses in Uzbekistan. Instructors trained via an online program, which also included simulation-based education, could successfully provide an emergency medical advanced course comprising lecture, practice, and simulation to other healthcare professionals.

INTRODUCTION

According to a recent study, official development assistance (ODA) projects in the healthcare sector of underdeveloped countries are undergoing significant changes.[1,2] The focus of the current strategy is on controlling infectious diseases, but it is shifting to improving the emergency medical system for life-threatening diseases and injuries, as well as the emergency management abilities and education of emergency medical services (EMS) providers. This shift is primarily due to a decrease in infectious disease deaths in underdeveloped countries by the continued supply of essential vaccines and intensive disease management, while an increase in mortality from chronic diseases, specifically, emergent diseases like cardiovascular disease and major injuries.[1,2]

According to Uzbekistan's health statistics, the country's average life expectancy is 72.0 years (female, 74.3 years; male, 69.8 years). The population is relatively young, with 41% under 14 years. There are 4.8 beds and 2.6 doctors for every 1,000 people. It has 81,500 doctors and 259,700 mid-level medical personnel comprising nurses, midwives, and laboratory assistants. Deaths due to chronic metabolic and circulatory diseases, such as cerebrovascular disease and heart disease, account for a significant percentage.[2,3] Furthermore, based on the comparison between major causes between 2009 and 2019, ischemic heart disease rose by 6.1% and stroke increased by 2.8%, metabolic diseases such as cirrhosis rose by 22.6%, and infectious diseases such as lower respiratory tract infections decreased by 25%. Hence, it is imperative to provide appropriate EMS for acute diseases such as cerebrovascular and cardiovascular diseases to promote the community health in Uzbekistan. Appropriate EMS should be accompanied by improving the equipment of the EMS, and the curriculum and training for emergency medical personnel.[3]

ODA projects such as the introduction of emergency patient transport ambulances and utlizing the latest emergency management equipment are actively underway in Uzbekistan to help strengthen the emergency medical system. Since 2017, the Korea Foundation for International Healthcare has signed a Memorandum of Understanding with the Uzbekistan Ministry of Health to strengthen EMS capabilities, and provided theoretical and practical training for the workers through onsite training trips of Korean professionals. The Ministry of Health, after consultation with the director of the Tashkent Ambulance Center, certified the EMS training for this project as a regular curriculum, and recognized the completion time for the trainees. However, due to the rapid spread of coronavirus, countries have banned human resource exchanges under the national quarantine guidelines (Ministry of Foreign Affairs; March 23, 2020), making it impossible for professionals to hold training seminars in Uzbekistan.[4] Consequently, it is challenging to train emergency medical workers to reinforce their competency.

Therefore, since onsite education is difficult during COVID-19, the authors have implemented an online training of trainers (ToT) for Uzbekistan emergency medical professionals to facilitate the local application of emergency medical advanced courses. Through these trainers, the Emergency Medical Advanced Course was conducted for local emergency medical workers who boarded ambulances. Accordingly, the authors shared the experience of running online ToT and an emergency medical advanced course centered on local instructors as a part of the ODA project, and discussed its results and effects.

METHODS

Study design

This study was a retrospective descriptive study of online ToT among emergency medical personnel experts and emergency medical advanced courses provided by trained instructors in Uzbekistan. This study was approved by the Institutional Review

Board of Inje University Ilsan Paik Hospital (No. 2021-02-006-002). This comprised lecture-based education, practice, and simulation-based training (Fig. 1), for 5 days for emergency medical experts who had experienced simulation-based education in Uzbekistan. This curriculum was similar to that of the Emergency Medical Advanced Course and the "becoming good instructors" curriculum. ToT trainees were educated using video lecture materials dubbed in Russian, and those were made available to trainees through ubiquitous-based learning (UBL) Cloud (NSDevil Co., Daejeon, Korea). For practice sessions, video conferencing was used to demonstrate key procedures in real-time, and ToT trainees directly participated in the practice using the same educational equipment. The simulation training was conducted by emergency medical experts using the same simulation equipment and ToT trainees. In these curriculums, researchers used video conferences to evaluate trainees' performance and to provide direct feedback.

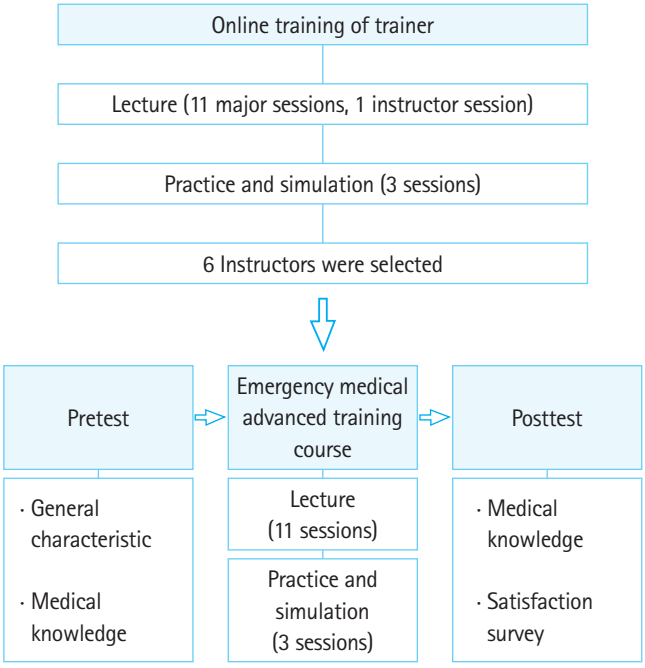

Fig. 1. Study outline.

After the online ToT, instructors were selected based on written tests and video monitoring of practice and simulation performance of trainees who completed the program. We provided the syllabus, instructor manuals of practice, and simulation operation for the courses. To guarantee the quality, the researchers directly instructed through video conference on how to conduct practice and simulation-based training two hours before this training course began.

Operation of the emergency medical advanced course

The participants were emergency medical staff at the Tashkent Ambulance Center in Uzbekistan. Emergency medical personnel who were certified general physicians and boarded ambulances were primarily selected. Considering the characteristics of practice and simulation-based training, four or fewer trainees were recruited per instructor in each course, totaling around 24 trainees, and the course was opened as face-to-face over a period of 5 days.

During the online lecture, the instructors utilized notes from the researchers and taught as per the prescribed curriculum. Top-

Time	Day 1	Day 2	Day 3	Day 4	Day 5
09:00–09:30	Registration	Registration	Registration	Registration	Registration
09:30–10:00	Introduction	ECG: narrow complex tachycardia	ACLS simulation	Lecture[a]	Introduction of emergency institution in Korea
10:00–10:30	Pretest				
10:30–11:00	Basic ECG preliminary lecture	ECG: wide QRS tachycardia			Posttest, satisfaction, and education evaluation
11:00–11:30					
11:30–12:00		ECG: myocardial infarction	Trauma lecture[b]	Pediatric emergency	Q&A and closing remarks
12:00–12:30	New guidelines for 103 system in Tashkent[b]				
12:30–13:30	Lunch	Lunch	Lunch	Lunch	-
13:30–14:00	ECG: basic block and arrest	Practice airway, Defib, BLS	Chest pain and dyspnea	Pediatric practice[a]	-
14:00–14:30			Neurologic examination		
14:30–15:00					
15:00–15:30	ECG record 12 lead	Wrap up and DIY	Wrap up and DIY	Wrap up and DIY	-
15:30–16:00					

Fig. 2. Schedule for the emergency medical advanced course. ECG, electrocardiogram; Defib, defibrillation; BLS, Basic Life Support; DIY, do it yourself; PALS, Pediatric Advanced Life Support; NRP, Neonatal Resuscitation Program. [a]Pediatric advanced life support, neonatal resuscitation program, and home delivery. [b]This lecture was provided by Uzbekistan experts.

ics included basic electrocardiography (ST elevation, tachycardia, and bradycardia), pediatric emergencies, pediatric advanced life support, home delivery, neonatal resuscitation program, prehospital neurologic examination, and approach to chest pain, headache, and syncope. Moreover, the UBL cloud allowed trainees to access the course contents for review at any time. Two lectures were given by Uzbekistan experts. The new guidelines of the emergency system in Tashkent and prehospital trauma management lecture were taught to trainees by the director of Tashkent Ambulance Center and a trauma surgeon.

The practice session comprised 12-lead electrocardiography recording, airway and bag valve mask ventilation, basic life support, and defibrillation (Fig. 2). Training equipment was used to increase accessibility for trainees. The 12-lead electrocardiography recording required three to four trainees to monitor the electrocardiogram (ECG). Airway and bag valve mask ventilation required trainees to directly apply oxygen masks to a manikin and insert endotracheal tubes. Basic life support required chest compression and mouth-to-mouth ventilation. Defibrillation required trainees to attach electrodes to a manikin and monitor, charge, and perform it directly.

The simulation course consisted of home delivery, neonatal care, neonatal resuscitation, and advanced cardiac life support (ACLS) (Fig. 2). Simulation on pediatric advanced life support was omitted due to time. Home delivery, neonatal care, and resuscitation were from delivery to early management of normal newborns (wiping, stimulating, and using oral aspirators) and neonatal asphyxia and resuscitation. The trainings were provided using neonatal maternal training equipment. The number of trainees in the ACLS simulation were limited to eight in one scenario, and two instructors participated, with one manipulating the manikin control and the other guiding the scenario. ACLS scenarios focused on cardiac arrest, and a series of courses were taught via simulation using checklists, including chest compression and ventilation support, drug administration, defibrillation, and patient evaluation.

Evaluation and survey of emergency medical advanced course

We tested all trainees using written tests in Russian regarding their clinical knowledge before and after the emergency medical advanced course (Supplementary Material 1). Trainees participated in the pretest before the course and the posttest after completing it. To accurately assess educational effectiveness, questions were randomly allocated, and trainees were tested for an hour under onsite supervision. The questions centered around ECG reading, emergency management at the scene, and resuscitation for children and adults. Questions regarding ECG consisted of four basic and six advanced questions, and the results were calculated out of 100 points. There were eight questions on emergency management at the scene, including those related to pediatric emergencies, emergency childbirths, neonatal resuscitations, chest pain assessments, and neurological tests, and the results were calculated out of 100 points. There were seven questions on pediatric and adult cardiopulmonary resuscitation (CPR), ranging from basic to drug administration for advanced cardiac life support, with the results calculated out of 100 points. Based on the summation of ECG readings (100 points), emergency management at the scene (100 points), and CPR (100 points), the educational assessment results were evaluated out of 300, and then compared and analyzed.

On a Likert scale, all participants were surveyed about the contents and relevance of the emergency medical advanced course. The questionnaire on the content included items on the training content, its difficulty, and appropriateness of the course time. Questions on relevance to the workplace, utilization in the prehospital field, and competency and confidence in prehospital procedures were examined. Based on a Likert scale summing rating of the sub-items, satisfaction was evaluated on a 30-point scale. Each course curriculum was compared and analyzed. A satisfaction survey on education methods was administered to obtain trainees' understanding, effectiveness, and interest as sub-items using a Likert scale, rated with 15 points. Moreover, each method of education was individually examined for satisfaction and compared.

Statistics

Using the D'Agostino-Pearson test, continuous variables were expressed as the mean ± standard deviation for normally distributed data and as the median value (interquartile range [IQR], 25%–75%) for non-normally distrubted data. The statistical significance between pretests and posttests was assessed with a paired t-test and the Wilcoxon signed-rank test. The statistical significance among the three groups was assessed with the Kruskal-Wallis test, followed by multiple comparisons post-hoc analyses with Bonferroni correction. A P-value <0.05 was statistically significant. Data were analyzed using IBM SPSS Statics ver. 20 (IBM Corp., Armonk, NY, USA).

RESULTS

We selected six instructors to conduct the emergency medical advanced course that was voluntarily attended by 22, 23, and 23 emergency medical workers in the first, second, and third sessions respectively. Four trainees were excluded because they did not

complete the course. All 64 trainees (52 men and 12 women) were certified general physicians, with an average age of 40.5±10.0 years. The median clinical experience of trainees, including those working with ambulances, was 15.0 years (IQR, 6.0–22.0 years), and the median ambulance staff experience was 10.5 years (IQR, 3.0–15.8 years).

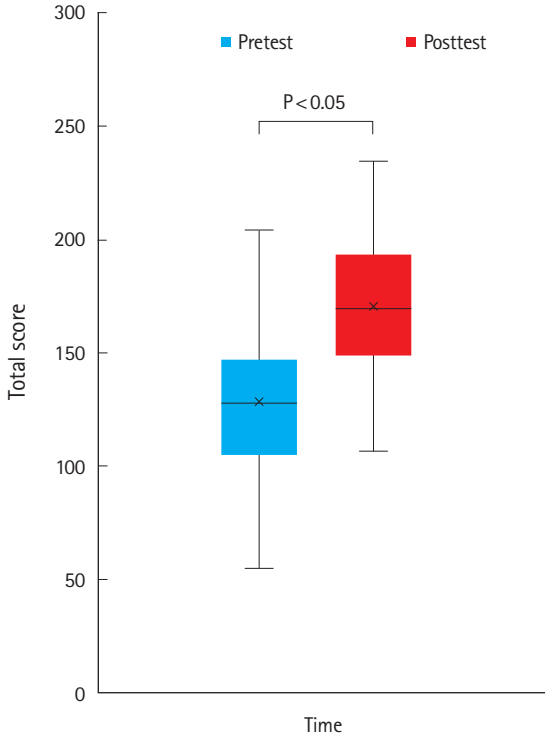

Fig. 3. Comparison of prewritten and postwritten test scores.

The total score on the pretraining test was 129.2±34.8, and on the posttraining test was 170.8±31.2, which was significantly higher (P<0.05) (Fig. 3). According to the test questionnaires, the analysis is as follows: for pretraining test, ECG scores were 40 (IQR, 30–50), emergency management at the scene scores were 50 (IQR, 37.5–75.0), and pediatric and adult CPR scores were 28.6 (IQR, 14.3–42.9); for posttraining test, ECG scores were 50 (IQR, 40–60), emergency management at the scene scores were 75 (IQR, 62.5–87.5), and pediatric and adult CPR scores were 42.9 (IQR, 42.9–57.1). In summary, the statistical significance of all sub-items was high (P<0.05) (Fig. 4).

According to the survey on the emergency medical advanced course, 34 respondents were very satisfied (53.1%), 25 were satisfied (39.1%), three were neutral (4.7%), and two were dissatisfied (3.1%). Regarding the level of difficulty, 44 responded very satisfied (68.8%), 16 satisfied (25.0%), and four neutral (6.3%). On the appropriateness of course time, 36 responded very satisfied (56.3%), 24 satisfied (37.5%), and four neutral (6.3%). Regarding the utilization of fields, 43 responded very satisfied (67.2%), 18 satisfied (28.1%), and three neutral (4.7%). On confidence, 43 responded very satisfied (67.2%), 19 satisfied (29.7%), and two neutral (3.1%). On competency, 47 responded very satisfied (73.4%), 16 responded satisfied (25.0%), and one neutral (1.6%). Curriculum satisfaction calculated by adding the values of survey items was 28.0 (IQR, 26.0–30.0), and there was no statistical difference

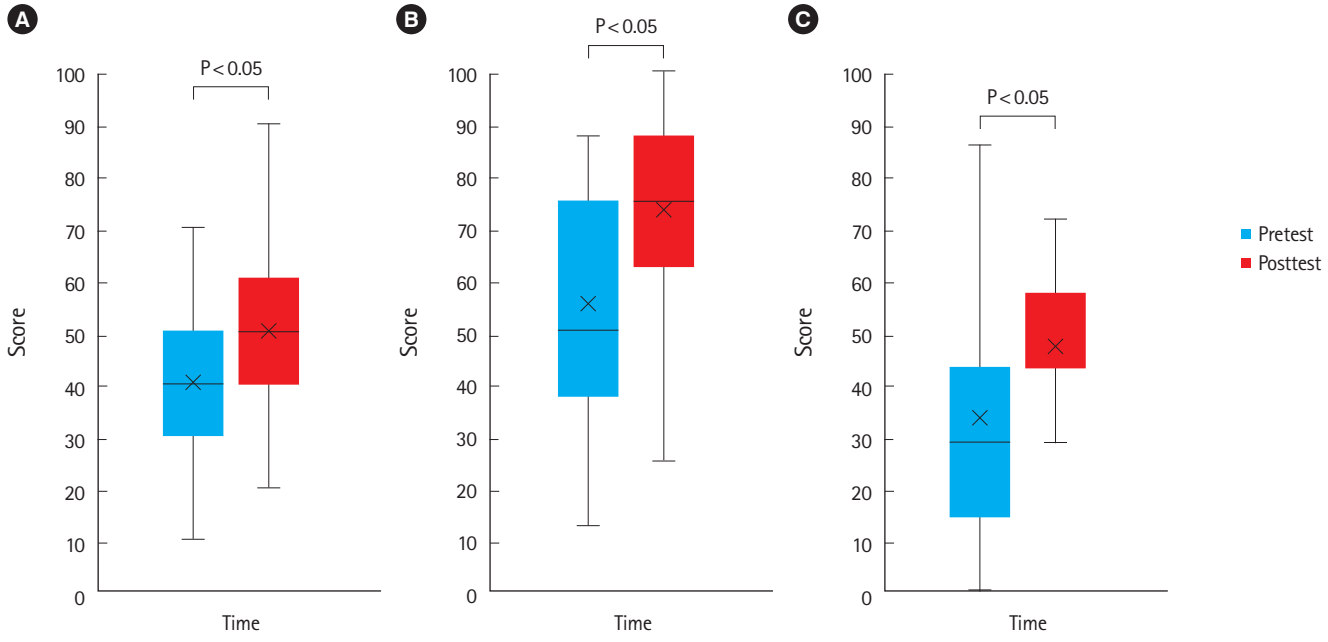

Fig. 4. Comparisons of prewritten and postwritten test score of (A) electrocardiography, (B) emergency management, and (C) resuscitation.

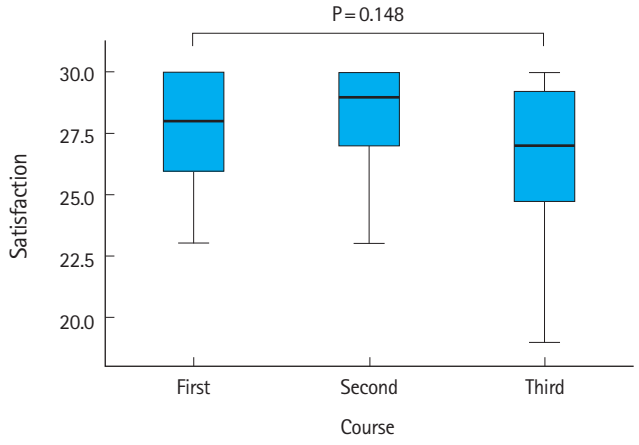

Fig. 5. Satisfaction survey of the three courses of the emergency medical advanced course.

in trainee satisfaction among the three sessions (P=0.148) (Fig. 5).

In the survey on the emergency medical advanced course, satisfaction with the lecture-style training method was 14.0 (IQR, 12.0–15.0), and the training method using practice and simulation was 15.0 (IQR, 14.0–15.0). There was no statistical difference between the lecture-style method and practice and simulation method across the three sessions (P=0.095 and P=0.067, respectively).

DISCUSSION

This study described the online ToT experience of tutoring instructors of emergency medical advanced courses in Uzbekistan during the COVID-19 pandemic. We observed that the instructors trained via the online program could successfully provide an emergency medical advanced course for local emergency medical workers. In Uzbekistan's capital Tashkent, EMS are provided by 12 branches and 204 ambulance stations, managed by the Central Emergency Medical Center, which has 140 ambulances and 1,642 paramedics on duty. EMS providers mainly comprise general physicians, feldshers, and nurses. Physicians can earn their licenses after completing a 3-year college degree and a 7-year medical school curriculum, while feldshers must complete courses focused on emergency treatment, EMS, obstetrics, and surgical care after 4 years of professional training. The nurse's curriculum entails 3 years of university or lyceum study.[5]

All emergency medical workers who use ambulances are required to complete a 1-year curriculum certified by the Ministry of Health of Uzbekistan. In Uzbekistan's emergency medical system, these workers are responsible for more than transferring and managing emergency patients. They also diagnose the patient's condition at the scene and make out a prescription for them. As part of primary treatments, patients in nonemergency conditions can be prescribed or administered medication, or in emergencies, they can be transferred to a hospital while receiving prehospital treatment. Since ambulance services and primary health care are free in Uzbekistan, local demand is high. Hence, proper emergency management and clinical decision-making by EMS providers is essential.

By partnering with the American International Health Alliance, the ODA project, initiated for emergency medical systems in Uzbekistan, conducted a multimedia lecture and workshop in 1999.[6] As of 2002, 1,467 were trained, including 112 general physicians and 749 feldshers. It has been a meaningful curriculum as the first ODA project focused on EMT in Uzbekistan.[6] However, a lack of financial support and educational facilities prevented the provision of regular training courses based on practice to emergency medical staff in the field.[6]

A preliminary survey of emergency medical staff in Tashkent revealed that only 22% to 38% of emergency medical staff had experience and were confident with advanced airways and endotracheal intubation, and only 18% to 20% had experience with defibrillators and cardioversion.[7] Moreover, according to the test results conducted to confirm the medical knowledge level, only half of the participants chose the proper diagnosis and clinical decision in the questions on basic CPR, ECG, and neonatal resuscitation. These findings suggest that the absence of practice and simulation-based curriculums and clinical experience in Tashkent will hinder their ability to provide emergency management and make good clinical decisions during emergencies.[7]

Korea Foundation for International Healthcare supported training courses developed for emergency medical staff boarding ambulances through the "Emergency Medical System Reinforcement Project in Tashkent city, Uzbekistan" in 2017 and the "Uzbekistan Emergency Medical Service Capability Building Project" in 2019. Furthermore, due to the growing importance of emergency medical systems as a result of various ODA projects, an emergency medical curriculum that can be opened independently was required to quickly strengthen the staff's capacity. Considering the pretest/posttest and satisfaction results of the emergency medical advanced course, it is feasible to continuously provide high-quality emergency medical education by training excellent instructors through ToT programs that do not require in-person instruction.

In emergency medical education, simulation-based has been gaining attention since the 1990s. Simulators allow the hands-on practice of procedures, repeated learning, and less risk of harm. Moreover, it is considered an efficient teaching method as the same learning situations can be presented to various learners with immediate feedback.[8] Several studies have confirmed the effec-

tiveness of practice and simulation-based educational methods. According to a report by Tavares et al.[9] when the simulation-based curriculum was conducted and simulation-based assessment was implemented for 49 paramedic trainees, the average competency among participants improved in scene assessment, medical history listening, patient evaluation, decision-making, and communication. Moreover, Jang et al.[10] revealed that an eight-week course of ECG education for first-class emergency medical personnel improved knowledge from 26.8 points before training to 45.3 points after, and Funk et al.[11] reported a significant enhancement in knowledge after medical training for myocardial infarction patients.

The posttest results were significantly higher (pre-education test 129.2 ± 34.8, post-education test 170.8 ± 31.1, $P < 0.05$). Moreover, the results from the posttest were significantly higher in the ECG, emergency management, and pediatric and adult CPR domains. Furthermore, according to the satisfaction survey conducted on the training methods, the lecture-based training was rated 14.0 (IQR, 12.0–15.0), while the practice and simulation-based training was rated relatively higher at 15.0 (IQR, 14.0–15.0). These results highlight the importance of training emergency medical personnel through programs that use practice and simulation. Hence, the effectiveness and satisfaction of future education for emergency medical personnel can be increased by combining these two aspects along with simulations similar to the prehospital fields.

This study had several limitations. First, a significant portion of practical training focused on prehospital procedures and techniques; however, environmental factors that could limit prehospital performance on the scene were not considered. As various factors related to the prehospital environment play a role, the testing of emergency management and clinical decision of trainees based on only practical curriculum has limitations. Thus, in future research, the effectiveness of education can be verified using major indicators in EMS within the community after the completion of the curriculum for emergency medical workers. Second, the Emergency Medical Advanced Course was unable to provide standardized education in practice and simulation-based training. Due to the physical and linguistic limitations caused by COVID-19, ToT was conducted through video conferencing, online lectures, and instructor manuals for local experts with prior experience in the curriculum. Despite this, education involving practice and simulation cannot provide immediate feedback. Hence, it is inevitable that curriculum standardization is limited by differences in instructor competencies, which may negatively impact test results and trainee satisfaction. Hence, deploying experts to local sites for emergency medical staff education is important for advancing and researching emergency medical worker education projects. Third, the fundamental gap among trainees who participated in the three sessions was not considered. While the effectiveness of the course on medical knowledge could be determined pretest and posttest, the testing of trainees for practice and simulation-based training did not consider their practices and clinical experiences. As there is a significant difference in the educational effectiveness of emergency medical staff based on levels of knowledge and clinical experience, the selection process of future trainees should include the pretest scores and clinical experience. Fourth, as the major religion followed in Uzbekistan is Islam, death is perceived not as termination of life, rather its continuation in another form. At the scene of cardiac arrest in the emergency department, the rate of performing CPR is less than in other countries. Hence, in training emergency medicine specialists, education on persuading patient's family is needed.

To summarize, we trained instructors of the emergency medical advanced courses through online ToT among experts of emergency medical personnel in Uzbekistan. The instructors could successfully provide the emergency medical advanced course comprising lecture, practice, and simulation. Results suggest that the qualified education of instructors through online ToT programs could result in effective training of other healthcare providers.

SUPPLEMENTARY MATERIAL

Supplementary Material 1. Posttest for online training
Supplementary material is available at https://doi.org/10.15441/ceem.21.164.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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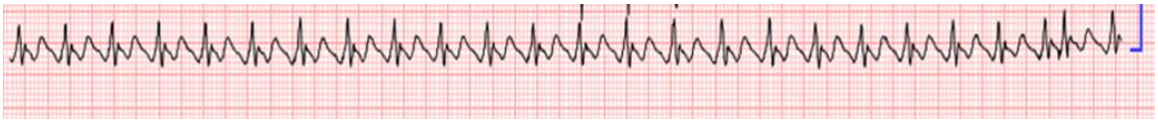
Post-test for online training

Цель этого теста – оценить эффективность онлайн-обучения, проводимого INJE UNIVERSITY ODA CENTER. Этот тест проводится с целью повышения качества будущей учебной программы и укрепления знаний и навыков участников в области оказания неотложной медицинской помощи. Он используется только в исследовательских целях, поэтому, пожалуйста, проведите тест внимательно. Спасибо за Ваше участие в пост-тестировании

Фамилия имя: _____

1. Пожалуйста, определите ритм, выбрав правильный ответ.



① синусовая тахикардия

② мультифокальная предсердная тахикардия

③ трепетание предсердий с проводимостью 2: 1

④ пароксизмальная наджелудочковая тахикардия

2. Правильной последовательностью распространения электрического импульса по проводящей системе сердца, является?

① СА узел-АВ узел- пучок Гиса - ножка пучка Гиса -волокна Пуркинье

② СА узел - пучок Гиса -AV узел- ножка пучка Гиса-волокна Пуркинье

③ СА узел -AV узел- ножка пучка Гиса - волокна Пуркинье - пучок Гиса

④ АВ узел - волокно Пуркинье - СА узел - ножка пучка Гиса - пучок Гиса

⑤ АВ узел - пучок Гиса - волокно Пуркинье - ножка пучка Гиса - узел СА

3. В отделение неотложной медицинской помощи поступил 4-летний мальчик с остановкой сердца, в результате определения первоначального ритма сердца, была диагностирована фибрилляция желудочков, в связи с чем была предпринята попытка проведения дефибрилляции. Разряд какой мощности, в данном случае, требуется для осуществления дефибрилляции? (Вес ребенка 15 кг)

① 1 5Дж – 15Дж – 30Дж

② 1 5Дж – 30Дж – 30Дж

③ 3 0Дж – 30Дж – 60Дж

④ 3 0Дж – 45Дж – 60Дж

⑤ 3 0Дж - 60Дж - 90Дж

4. Почему настолько важно проведение ранней дефибриляции взрослым пациентам?

1) Это "запустит" сердце
2) Фибрилляция предсердий - наиболее частый присутствующий ритм
3) Шанс на успех быстро уменьшается со временем
4) Кардиоверсия является главным эффективным средством для оказания помощи при остановке сердца

5. Пациент не реагирует и не дышит. Пульс на бедренной артерии определяется. Какое действие вы предпримете дальше?

① Применить дефибриллятор
② Применить 12 канальное ЭКГ
③ Начать осуществление внутривенного доступа
④ Начать искусственное дыхание

6. Сообщается, что у матери на 35 неделе беременности появились боли. Какие из следующих результатов можно охарактеризовать как настоящие схватки ?

① Периоды облегчения боли нерегулярны.

② Интервал между схватками со временем становится все короче.

③ Интенсивность схваток не меняется со временем.

④ Возникает боль, при этом жалоба характеризуется болью в области- в основном в нижней части живота.

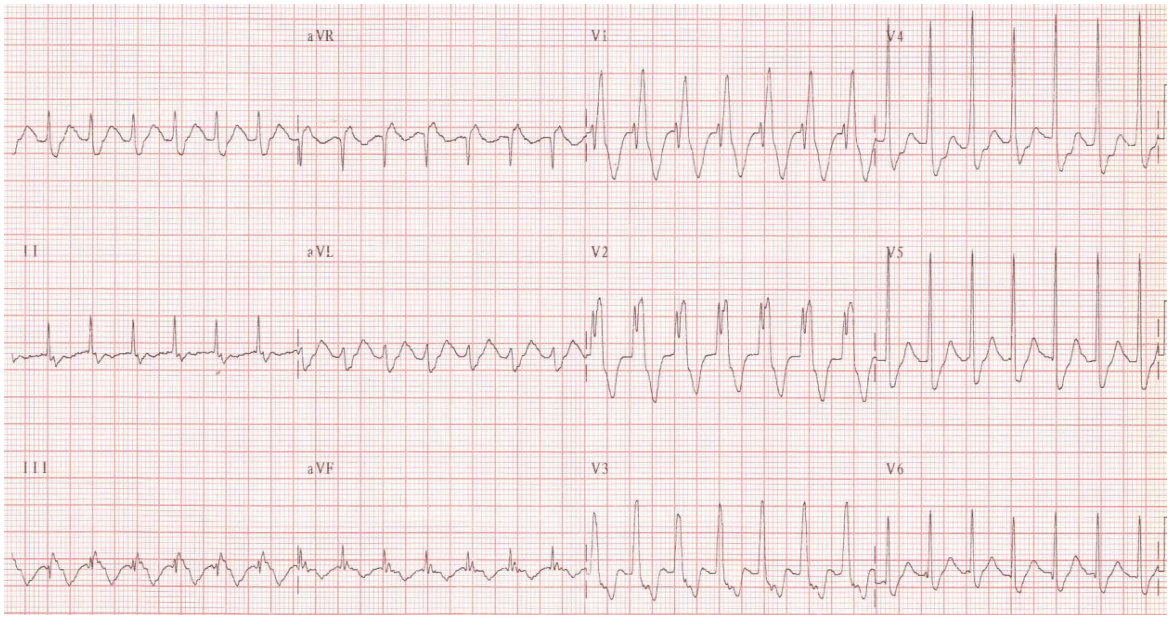
⑤ Нет раскрытия шейки матки

7. Больной 50-ти лет, жалоба на боли в груди. Артериальное давление 120/80 мм рт. Ст., Пульс 95 раз, частота дыхания 24 раза, температура тела 38 градусов. Со слов больного 2 дня назад у него был кашель с выделением желтой мокроты, а за 1 день до появления данных симптомов, в пораженном участке постепенно усиливалась боль при дыхании. При нажатии на пораженный участок болезненность не определяется.

Как по вашему мнению, в какой из систем находится проблема?

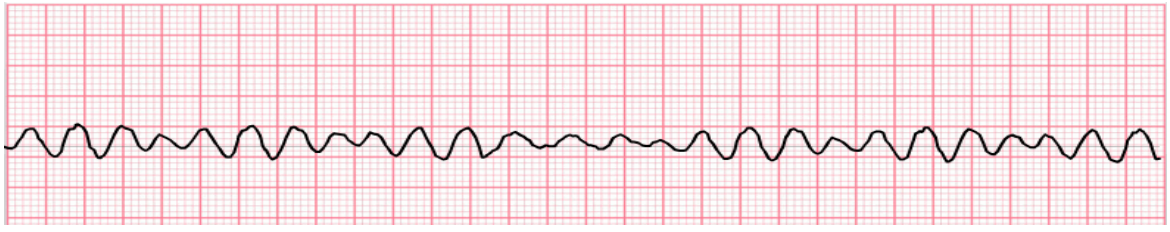
1) Сердечно-сосудистая система
2) Дыхательная система.
3) Пищеварительная система.
4) Нервная система.
5) Кожа

8. Выберите правильный диагноз



1) Желудочковая тахикардия
2) Гиперкалиемия
3) Полиморфная желудочковая тахикардия (Torsade de pointes)
4) Фибриляция предсердий с синдромом Вольфа-Паркинсона-Уайта (WPW)
5) Атриовентрикулярная реципрокная тахикардия (АВРТ)

9. Пожалуйста, определите ритм, выбрав правильный ответ



① Трепетание предсердий
② Полиморфная желудочковая тахикардия (Torsades de pointes)
③ Фибрилляция желудочков
④ Мультифокальная предсердная тахикардия

10. Что из нижеперечисленного неверно в отношении ухода за новорожденными?

1) Быстро обтереть новрожденного после родов, сразу же снять с него мокрые полотенца и укутать теплым одеялом.

2) Если новорожденный плачет, дыхание нормальное, а частота сердечных сокращений превышает 100 раз, вентиляция с положительным давлением не требуется.

3) Сразу после рождения пуповину перевязывают и как можно раньше перерезают для быстрого заживления.

4) Если новорожденный находится в стабильном состоянии, следует проводить уход за новорожденным во время транспортировки в кенгуру.

5) По крайней мере, 2 медицинских работника должны быть отправлены на место вызова, где может потребоваться проведение реанимационных мероприятий.

11. Какой из зубцов на ЭКГ соответствует зубцу, генерирующемуся при сокращении предсердия?

① P
② Q
③ R
④ S
⑤ T

12. Какие из нижеперечисленных препаратов входят в состав Кома коктейль?

① Декстроза, кислород, налоксон, тиамин
② Кислород, налоксон, флумазенил, глюкагон
③ Атропин, хлорид кальция, декстроза, налоксон
④ Флумазенил, налоксон, октреотид, физостигмин

13. 80-летний мужчина сообщил, что задыхается. Артериальное давление 90/60 мм рт. Ст., Частота пульса 50 уд/мин, частота дыхания 22 , температура тела 36 градусов. Со слов пациента неделю назад, он испытывал боль в груди продолжительностью около 20 минут в день, затем боль исчезла. 3 дня назад появилось выделение белой мокроты, он задыхался и при этом ему удавалось передвигаться только в пределах двора своего дома. Пять лет назад ему диагностировали инфаркт миокарда, в связи с чем он получал лечение в больнице. Какой наиболее вероятный диагноз?

1) Пневмония
2) Болезнь Лу Герига.
3) Астма
4) Сердечная недостаточность.
5) Пневмоторакс.

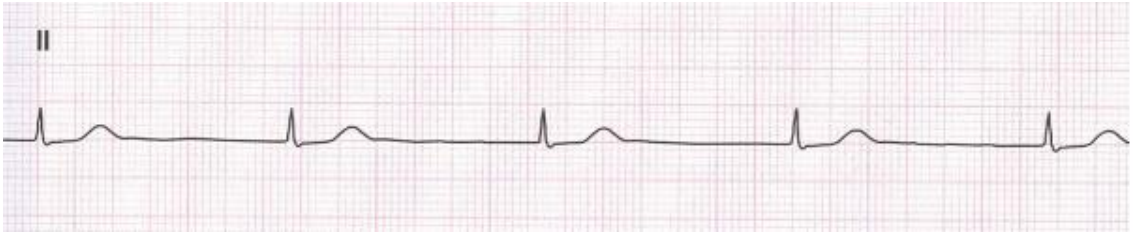
14. Выберете правильный ответ. Какой из показателей ЭКГ является характерным для БПНПГ (Блокада правой ножки пучка Гиса)?

① Глубокий зубец S в отведении V1
② Узкий комплекс QRS
③ Нечеткий зубец S в отведении V6
④ Удлиненный PR интервал
⑤ Отрицательный зубец T в отведении V 6

15. У 5-летнего мальчика во время госпитализации из-за миокардита развилась ЖТ (желудочковая тахикардия) без пульса, в связи с чем ему начали проводить СЛР. Входе чего было выполнено одно введение адреналина и два разряда дефибриллятора, несмотря на это ЖТ без пульса сохранилась. Какой препарат следует ввести этому пациенту в данный момент времени?

1) Глюконат кальция
2) Сульфат магния
3) Атропин
4) Аденозин
5) Лидокаин

16. Пожалуйста, определите ритм, выбрав правильный ответ.



1) Синусовая брадикардия
2) Узловой (Атриовентрикулярный) ритм
3) Идиовентрикулярный ритм
4) Полная AV-блокада

17. В отделение неотложной помощи поступил, ранее здоровый,18-месячный мальчик в связи с внезапно развившейся респираторной недостаточностью. Из анамнеза известно, что на протяжении последних 3 дней у ребенка наблюдался кашель, сопровождавщийся повышением температуры тела (лихорадкой). На момент обращения, общее состояние ребенка было относительно удовлетворительным, за исключением лихорадки и лающего кашля, с периодически возникающими эпизодами стридора. Отец мальчика, отрицает проглатывание ребенком инородного тела. Какой диагноз, в данном случае, является наиболее верным?

① Острый бронхиолит

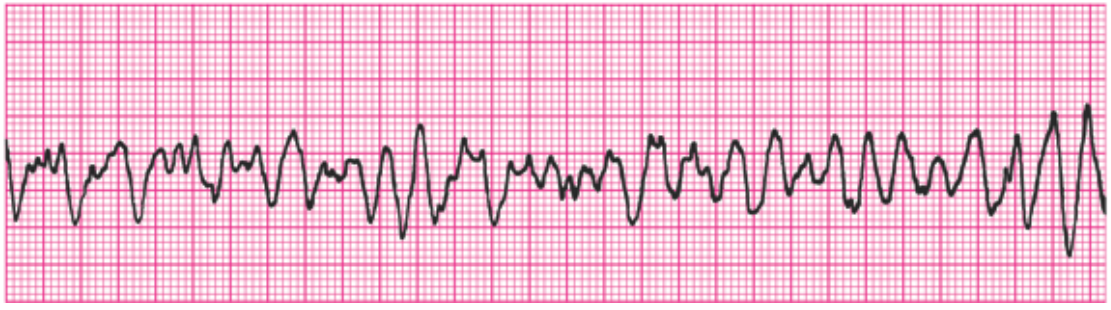
② круп

③ эпиглоттит

④ Бактериальный трахеит

⑤ Обструкция дыхательных путей инородным телом

18. 3-летний ребенок не отвечает, не дышит, пульс отсутствует. Высококачественная СЛР уже начата. Кардиомонитор подключен, на кардиомониторе отмечается ритм, указанный ниже. Какое следующее подходящее вмешательство, требуется провести в данном случае?



1) Разряд дефибрилятора, из расчета 2 Дж / кг

2) Разряд дефибрилятора, из расчета 4 Дж / кг

3) Адреналин, из расчета 0,1 мг / кг внутривенно

4) Лидокаин, из расчета 1 мг / кг внутривенно

19. Какой показатель жизненно важных функций не является нормальным для его или ее возраста?

1) 6 месяцев, ЧСС 80 уд/ мин
2) 11 месяцев, частота дыхания 40 / мин
3) 13 месяцев, систолическое артериальное давление 80 мм рт.
4) 4 года, пульс 110 уд/ мин
5) 10 лет, частота дыхания 20 / мин

20. У 35-летней женщины учащенное сердцебиение, головокружение, стойкая тахикардия. На мониторе отображается обычный комплекс QRS с узким комплексом с частотой 180 в минуту. Проведение Вагусных приемов не привело, к восстановлению ритма сердца. Венозный доступ осуществлен. Какой препарат следует ввести в данном случае?

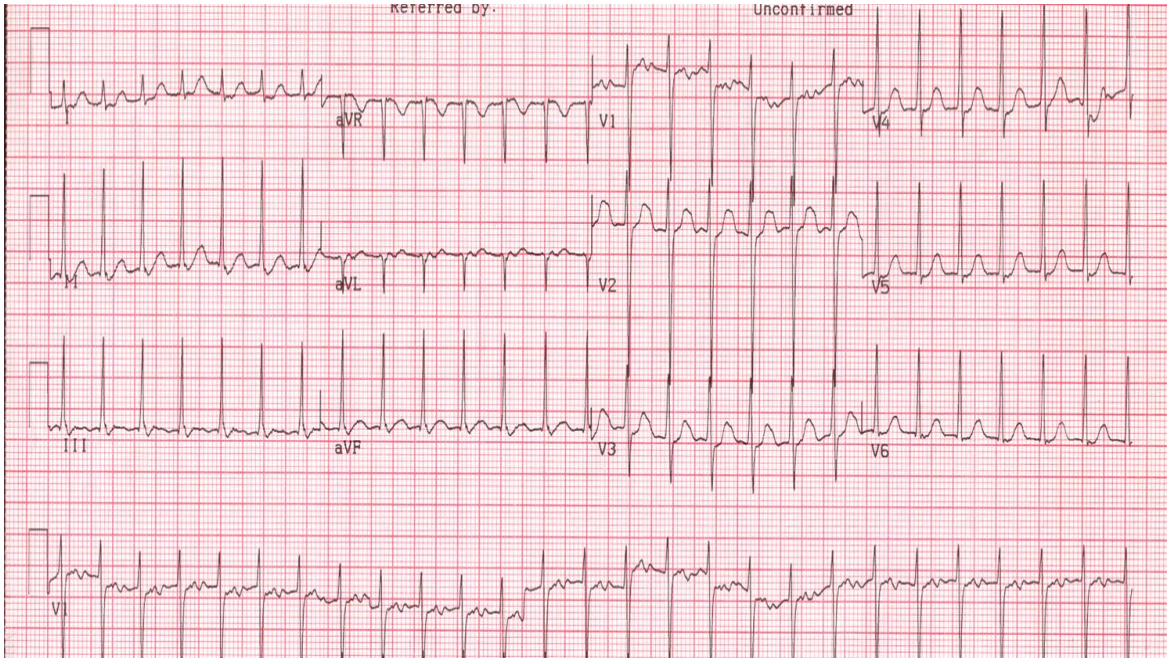
① Аденозин 6 мг

② Атропин 0,5 мг

③ Адреналин от 2 до 10 мкг / кг в минуту

④ Лидокаин 1 мг / кг

21. Выберите правильный диагноз



1) Синусовая тахикардия

2) Трепетание предсердий с атриовентрикулярной проводимостью 2: 1

3) Фибрилляция предсердий с быстрым желудочковым ответом

4) АВ-узловая реентерабельная тахикардия (АВНРТ)

5) Атриовентрикулярная реципрокная тахикардия (АВРТ)

22. Какой из нижеперечисленных ответов, является неверным, в отношении правил проведения реанимации новорожденных?

1) Компрессия грудной клетки выполняется в области нижней трети мечевидного отростка.

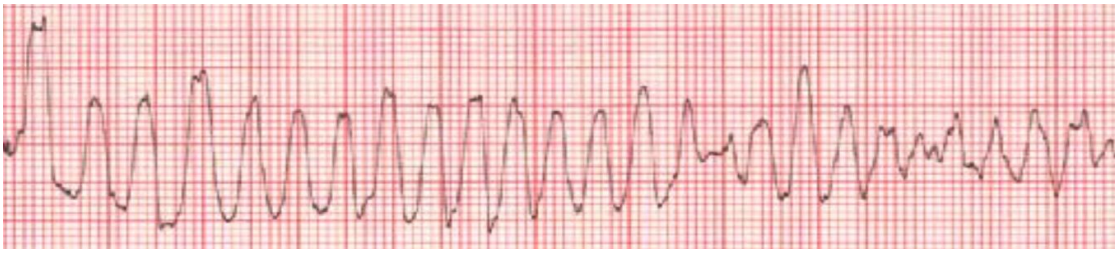
2) Соотношение компрессии грудной клетки : к вентиляции с положительным давлением составляет 15: 2.

3) У новорожденных с выделениями изо рта и носа, сначала выполняется аспирация из ротовой полости, при помощи сферического аспиратора, а затем проводится аспирация из полости носа.

4) Новорожденным, у которых частота сердечных сокращений не восстановилась до 100 уд. /мин. даже при адекватной вентиляции с положительным давлением, следует выполнять компрессионные сжатия грудной клетки.

5) У новорожденных, с затруднением дыхания или цианозом, следует проводить стимуляцию, постукивая по ступням или поглаживание по спине.

23. Пожалуйста, определите ритм, выбрав правильный ответ.



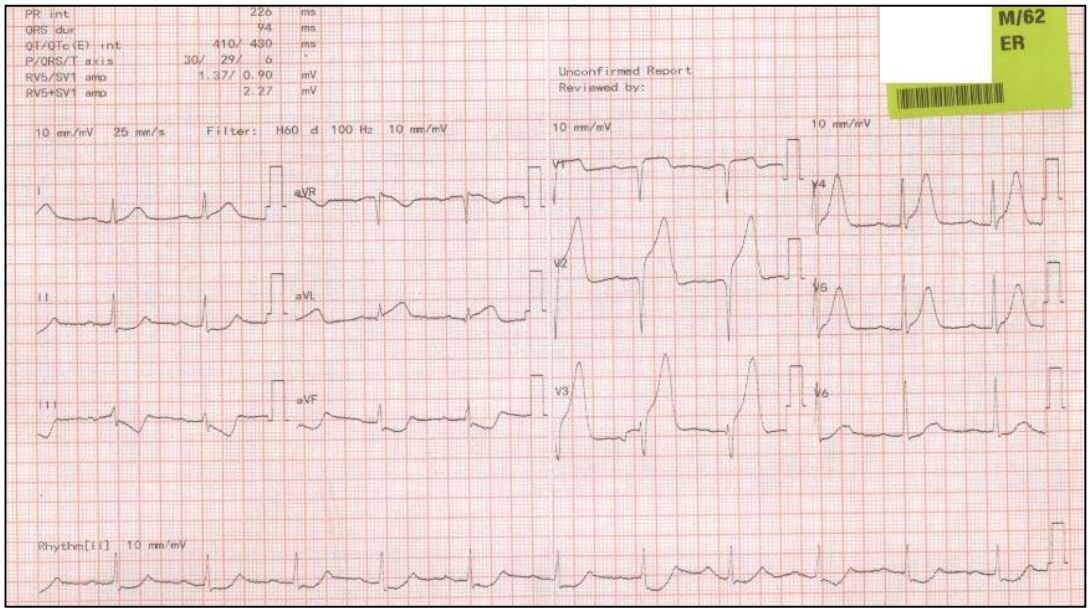
① мерцательная аритмия

② фибрилляция желудочков

③ мультифокальная предсердная тахикардия

④ полиморфная желудочковая тахикардия

24. Какая коронарная артерия является наиболее проблемной на приведенной ниже электрокардиограмме?



1) Левая передняя нисходящая артерия
2) Левая огибающая артерия
3) Правая Коронарная артерия
4) Нижняя коронарная артерия

25. СЛР проводится двумя спасателями. Каким должно быть соотношение компрессий и вентиляции?

1) 15: 1
2) 15: 2
3) 30: 1
4) 30: 2

<Пост-тестировании окончено. Спасибо.>

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Study Protocol

The DEXA-SEPSIS study protocol: a phase II randomized double-blinded controlled trial of the effect of early dexamethasone in high-risk sepsis patients

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Objective Steroids are used in cases of sepsis, especially in patients experiencing septic shock. However, clinical trials to date have reported contradictory results. Different patient endotypes and variations in the type and dose of steroid may be at fault for this discrepancy, and further investigation is warranted. In this paper, we propose a new DEXA-SEPSIS study design.

Methods We plan to conduct a multicenter, double-blinded randomized pilot study (DEXA-SEPSIS) investigating the feasibility and safety of early use of dexamethasone in sepsis. Participants will be high-risk septic patients presenting to the emergency department with a systolic blood pressure of <90 mmHg or serum lactate level of >2 mmol/L. Participants will be randomized to the following three groups: control, 0.1 mg/kg of dexamethasone, or 0.2 mg/kg of dexamethasone per day for 1 to 2 days. The primary outcome will be 28-day mortality. Secondary outcomes will include time to septic shock, shock reversal, additional steroid administration, number of ventilator-free days, use of continuous renal-replacement therapy, length of stay in the intensive care unit and/or hospital, delta Sequential Organ Failure Assessment score on days 3 and 7, superinfection, gastrointestinal bleeding, hypernatremia, and hyperglycemia.

Discussion The DEXA-SEPSIS study will provide insight regarding the feasibility and safety of early use of dexamethasone in high-risk sepsis. The results could provide data to design a future phase III study.

Trial registration ClinicalTrials.gov identifier: NCT05136560

Keywords Dexamethasone; Glucocorticoids; Sepsis

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CEEM

Capsule Summary

What is already known

Steroids are being used in cases of sepsis, especially in patients with septic shock. However, clinical trials to date have reported contradictory results.

What is new in the current study

We propose a new phase IIa study protocol to use dexamethasone in early high-risk sepsis in the emergency department.

INTRODUCTION

Sepsis is defined as a life-threatening type of organ dysfunction caused by dysregulated host responses to infection.[1] Worldwide, it has high incidence and mortality rates and has become a public health problem.[2-4] Given these characteristics, the World Health Organization has announced sepsis management to be a global health priority.[5] Many drugs have been developed for treating sepsis, but none to date have shown clinical efficacy.

Low-dose steroids are recommended by current guidelines in cases of septic shock requiring ongoing vasopressor therapy, but the evidence in support of this approach is weak.[6] A survey of the available studies covering the effects of steroids in sepsis reveals that steroid dose, sepsis severity (as manifested by the mortality rate of the control group), and timing of steroid administration have varied between them. Steroids may be beneficial in patients with a higher baseline mortality rate[7,8] compared to those with a relatively lower mortality rate. Concomitantly, considering the immunosuppressant nature of steroids, they may actually be harmful when administered in the immunosuppressant phase of sepsis, i.e., usually the late phase of sepsis. Therefore, steroids could be more effective as early therapeutics.

Historically, high-dose steroids have been used to treat sepsis, but no ultimate survival gains have been reported in the literature as a result of this approach.[9-11] Subsequently, low-dose steroids were advocated for, but, in recent years, large and well-designed clinical trials have offered contradictory results,[8,12] raising questions about the utility of steroids in septic shock. One meta-analysis has advocated for using a dose of steroids (200–400 mg of hydrocortisone per day), which contrasts with the current guideline in sepsis.[13] This dose could be converted to 8 to 16 mg of dexamethasone; in patients weighing 80 kg, the dose would be 0.1 to 0.2 mg/kg. In addition, there is a small-sized randomized controlled trial that adopted a higher steroid dosage (0.2 mg/kg of dexamethasone) in sepsis than that used in the guideline, and the results favored steroid use, but the study lacked a group taking a routine dose of steroid.[14] In one animal study, the administration of 0.2 or 5 mg/kg of dexamethasone improved the survival rate more significantly than 0.1 mg/kg of dexamethasone.[15] Dexamethasone has only anti-inflammatory effects and has a longer half-life, which makes it easier to use in the emergency department. Moreover, another meta-analysis suggested that dexamethasone has the best therapeutic efficacy among various steroids.[13]

Considering these results, we hypothesized that the effect of steroids on sepsis might differ according to the steroid dosage and the severity and phase of sepsis. In a pilot study investigating the validity of this hypothesis, we plan to assess the effect of early bolus administration of different doses of dexamethasone in high-risk septic patients.

METHODS

Ethical statements

This study has been reviewed and approved by the Institutional Review Board of CHA Bundang Medical Center (No. CHA 2021-02-035), the Institutional Review Board of Samsung Medical Center (No. SMC-2021-03-078), and the Korean Food and Drug Agency.

Design and setting

The proposed study is a multicenter double-blinded randomized phase IIa pilot clinical trial that will be undertaken at two academic emergency departments in Korea. The trial protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.

Operational definitions

Sepsis

The definition of sepsis in this study will rely on the sepsis-3 definition, which contends that sepsis is a life-threatening type of organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in the total Sequential Organ Failure Assessment (SOFA) score of

≥ 2 points consequent to the infection. High-risk sepsis patients are defined as sepsis patients with a systolic blood pressure of < 90 mmHg or serum lactate level of > 2 mmol/L.

Adverse events

Adverse events will be defined as all adverse events that occur after a study participant is given the study drug. The causality between the events and the study drug does not need to be clear, but events considered as part of the clinical course of sepsis will be excluded.

Renal replacement therapy

Renal replacement therapy will be defined in this study as therapy for patients with kidney failure that replaces the blood-filtering function of the kidneys.

Time to shock reversal

Time to shock reversal will be defined in this study as the time (in hours) from a state of shock to shock reversal. A state of shock will be defined in this study as a condition that requires a vasopressor to maintain a mean arterial pressure > 65 mmHg. Shock reversal will be defined in this study as a point at which the mean arterial pressure had remained > 60 mmHg without any vasopressor and 24 hours have passed.

Ventilator-free days

Ventilator-free days will be calculated as follows: 1 point for each day during the measurement period where patients are both alive and free from mechanical ventilation. The total number of ventilator-free days will be measured for up to 3 months during the hospital stay.

Eligibility criteria for study participation

Patients visiting the emergency departments of CHA Bundang Medical Center and Samsung Medical Center who meet all the inclusion and exclusion criteria may be enrolled in this study (Table 1).

Trial protocol

Description of study flow

The present study will be conducted in two emergency departments in Seongnam and Seoul, Korea. We plan to enroll 30 patients in each group, for a total of 90 patients (Fig. 1). Informed consent will be obtained from each patient or their legally authorized representative if the patient meets the inclusion criteria and no exclusion criteria. After informed consent is obtained, randomization will be performed using a random number table. Patients will be treated with the study drug. The usual management for sepsis will be guided by the Surviving Sepsis Campaign international guideline.[6]

Study interventions

Patients will be randomly assigned to one of three groups as follows: a control group (placebo), a 0.1 mg/kg of dexamethasone bolus group, and a 0.2 mg/kg of dexamethasone bolus group. The treatment groups will receive their allotted dexamethasone bolus amounts once per day for 1 to 2 days (Fig. 2).

Patients will be allocated to receive a bolus injection of either the intervention (0.1 mg/kg or 0.2 mg/kg of dexamethasone) or identical placebo (0.9% saline). The study infusion package will

Table 1. DEXA-SEPSIS study inclusion and exclusion criteria

DEXA-SEPSIS study inclusion and exclusion criteria	
Inclusion criteria[a]	Age of 19–89 years
	Systolic blood pressure of < 90 mmHg or plasma lactate level of > 2 mmol/L
	Delta SOFA score of ≥ 2 points consequent to the infection
Exclusion critiera[b]	Decision to limit or withdraw active treatment (i.e., do not resuscitate)
	Steroid use within 4 weeks
	Chemotherapy for underlying malignancy within 4 weeks
	Immunosuppressive therapy within 4 weeks
	Underlying disease with a life expectancy of < 90 days
	Patient was hospitalized at another hospital for sepsis and referred (not including those transferred from another ED)
	Sepsis diagnosed 24 hours after ED admission
	Etomidate use during hospitalization
	Pregnancy or lactation
	Informed written consent cannot be obtained from a patient or legal representative
	Any other condition considered harmful in conjunction with the use of steroids by the physician

SOFA, Sequential Organ Failure Assessment; ED, emergency department.
[a]All of the following inclusion criteria must be met. [b]The patient will be excluded if ≥ 1 of the following exclusion criteria are present.

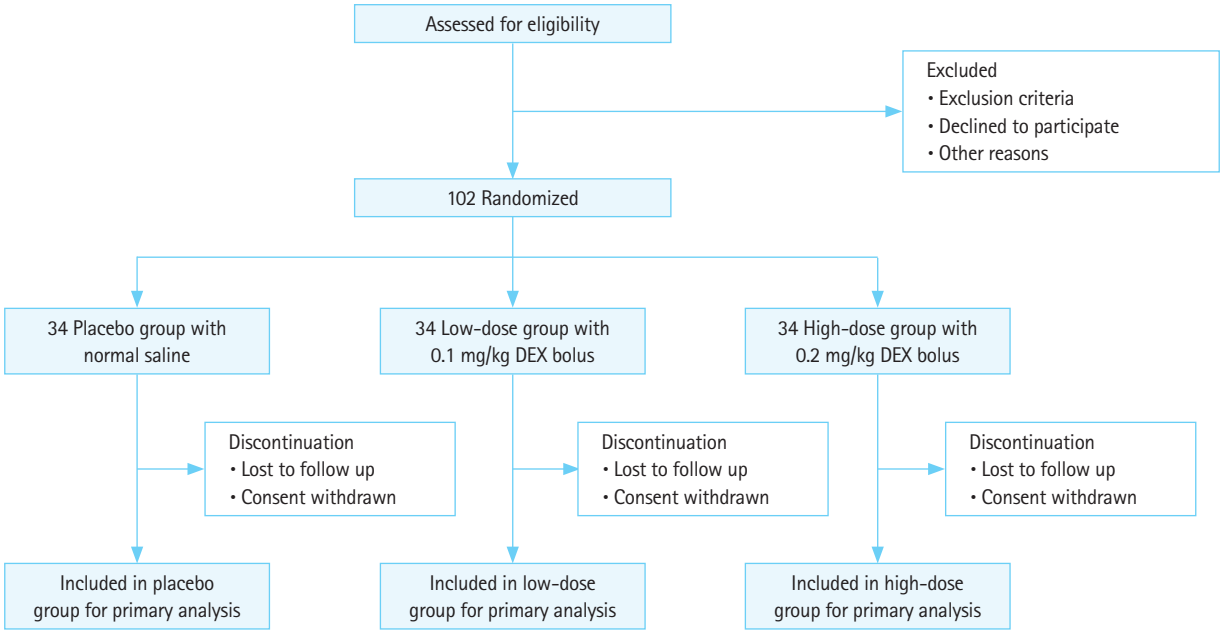

Fig. 1. DEXA-SEPSIS study flow. DEX, dexamethasone.

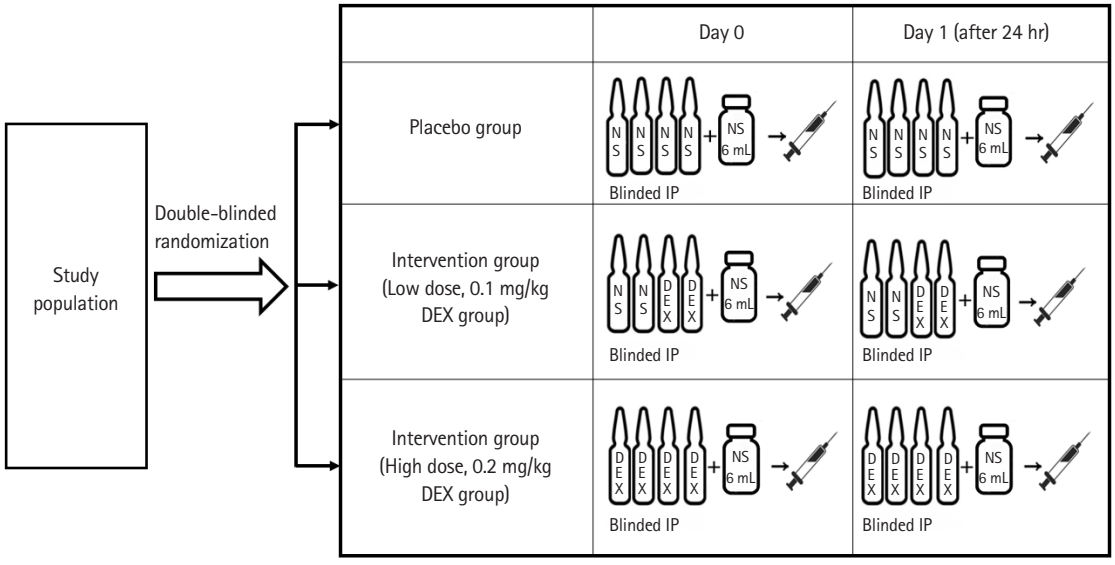

Fig. 2. Blinded technique. NS, normal saline; IP, investigational product; DEX, dexamethasone.

contain four ampules, each of which has 1 mL of content. The package of the 0.2 mg/kg of dexamethasone group consists of four ampules of dexamethasone, while the package of the 0.1 mg/kg of dexamethasone group consists of two ampules of dexamethasone and two ampules of normal saline; lastly, the package of the placebo group consists of four ampules of normal saline. All ampules will be opened and mixed with 6 mL of normal saline to create 10 mL of the study drug, and a volume of 0.1 times the patient's body weight will be injected to administer an appropriate dose of the drug while retaining the study blinding.

The appearance of the study infusion packages will be identical and there will be no markings on the package other than a four-digit code identifying the study number. Administration of the study drug could be repeated once in a 24-hour interval if there is no other routine use of steroids at the discretion of the treating physician.

Standard therapy

Known management options for sepsis, e.g., fluid, antibiotics, vasopressors, and respiratory care, should be used at the discretion of the treating physician. The use of steroids for the standard treatment of sepsis is possible without unblinding. However, the administration of etomidate during hospitalization will require the withdrawal of the patient from the study.

Randomization, concealment, and blinding

Patients will be randomly assigned (1:1:1) via computer-generated permuted block randomization (block size of 3 and 6 to achieve between-group balance) to receive 0.2 mg/kg of dexamethasone, 0.1 mg/kg of dexamethasone, or a placebo. The randomization table will be prepared by a statistician working independently of the study. The investigators, research coordinators, treating physicians, nurses, and patients/family members will remain blinded to the allocated group.

Data collection

The SOFA score and lactate level will be recorded before study enrollment. Then, during the study period, data will be acquired according to a predefined schedule (Table 2). All data will be collected by research coordinators who have been trained for sepsis registry work over years.

Outcomes

Primary and secondary outcomes will be assessed by a group-blinded research coordinator. Patient electronic medical records will be used to assess the outcomes, and final outcomes, such as 28-day or 90-day mortality, will be determined on the basis of medical records and telephone interviews.

Primary outcome

The primary outcome will be 28-day mortality (Fig. 3).

Secondary outcomes

Secondary outcomes will include 90-day all-cause mortality, time to septic shock, shock reversal, number of vasopressor-free days, use of continuous renal-replacement therapy, additional steroid administration, number of ventilator-free days, length of stay in the intensive care unit and/or hospital, delta SOFA score on days 3 and 7, superinfection (defined as a secondary infection within 28 days), gastrointestinal bleeding within 14 days, hyperglycemia (defined by a serum glucose level of >150 mg/dL within 7 days),

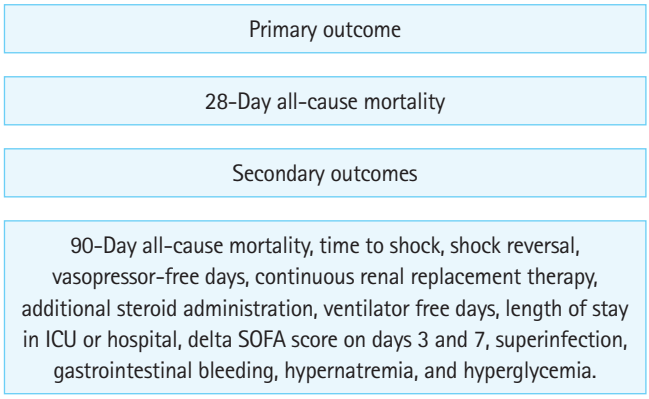

Fig. 3. Primary and secondary outcomes. ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

Table 2. Study schedule

Period	Screening	Treatment		Follow-up				
	-	Day 0	Day 1	Day 3	Day 7[a]	Day 14[a]	Month 1[a]	Month 3[b]
Written consent	√							
Screening numbering	√							
Demographic survey	√							
Medical history	√							
Physical examination	√	√	√	√	√	√	√	√
Vital sign measurement	√	√	√	√	√	√	√	√
Laboratory test	√							
Blood culture	√							
SOFA score	√			√	√			
Eligible criteria check	√							
Randomization		√						
Administration of clinical investigational drug		√	√					
Check for adverse effects		√	√	√	√	√	√	√
Confirmation of concomitant drugs and treatment		√	√	√	√	√	√	√

SOFA, Sequential Organ Failure Assessment.
Window period of [a] ± 3 and [b] ± 5 days.

and hypernatremia (defined by a serum sodium level of >150 mmol/L within 7 days).

Statistical analysis and sample size calculation

Primary data will be analyzed by intention-to-treat analysis. Data will also be presented stratified by center and the severity of septic shock according to the use of vasopressors. The statistical analysis will be performed by an independent and blinded statistician. Descriptive data will be presented using median and interquartile range values or mean±standard deviation values, as appropriate. Treatment groups will be compared using the chi-squared test, Fisher exact test, Student t-test, Mann-Whitney U-test, one-way analysis of variance, or Kruskal-Wallis test with post-hoc analysis.

A Kaplan-Meier survival curve with the log-rank test will be used in the time-to-event analysis. Multiple testing corrections will be performed with the Bonferroni method. Since this is a phase IIa study, a sample size calculation will not be required. The sample size would be 102 patients, considering a dropout rate of 10% and allocation of 30 patients to each group.

$P<0.05$ will be considered statistically significant, and all statistical analyses will be two-sided. All analyses will be performed using R ver. 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and Stata ver. 17.0 (StataCorp., College Station, TX, USA).

Data safety and monitoring

The data safety and monitoring board for this study will be composed of two clinicians and one statistician working independently of this study. These individuals will verify adherence to trial procedures and the accuracy of data collection according to national and international requirements and Good Clinical Practice guidelines. This assessment will be performed on a monthly basis by each participating center. They will check the case report forms and verify they are consistent with the source of documentation. They will also confirm that the study process complies with the study protocol.

DISCUSSION

The current guideline about sepsis suggests using intravenous corticosteroids for adults with septic shock and an ongoing requirement for vasopressor therapy.[6] However, it also noted that the optimal dose, timing of initiation, and duration of corticosteroids remain uncertain. The use of dexamethasone is recommended in patients with COVID-19 or bacterial meningitis without the use of vasopressor therapy and in those with postoperative nausea and vomiting as a single bolus. Given these facts, we propose the use of dexamethasone in the early phase of high-risk sepsis in patients not on vasopressor therapy, which is the motive behind conducting this study.

The results of this phase II study could lead to the design, development, and conduct of a phase III trial powered to evaluate the effects of the use of early dexamethasone in high-risk sepsis patients.

CONFLICT OF INTEREST

Kyuseok Kim serves as an editor of the *Clinical and Experimental Emergency Medicine*, but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

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Commentary

Palliative and end-of-life care in the emergency department

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With current medical advances, the human population continues to age. This presents health-care practitioners with the increasing complexity of providing care to elderly patients with multifactorial medical and personal needs. This is a particular challenge in the emergency department, where patients often present for care in the last months of their lives. Early identification of palliative care needs and initiation of comfort care can drastically improve patient care and quality of life. Although emergency physicians agree that palliative care is an important area of knowledge, there is a gap in palliative care training in emergency medicine residencies. It is increasingly important for emergency medicine providers to have the resources and training to provide palliative care and to understand end-of-life issues.

Keywords Palliative care; Hospital emergency service; Emergency medicine; Terminal care

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INTRODUCTION

With current medical advances, the human population continues to age. This is a growing challenge, particularly in the emergency department (ED), where patients often present in the last months of their lives. A study conducted by the University of California San Francisco indicated that 75% of patients visited the ED in their last 6 months of life.[1] A study has shown that 56% to 99% of older adults do not have advance directives available at ED presentation.[2] Therefore, ED visits toward the end of life are opportune teaching moments for emergency physicians to empower patients who are still well enough to communicate their goals and choices. In addition, 77% of patients seen in the ED during the last month of life were admitted to the hospital, and 68% of those admitted died there. In contrast, patients who enrolled in hospice at least 1 month before death rarely visited the ED during that time period. Most people say they prefer to receive end-of-life care at home. Early identification of palliative care needs and initiation of comfort care can improve quality of life, decrease in-hospital mortality, decrease ED visits, and decrease hospital costs.[3] Therefore, it is increasingly relevant for emergency medicine (EM) providers to have the resources needed to provide palliative and end-of-life care.

WHAT IS THE ROLE OF PALLIATIVE CARE IN EM?

The Model of the Clinical Practice of Emergency Medicine includes health care coordination at the end of life and palliative care as essential skills for emergency physicians.[4] According to the American College of Emergency Physicians, the core topics of palliative care relevant to EM are recognition of palliative care and hospice needs in patients, primary-level provider skills in palli-

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ative care, and an understanding of how palliative care can be implemented in the ED.[5,6] ED initiation of palliative care is helpful because patients who participated in palliative care conversations in the ED have higher incidence of inpatient palliative consultation and shorter time to a palliative care consultation compared to traditional ED care.[7] Inpatient palliative care consultation within 24 hours is associated with shorter hospital stay, decreased total cost of hospitalization, and decreased in-hospital mortality. However, emergency physicians are only responsible for 3% of palliative care referrals. In a survey that asked medical residents how comfortable they are with end-of-life discussions, 26% stated they were not comfortable with such discussions.[8,9]

WHAT ARE THE BARRIERS IN THE USE OF PALLIATIVE CARE IN THE ED?

A literature review identified several barriers to palliative care in the ED, including lack of prior provider-patient relationships, uncertain knowledge about prognosis, lack of time, lack of access to medical records, and lack of availability of a palliative care team.[10] There is evidence of discrepancy between the perceived importance of palliative care skills and medical resident training. A survey of emergency physicians showed that 88% of residents agreed or strongly agreed that palliative care skills are an important competency for EM.[11] Of the respondents in the study, 79% stated they would like to receive more training and education in palliative care, 46% reported minimal training in managing the imminently dying, and 54% reported minimal training in managing hospice patients.

WHAT ARE THE ADVANTAGES TO ENHANCED ED TRAINING IN PALLIATIVE CARE AND END-OF-LIFE CARE?

The literature indicates significant advantages of early palliative care in management of patients with life-limiting or chronically debilitating disease. For older adults with serious illness, advanced care planning conversations are associated with improved quality of life, earlier hospice referral, lower in-hospital death, and greater likelihood of wishes known and followed.[12] Moreover, for caregivers, early end-of-life conversations are associated with better bereavement adjustment, reduced trauma, and distress in decision-making.[13,14] Many patients with serious, life-limiting illness have a high incidence of ED visits, especially during the last months of life.[15] Therefore, it is increasingly important to recognize the ED as an opportunity to have advanced care planning discussion and the development of end-of-life care plans. These decisions have a profound impact on patient care. However, while there is an acknowledgement of the importance of palliative care skills in EM, there is a significant gap in palliative care training for EM residents.

Successful implementation of palliative care screening tools has shown positive outcomes in patient care. One medical center has developed a set of evidence-based screening criteria and algorithms to identify patients who might benefit from earlier palliative care involvement. In the post-implementation survey, staff reported increased confidence in palliative care skills and a 400% increase in palliative care consult requests.[15] A study using an ED-based, brief negotiated interview to stimulate conversations showed improved palliative care engagement. The duration of such ED interventions averaged 11.8 minutes.[16]

WHAT ARE SOME SCREENING TOOLS FOR USE IN THE ASSESSMENT OF PATIENTS WHO MAY BE HELPED BY PALLIATIVE CARE AND END-OF LIFE CARE?

Currently, there are multiple screening tools available for identifying palliative care patients that can be effectively integrated into the ED.[17] Of note, the Screen for Palliative and End-of-life care needs in the Emergency Department (SPEED) is a 13-symptom assessment tool that demonstrated high reliability in identifying palliative care patients in the ED.[18] A retrospective cohort study on the CARING criteria (Cancer, Admissions ≥ 2, residence in a nursing home, Intensive care unit admit with multiorgan failure, ≥ 2 Noncancer hospice Guidelines) demonstrated that they were highly predictive of death at 1 year in a hospitalized veteran population.[19] Even the simple question, "Would I be surprised if this patient dies in the next 12 months?" is highly predictive of death within 1 year, with a prospective cohort study demonstrating a positive predictive value of 84%.[20]

CONCLUSION

As our population ages, the early incorporation of palliative care as a part of patient care is increasingly urgent. The literature shows significant benefits of palliative care for patients, their families, and the healthcare system. Studies have shown that the ED can play an important role in addressing the palliative care needs of patients with serious illnesses. Beyond equipping healthcare workers in the ED with tools to recognize patients who can benefit from palliative care, it is essential to empower EM physicians with the required skills to engage patients in advanced care planning and end-of-life care conversations. This can be addressed by closing

the gap of palliative care training in EM residencies. Studies have shown that early palliative care interventions in the ED can effectively change the trajectory of patient care. They also can reduce the burden on the healthcare system by reducing ED visits, intensive care unit admissions, and length of stay. More importantly, they allow seriously ill patients to reflect on their end-of-life wishes.

CONFLICT OF INTEREST

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Case Report

Emergent use of a King laryngeal tube for traumatic intraoral bleeding: two case reports

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Maxillofacial trauma occasionally presents a serious challenge for physicians, and an orofacial injury can be considered life-threatening. It is difficult to control the bleeding and prevent airway obstruction simultaneously with conventional treatment. Herein, we share two cases in which we managed massive orofacial bleeding using a King laryngeal tube, a supraglottic airway device equipped with an inflatable balloon. Both patients had uncontrolled orofacial bleeding. In one of the patients, endotracheal intubation was possible; however, bleeding continued, and vital signs became unstable. The second patient had failed endotracheal intubation due to uncontrolled bleeding. We deployed the King laryngeal tube in both patients and achieved bleeding control and airway maintenance. Both patients were discharged without complications after 3 to 4 weeks. The King laryngeal tube method can be considered a useful management option for addressing massive orofacial bleeding that is uncontrollable with conventional treatment.

Keywords Wounds and injuries; Airway management; Hemostasis; Case reports

Capsule Summary

What is already known

Maxillofacial trauma occasionally presents a serious challenge for physicians, and orofacial injury may be considered life-threatening. It is difficult to control the bleeding and prevent airway obstruction via conventional treatments.

What is new in the current study

King laryngeal tube as the extraglottic airway device with a balloon structure may be considered a useful management option for significant orofacial hemorrhage and hematoma that are uncontrollable with conventional therapy.

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INTRODUCTION

Patients with maxillofacial trauma occasionally present serious challenges for physicians due to several factors. Two major factors that should be considered by a physician are airway maintenance and bleeding control.[1,2] Airway maintenance is easily compromised by fracture of the surrounding bony tissue and/or swelling of soft tissues.[1] In particular, any injury associated with the soft palate is difficult to compress and control bleeding due to its anatomical characteristics.

We used an alternative airway device consisting of a pharyngeal balloon, King laryngeal tube (LT) (King Systems Corp., Noblesville, IN, USA) to control the intractable bleeding and prevent airway obstruction due to a hematoma associated with orofacial trauma. The King LT is a supraglottic airway device composed of a simple airway tube with an oropharyngeal and esophageal balloon.[3] Its location of sealing is the base of the tongue, and the sealing mechanism is an inflatable balloon. In addition, it can protect the airway from aspiration with the said esophageal balloon. In our attempts, King LT was effective in controlling bleeding and preventing airway obstruction. In this article, we report two cases treated using this device. The patients provided informed consent for publication of the research details and clinical images.

CASE REPORT

Case 1. Blunt trauma case

The patient was a 53-year-old male with a history of hypertension, diabetes mellitus, and end-stage renal disease. He was brought to the emergency department after being hit by a car while riding his bicycle.

On physical examination, the patient was alert, and his general appearance was good. Upon arrival at the emergency department, the patient's blood pressure was 170/90 mmHg, pulse rate was 90 beats per minute (bpm), respiratory rate was 14 breaths/min, and body temperature was 36.0°C. The patient complained of facial pain and intraoral bleeding, and a hematoma and pulsatile bleeding were observed on his soft palate (Fig. 1). Anemia was present in the patient's initial laboratory findings, with a hemoglobin concentration of 6.6 g/dL and a hematocrit value of 18.8%. Approximately 1 hour later, the patient became drowsy, and his hemodynamic status became unstable. At this point, his blood pressure was 87/61 mmHg, and his heart rate was 104 bpm. Endotracheal intubation and blood transfusion were performed; however, the patient's hemodynamic status remained unstable. His soft palate was examined, and active pulsatile bleeding was noted. Sengstaken-Blakemore (S-B) tube insertion into the oral cavity was attempted at first, but it failed to control the bleeding. Of the two tube pieces constituting the S-B tube, the esophageal balloon was not used, and the gastric balloon was placed in the oropharyngeal cavity and then inflated by about 100 mL. We removed the S-B tube and inserted a King LT of size 4, which is an average adult size, and 60 to 80 mL of air, which is normally injected in conjunction with a size 4 device, was injected into the oropharyngeal balloon (Fig. 2). Subsequently, the active bleeding of the soft palate was stopped, and the patient became hemodynamically stable. His blood pressure increased to 130/60 mmHg, and his pulse rate dropped to 95 bpm after 30 minutes. Computed tomography imaging of the neck showed a right soft palate laceration and swelling of the adjacent structures (Fig. 3).

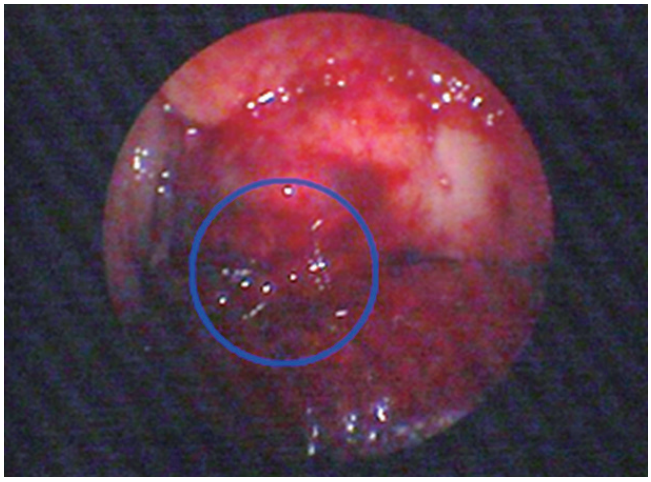

Fig. 1. Bleeding in the right soft palate is shown with laceration and contusion.

The King LT was removed the next day. On day 6 after admission, the patient was taken off the ventilator, and his soft palate laceration was sealed off spontaneously. The patient was discharged from the hospital on day 21 without any complications.

Case 2. Knife injury case

The patient was a 36-year-old male who had been stabbed in zone 3 of the neck. Upon arrival at the emergency department, his vital signs were stable. The patient presented with a drowsy mental status and intraoral bleeding. The inlet size of the stab wound was 3 cm, while the depth of the stab wound was not exactly measured; however, his sustained oral bleeding warranted the rough assumption of a through-and-through stab wound of the neck.

Computed tomography imaging (Fig. 4) revealed airway narrowing due to a hematoma and soft tissue swelling, and total airway obstruction was deemed imminent. There were four failed endotracheal intubation attempts due to his narrowed airway and

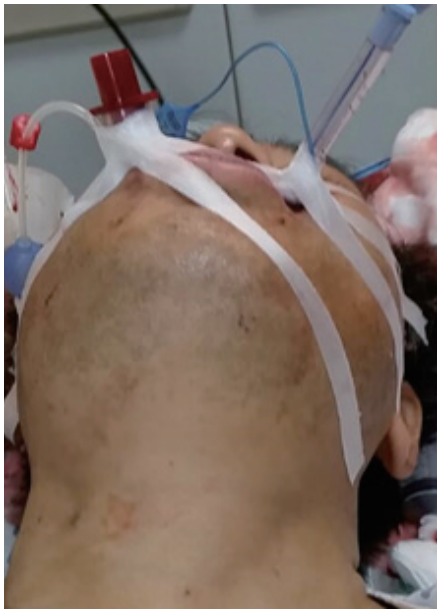

Fig. 2. The King laryngeal tube (A) was inserted for bleeding control, and the endotracheal tube (B) was inserted for mechanical ventilation. The patient provided informed consent for publication of the research details and clinical images.

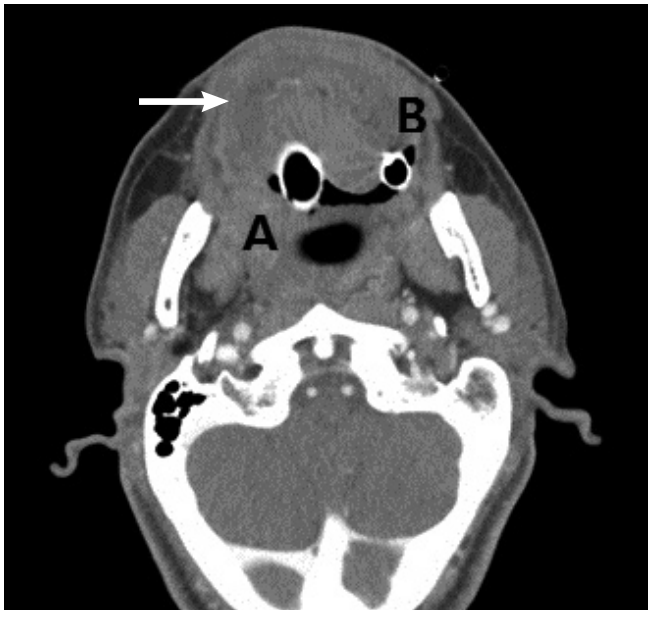

Fig. 3. Computed tomography imaging after King laryngeal tube (A) and endotracheal tube (B) insertion. The laceration is shown (arrow).

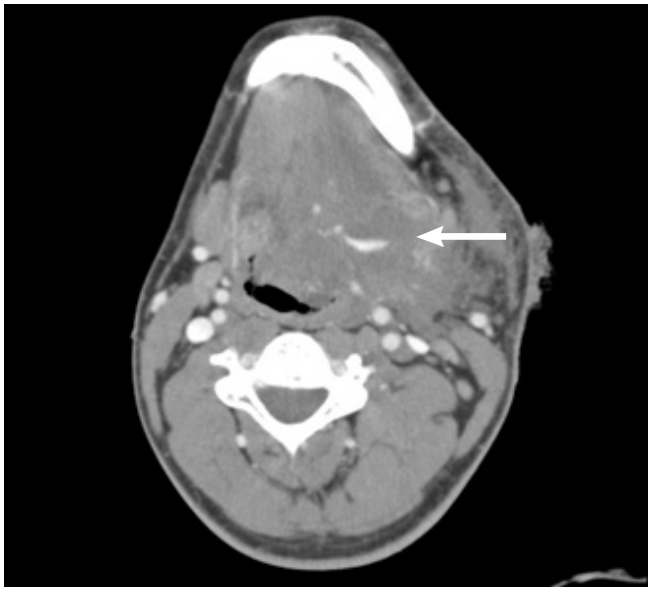

Fig. 4. The first computed tomography image of the neck revealed an active bleeding focus (arrow) in the left mandibular space.

Fig. 5. Stab wound (arrow) is in zone 3 of the neck. After a cricothyroidotomy with mechanical ventilation, the King laryngeal tube for hemostasis is inserted. The patient provided informed consent for publication of the research details and clinical images.

sustained oral bleeding. Therefore, the King LT of size 4 was used as an emergency countermeasure, and 60 to 80 mL of air was injected into the oropharyngeal balloon. After securing airway maintenance via insertion of the King LT, the otolaryngologist who performed the operation voiced concerns that airway maintenance would fail while manipulating the King LT during the operation, so we discussed measures together. Ultimately, cricothyroidotomy was performed on the patient to protect airway maintenance during the operation (Fig. 5). With this status, the patient was brought to the operating room.

In the operating room, the stab wound on the neck was explored. A bleeding site in the left lateral oropharynx was identi-

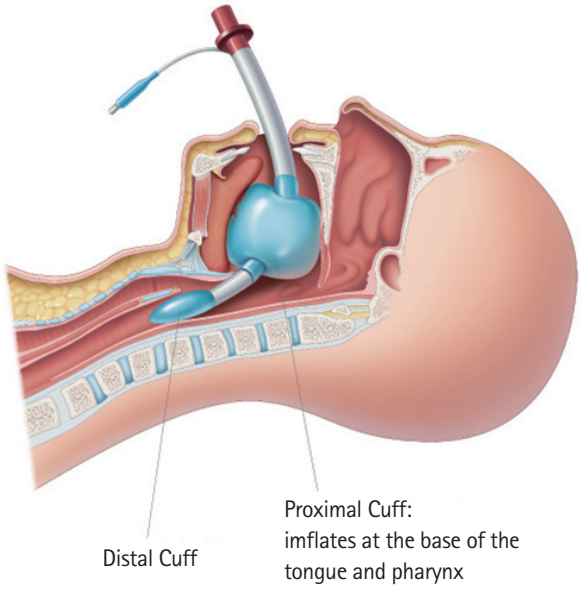

Fig. 6. The balloon of the King laryngeal tube is located between the soft palate and mandible due to its structural characteristics, and the balloon can be used to maintain hemostatic pressure.

fied, but the opening site was not found. As a result, the bleeding site in the oropharynx was packed with TachoComb (CSL Behring, Tokyo, Japan), and a Penrose drain was placed to allow drainage of the wound.

On day 6 after admission, the patient was taken off the ventilator. He was discharged from the hospital on day 29.

DISCUSSION

An orofacial injury can be life-threatening. This is a rare occurrence involving both irreversible shock and airway obstruction in some cases.[2] In such a case, it is difficult to control the bleeding and prevent airway obstruction by conventional treatment. The patient can also become hemodynamically unstable.[1,4] Transcatheter arterial embolization and other operative techniques are considered effective methods for controlling arterial bleeding[5]; however, they focus solely on managing arterial bleeding, not venous bleeding. Further, such methods are not always carried out immediately in all institutions due to the limited time allowed for preparation.[4-8]

The King LT was used in both of our cases. It was developed as an alternative airway device for patients with difficult airways; however, its structural characteristics offer an additional function. In both cases, the device's inflated balloon took on the role of a compressor, and the King LT acted as an airway-maintenance device (Fig. 6). In our hospital, the King LT was used as it was available. For adults 155 to 180 cm in height, size 4 of this device is typically used, and the oropharyngeal balloon in the King LT is inflated by 60 to 80 mL with 60 mm$H_2$0. Similar to the King LT, a supraglottic airway device with a ballooning structure in the oropharynx can be placed as an alternative. Conversely, supraglottic airway devices that do not have a ballooning structure in the oropharynx cannot be used for the purpose outlined in our cases.

As previously mentioned, the described hemostatic method incorporating the King LT is a simple treatment that can be available in underequipped institutions. There are many balloon catheters that can act as compressors (e.g., an S-B tube or a Foley catheter).[8] Among them, the S-B tube is more advantageous for controlling nasal cavity bleeding due to the long cylindrical structure of its balloon, but it is unfavorable for controlling oropharyngeal cavity bleeding. In addition, compared to the King LT, the S-B tube has the disadvantage of requiring additional procedures to protect the airway. The Foley catheter has a balloon size of 10 or 30 mL, which is too small for the adult oropharyngeal cavity. There have been attempts to use alternative airway devices, such as the laryngeal mask airway (Intavent Orthofix, Maidenhead, UK) and various surgical airway-management methods (e.g., submental intubation, cricothyroidotomy).[1,9] Although such devices can ensure airway maintenance, they are not suitable for oropharyngeal bleeding control because they do not have a structure that can inflate while applying adequate pressure to the oropharynx.

However, supraglottic airway devices with a balloon structure in the oropharynx, like King LT, can function as a compressor simultaneously with an airway device. Intubation of patients with orofacial injuries is difficult because such injuries obstruct the visual field, increasing the difficulty of inserting two tubes, i.e., for preventing airway obstruction and bleeding control, respectively.[1] Under these circumstances, the King LT device can be considered a useful management tool for patients with massive orofacial bleeding and hematomas that are uncontrollable via conventional treatment.[6,8]

In conclusion, our cases contribute evidence to the literature that a LT with an inflatable balloon, including the King LT, can be effective in managing life-threatening orofacial injuries. Furthermore, such a device is applicable in institutions where surgical treatment is not possible due to inadequate equipment. Prospective randomized studies are needed to further assess the effectiveness of a LT with an inflatable balloon in life-threatening orofacial injuries.

CONFLICT OF INTEREST

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Case Report

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Exposure to an accidental trichlorosilane spill: three case reports

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Chlorosilane is a hazardous chemical compound which is used as a raw material in the production of silicone. Despite strict restrictions, accidental spillage of chlorosilane is often reported. However, human exposure was rarely reported in the past decades and the effect on humans is barely known. We report cases of human exposure to an accidental trichlorosilane spill. Three middle aged male industrial workers visited our emergency department after exposure to trichlorosilane. They presented with shortness of breath and burns on multiple sites. Chest radiograph and laboratory studies were performed. None of the reports showed serious results and were discharged after conservative management.

Keywords Silicones; Trichlorosilane; Occupational medicine; Chemical hazard release; Case reports

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Capsule Summary

What is already known

The human clinical data after chlorosilane exposure has not been reported worldwide.

What is new in the current study

Various symptoms, including skin, respiratory, and gastrointestinal, could be developed after chlorosilane exposure.

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INTRODUCTION

Chlorosilane is a chemical compound that consists of chlorine and silicone atoms. After a chemical process, purified silicone can be derived from chlorosilane. This material is widely used in the modern industries like semiconductor manufacture. Physiological effects of chlorosilane exposure have been reported in some animal studies.[1] However, human exposure has rarely been reported and clinical effect on humans are barely known.[2] We report three cases of human exposure to an accidental trichlorosilane spill.

CASE REPORTS

On 21 July 2020, at 1:47 a.m., trichlorosilane gas spilled out from an underground chemical storage tank of an industrial plant in a city. The government announced that some part of the storage tank valve was broken. A total of 113 kL of trichlorosilane gas was released and seven plant workers were exposed to the gas. They were mechanics who came to the scene to fix the problem without adequate protective equipment. Evacuation of citizens was conducted following the national disaster protocol, and no injuries resulting from exposure to the gas among citizens were reported. Among the seven exposed workers, three visited our emergency medical center at 2:03 a.m. on the same day. They were at the scene during the early stages of the event. Each of them was exposed to trichlorosilane for a few minutes, but the exact amount of contact with the toxic material was not reported. On arrival, they appeared acutely ill, and all of them presented with mild shortness of breath and irritation of the skin. Oxygen supplementation was administered by the first responders at the scene, but the patients reported to the emergency department (ED) without oxygen. Oxygen therapy via non-rebreather mask with reservoir bag was initiated. Chest radiography and laboratory examinations were performed. General characteristics and clinical information are provided in Table 1. Chest radiographs

Table 1. General characteristics and clinical information

Variable	Case 1	Case 2	Case 3
Age (yr)	51	46	57
Sex	Male	Male	Male
Underlying disease	None	None	Hypertension
Vital signs on arrival			
Blood pressure (mm/Hg)	130/80	170/100	130/80
Pulse rate (/min)	100	120	115
Respiratory rate (/min)	20	20	22
Body temperature (°C)	36.3	36.2	36.8
Oxygen saturation (%)	100	100	100
Arterial blood gas analysis			
pH	7.397	7.382	7.381
pCO_2 (mmHg)	33.2	36.1	42.4
pO_2 (mmHg)	85.7	78.8	83.1
HCO_3^-, actual (mmol/L)	20.0	21.0	24.6
Base excess, vitro (mmol/L)	-3.8	-3.4	-0.6
Clinical presentations			
Skin			
Location	Both shoulder to hand Both knee to foot	Anterior and posterior neck Both shoulder to wrist	Genital area to anus Both scapular area Both ankle and foot
Degree of burn	1st degree	1st degree	1st degree
Respiratory	Mild	Mild	Mild
Gastrointestinal	Nausea	Nausea	Bitter taste

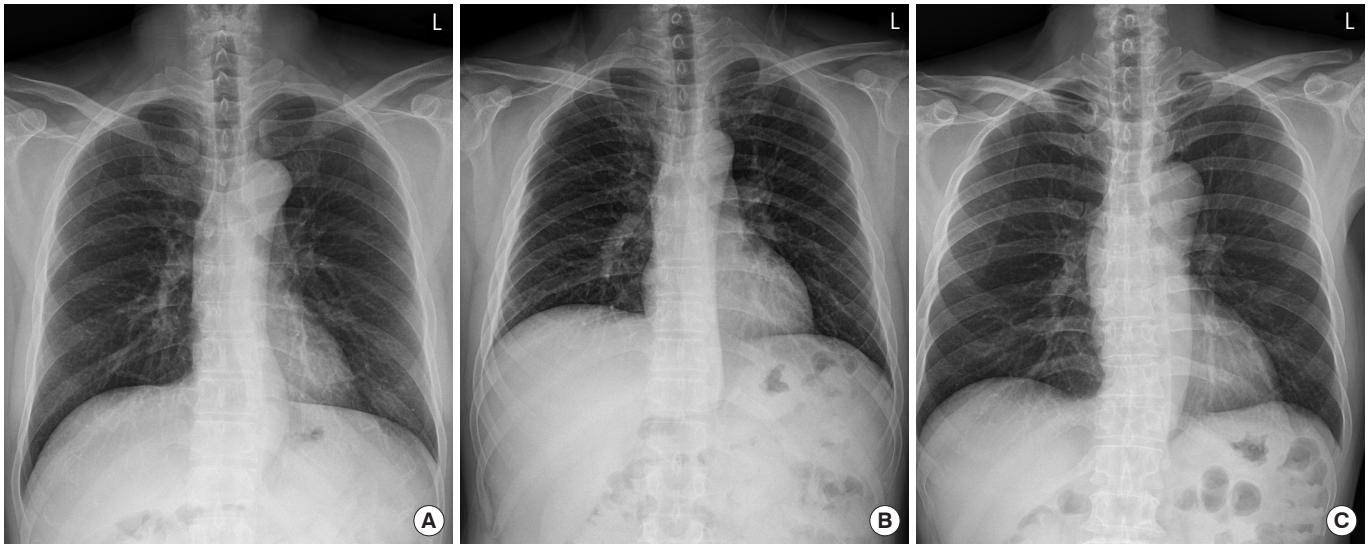

Fig. 1. Chest radiographs of the patients. (A) Case 1, (B) case 2, and (C) case 3. L, left side.

showed no significant abnormality in any of the three patients (Fig. 1). There was no significant hypoxemia in any of the patients and the amount of oxygen was gradually reduced. Injury to the skin was limited to localized redness with pain. There was no swelling, bullae formation, or necrotic changes to the skin in any patients. Symptomatic management including control of pain was provided. Respiratory symptoms were relieved 3 hours after exposure, and the patients were discharged with ointment for managing skin irritation. None of them visited the outpatient clinic or ED after the event. One month after exposure, no specific sequelae were noted in any patients. The patients provided informed consent for publication of the research details and clinical images.

DISCUSSION

The city Gumi is one of the main industrial areas in the country. The main products that are manufactured are electronics such as mobile devices, household appliances and computer parts. Several accidental chemical spills have previously been reported in this city.[3,4] This is the first report of human exposure to the chlorosilane chemical in our country.

Chlorosilane is a chemical compound which is used as a raw material in the production of silicone. It is produced by synthesis of silicon and hydrochloride by the Muller-Rochow process.[5] Trichlorosilane (CAS RN 10025-78-2) is the main product of this process and pure silicone can be derived from hydrolysis of trichlorosilane. For this reason, chlorosilane is widely used in semiconductor and photovoltaic industries, which need ultrapure silicone for their manufacture. Chlorosilane is classified as a hazardous substance. In several countries, protocols for handling, storage, transportation and a response plan of exposure control are in force. According to the National Fire Protection Association hazard classification in the United States, trichlorosilane is classified as level 3 (extremely dangerous) as a health hazard, level 4 (extreme) regarding flammability, and level 2 (moderate) regarding instability.[6] Further, this material is classified as level 4 for acute oral toxicity (H302), level 3 for acute inhalation toxicity (H331), and level 1 for skin corrosion (H314), by the hazard classification of Korea.[7] Our government legally stipulated the essential level of personal protection equipment for any person who handles trichlorosilane.[8,9] Trichlorosilane is mentioned in division 4.3 of the Hazardous Material Classification of the Department of Transportation in the United States, which means 'dangerous when wet' hazardous material.[10] Storage and transportation of the trichlorosilane, like the material of the storage container, degree of filling in the storage or maintenance temperature, are strictly controlled by documented protocols.

Despite precautions, around 70 cases of chlorosilane spills were reported during a period of 18 years in the United States.[11] One case of human exposure of chlorosilane was reported in 1984.[2] In that case, 4,560 L of tetrachlorosilane were spilled which is thousands of times less than the spill in our case. A total of 28 people visited medical facilities and no death or hospitalizations were reported in that spill in the United States.

Trichlorosilane is a liquid in its standard state and vaporizes quickly on exposure to air. Once it spills, it reacts with water in the air rapidly. Hydrochloride gas, one of the main products of hydrolysis, is released concurrently with chlorosilane. Clinical effects of chlorosilane exposure should be considered as exposure to hydrochloride acid. Skin and eyes are the major route of direct contact. Nasal or intraoral mucosa may be injured. Both chlorosilane and hydrochloric acid have a corrosive effect. Irritation of the nasal, oral, oropharyngeal, respiratory tract or skin after exposure causes clinical symptoms and signs. In severe cases, esophageal and/or deep gastric burns or mucosal necrosis could develop after oral ingestion. Permanent visual loss after ocular exposure, tissue necrosis after skin exposure and acute lung injury after inhalation has been reported rarely.[6] Systemic toxicity including hypotension, cardiac arrhythmia, metabolic acidosis, renal failure, disseminated intravascular coagulation, and cardiac arrest could develop in fatal cases. The metabolic pathway of the substance and accumulation in the human body after exposure to the material is under investigation.[12] In the previous report of chlorosilane exposure in 1984, they reported that the patients had lacrimation, rhinorrhea, headache, coughing, and burning sensation of the mouth and throat.[2] In our case, patients mostly showed skin irritation and shortness of breath. There is no specific antidote for chlorosilane exposure. Supportive care with symptomatic management is the mainstay of treatment. No delayed complications of chlorosilane exposure have been reported yet; no data on carcinogenicity, developmental or reproductive problems have been reported either.[12]

In conclusion, we report three cases of massive trichlorosilane exposure to humans. Symptoms are relatively minimal and those exposed were discharged after management in the ED without hospitalization. Long-term complications should be evaluated, and industrial safety instructions must be strictly followed to prevent such accidents in the future.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Images in Emergency Medicine

Macklin effect in acute asthma exacerbation

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A 25-year-old male patient presented with persistent cough and deteriorating dyspnea. He regularly used short-acting beta$_2$-agonist inhalers for asthma. Arterial blood gas analysis revealed hypoxemia (PaO_2 62 mmHg). Spirometry showed that the forced expiratory volume in 1 second (FEV_1) was 30%, the forced vital capacity (FVC) was 60%, and the FEV_1 to FVC ratio was 55% of predicted values. Chest computed tomography demonstrated a small pneumomediastinum (Fig. 1). He received nebulized long-acting beta$_2$-agonists, muscarinic antagonists, corticosteroids, and oxygen therapy. He was discharged 3 days later. Repeat imaging revealed no evidence of pneumomediastinum, and spirometry values were unremarkable. Written informed consent for publication of the research details and clinical images was obtained from the patient.

Macklin[1] first described the "Macklin effect" in 1939; this explains the pathophysiology of spontaneous pneumomediastinum, which occurs when air leaks through small alveolar ruptures to the surrounding bronchovascular sheaths and spreads into the mediastinum. Spontaneous pneumomediastinum happens in 1 in 8,000 to 1 in 42,000 of emergency admissions, with common triggers including acute asthma exacerbation, respiratory tract infection, strenuous physical activity, coughing, and vomiting.[2,3] The presence of air in the pulmonary interstitium and adjacent to the bronchovascular sheaths strongly suggests the Macklin effect and obviates the need for further diagnostic investigations.

To avoid unnecessary hospitalization of patients with spontaneous pneumomediastinum, Okada et al.[4] have proposed a five-question guide. Patients without temperature >38°C, oxygen saturation <96%, progressive symptoms, vomiting at the onset, and anxiety are eligible for ambulatory care. The present case illustrates the self-limited nature of spontaneous pneumomediastinum by demonstrating rapid and complete resolution with conservative management. Follow-up imaging may not be needed in selected patients.

Capsule Summary

What is already known

The Macklin effect explains the pathophysiology of spontaneous pneumomediastinum, which can be observed in acute asthma exacerbation.

What is new in the current study

Spontaneous pneumomediastinum is usually self-limited.

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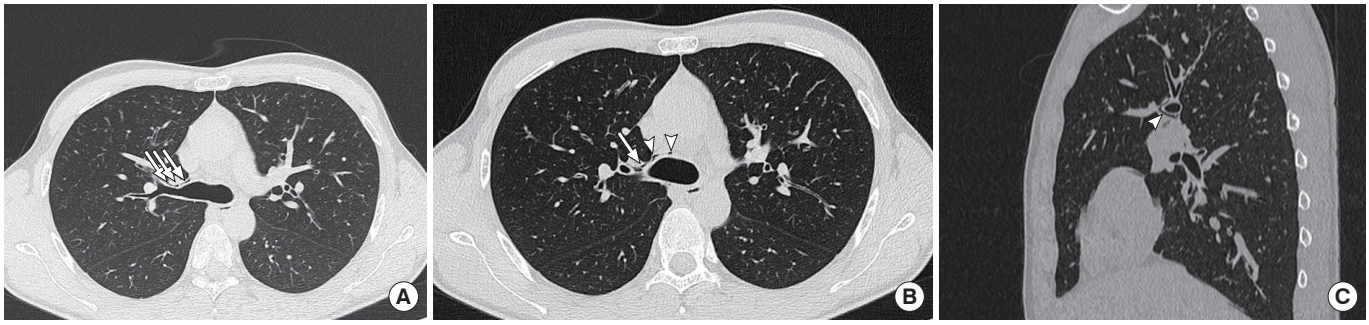

Fig. 1. Axial chest computed tomography image (lung window) showing (A) linear collection of air (arrows) adjacent to the bronchovascular sheath (Macklin effect) and (B) centripetal spread of air along the bronchovascular sheath to the right hilum (arrow) and to the mediastinum (arrowheads). (C) Sagittal chest computed tomography image (lung window) showing the presence of air around the right main bronchus (arrowheads).

CONFLICT OF INTEREST

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Instructions for Authors

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5. **Case report:** Cases must be brief descriptions of a previously undocumented disease process, a unique unreported manifestation or treatment of a known disease process, or unique unreported complications of treatment regimens. Entities previously reported in the emergency medicine literature will not be considered, and those reported elsewhere must be extremely important or pertinent to be considered. Case reports should contain a title page, capsule summary, abstract and keywords, main text, article information, and tables and figures. The main text should include introduction, narrative, and a discussion focusing on the implications of the case reported and should not exceed 1,500 words. The narrative abstract should not exceed 150 words. Tables and/or figures are limited to 4 and the number of references is limited to 15.
6. **Brief research report/review:** Brief research report/review should contain a title page, capsule summary, abstract and keywords, main text, article information, and tables and figures. Brief research reports are short manuscripts of original research that include preliminary results or small-scale studies. The main text should not exceed 2,000 words. The structured abstract (Objective, Methods, Results, and Discussion) should not exceed 250 words. Tables and/or figures are limited to 5 and the number of references is limited to 20. Brief reviews are short articles that summarize current research on a specific topic and provide evidence-based recommendations. The main text should not exceed 2,000 words. The narrative abstract should not exceed 200-words. Tables and/or figures are limited to 5 and the number of references is limited to 20.
7. **Correspondence (letter to the editor):** Correspondences or letters to the editor include discussions, observations, opinions, corrections, and comments on topics appearing in CEEM; very brief reports or other items of interest may be accepted. Letters discussing a CEEM article should be received within 8 weeks of the article's publication. The original authors will be given the opportunity to reply. Letters of political or oth-

er topics unrelated to the science of medicine, as well as those containing personal criticisms, will not be published. Correspondences should contain a title page, main text, article information, and tables and figures. Letters should not exceed 1,000 words and should not include more than 2 figures and/or tables. The number of references is limited to 10.

8. **Editorials:** Editorials are authoritative comments or opinions on controversial matters with significant implications for emergency medicine; or, if qualified, thorough analysis and criticism of articles appearing in CEEM. Editorials should contain a title page, main text, article information, and tables and figures. Editorials should not exceed 1,500 words and should not include more than 5 figures and/or tables. The number of references is limited to 50.
9. **Images in Emergency Medicine:** Images are photographs of interesting or classic presentations of disease, accompanied by one paragraph description of the patient's presentation and a one to two paragraph discussion of the final diagnosis and relevant teaching points. Images should contain a title page, capsule summary, main text, article information, and tables and figures. Images should not exceed 250 words and should not include more than 5 figures and/or tables. The number of references is limited to 10. Images may include radiographs or microscopy.
10. **Other submission:** Critical Care Corner present brief diagnostic or therapeutic "pearls" that should be very useful to practicing emergency and critical care physicians. This section should include a capsule summary and will be limited to 500–1,000 words, 10 references, and a single table or figure. Free open access medical education at home discuss information that we believe would be of interest to the readers of CEEM. In this section you can take on a variety of formats (e.g., audio, text, etc.). Commentaries will include discussion about a recent study or an important issue in emergency medicine (maximum 1,500 words, 20 references, 5 tables and/or figures).

Table 1. shows the recommended maximums of manuscripts according to publication type; however, any article longer than these limits should be discussed with the editor.

Table 1. Recommended maximums for articles submitted to CEEM

Publication type	Text (word)	Abstract (word)	Capsule summary	Table and Figure	Reference
Original research	4,000	250, structured	Required	10	50
Clinical review	5,000	250	Required	NL	NL
Systematic review	5,000	250, structured	Required	NL	NL
Study protocol	4,000	250, structured	Required	10	50
Case report	1,500	150	Required	4	15
Brief research report	2,000	250, structured	Required	5	20
Brief review	2,000	200	Required	5	20
Correspondence	1,000	NR	NR	2	10
Editorial	1,500	NR	NR	5	50
Image	250	NR	Required	5	10
Critical Care Corner	1,000	NR	Required	1	10
Commentary	1,500	NR	NR	5	20

NL, no limit; NR, not required.

B. Reporting Guidelines for Specific Study Designs

For the specific study design, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, it is recommended that the authors follow the reporting guidelines listed in the following table. If Table 2 does not include the study design relevant to the research design, authors are encouraged to consult other reporting guidelines. A good source for reporting guidelines is the EQUATOR Network (https://www.equator-network.org/) and the United States National Institutes of Health/National Library of Medicine (https://www.nlm.nih.gov/services/research_report_guide.html).

C. Preparing Documents for Publication

All text files should be in Microsoft Word format (DOC or DOCX) and all figures need to be in JPG/JPEG/TIFF format. Text or figure files should not be uploaded as PDF files.

The manuscript should use a 12-point font size and should be double spaced, with a plain font such as Times New Roman, Sans-Seriff, or Helvetica.

The manuscript must be written in English. The use of acronyms and abbreviations is discouraged and should be kept to a

Table 2. Reporting guidelines for study designs

Initiative	Type of study	Source
CONSORT	Randomized controlled trial	http://www.consort-statement.org
STARD	Studies of diagnostic accuracy	https://www.equator-network.org/reporting-guidelines/stard/
PRISMA	Preferred reporting items of systematic reviews and meta-analyses	https://www.prisma-statement.org/
STROBE	Observational studies in epidemiology	https://www.strobe-statement.org/
CARE	Case reports	https://www.equator-network.org/reporting-guidelines/care/
SPIRIT	Study protocols	https://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/

minimum. When used for the first time, the abbreviation should be added in parentheses after the written-out form. Radiation measurements and laboratory values should be in accordance with the International System of Units (SI).

The manuscript should be organized in the following order: full title page (including all the author details, acknowledgments, and statements on conflicts of interest) as a separate file; blinded main document in a single file, which starts with a blinded title page (title only), abstract and keywords, Introduction, Methods, Results, Discussion, references, tables, and figure legends.

CEEM performs double-blinded review of the submitted manuscripts. The authors' names, their affiliations, or any other remarks that may identify the authors should not appear in the blinded main document, figures, appendix, and supplementary materials for the blinded review. In case identifying details are found, the Editorial Office will ask the corresponding author to re-upload the files after masking such details or will delete them on behalf of the authors before sending the manuscript for an external peer review.

The names and locations (city and state/province or country) of the manufacturers of equipment and generic names should be given.

Please also refer to the most recent articles published in CEEM for style.

D. Registration of Clinical Trial Research

It is recommended that any research that deals with a clinical trial be registered with a primary national clinical trial registration site, such as https://cris.nih.go.kr/, or other websites accredited by the World Health Organization as listed at https://www.who.int/clinical-trials-registry-platform.

E. Full Title Page

Include the following items on the unblinded full title page.

1. **Title:** Titles should not exceed 50 words.
2. **Full names, affiliations, and order of all authors:** Each author's full name, not initials, must be provided in the order of first name, middle name (if it exists), and last name. When authors from different institutions/addresses are included, the authors should be matched with their organizations by placing the relevant organization number in superscript after each author's name.
3. **Contact information** of the corresponding author (address and e-mail).
4. **Type of manuscript**
5. **Abbreviated title:** The abbreviated title will be printed at the top of each page of the published paper and should be no longer than 50 characters (including spaces and punctuation).
6. **Capsule summary:** Papers submitted for publication in original research, clinical/systematic review, study protocol, case report, brief research report/review, image, and critical care corner must include a capsule summary. It should not contain abbreviations and should be composed of two following statements: (1) What is already known and (2) What is new in the current study.
7. **Article information:**
   - *Ethical statement:* When reporting experiments with human or animal subjects, the authors should indicate whether they received approval from the IRB for the study and whether informed consent from the patients was obtained.
   - *Conflict of interest statement:* All funding, other financial support, and material support for the work, if it exists, should be clearly identified in the conflict of interest statement. If no conflicts of interest exist for any of the authors, this should be noted.
   - *Funding:* Funding for the research should be provided here. Providing a FundRef ID is suggested, including the name of the funding agency, the country, and if available, the number of the grant provided by the funding agency. If the funding agency does not have a FundRef ID, please ask the agency to contact the FundRef registry (e-mail: fundref.registry@crossref.org). A detailed description of the FundRef policy can be found at https://www.crossref.org/services/funder-registry/.
   - *ORCID:* Providing Open Researcher and Contributor ID (ORCID) of all authors are recommended. ORCID is available through registration via ORCID website (https://orcid.org). Registration is free to all researchers in the world.
   - *Author contributions:* For transparency, the contributions of all authors must be described using CRediT (Contributor Roles Taxonomy; https://credit.niso.org/) roles: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing–original draft; Writing–review & editing.
   - *Acknowledgments:* Those who contributed to the work, but did not fulfill the requirements for authorship, should be included in the Acknowledgments.

F. Main Document (Original Research)

The main document is a blinded document for review and should contain the following components in a single Microsoft Word

file, with each component starting on a separate page: blinded title page, abstract, main body, references, tables, and figure legends. Images should not be embedded in the main document. Tables should not be mixed with the text. The tables should be placed collectively after the references, each on a separate page.

1. **Blinded Title Page:** On the blinded title page, only the title of the manuscript should appear. The authors' names and other details should not be included.

2. **Abstract:** The abstract should be 250 words or less, and divided into the following subheadings: Objective, Methods (including information on design, setting, participants, interventions, and main outcomes measured), Results, and Conclusion. In your results, you should emphasize the magnitude of findings over test statistics, ideally including the size of effect and its confidence intervals for the principal outcomes. The abstract of a study protocol should include the following section; Objective, Methods, and Discussion (implication of study). Reference citations should not be used in the abstract. Abbreviations should be minimized and, if used, must be defined within the abstract by the full term followed by its abbreviation in parentheses. Three to five keywords (index terms) should appear after the abstract. For the selection of keywords, refer to the list of Medical Subject Headings (MeSH; http://www.ncbi.nlm.nih.gov/mesh). If the study is a randomized controlled study, the trial's registry number should appear at the end of the abstract (e.g., ClinicalTrials.gov: NCT01616745.)

3. **Main Body**

1) **Introduction:** The most effective introduction sections are less than 500 words, and concisely argue how the topic is new, scientifically important, and clinically relevant. Usually, we recommend the following three paragraphs. The first paragraph to describe the circumstances or historical context that set the stage and led you to investigate the issue. The second to describe why your investigation is consequential: What are its potential implications? How does it relate to issues raised in the first paragraph? Why is this specific investigation the next logical step? The last to explain the goals of this investigation: clearly state the specific research objective or hypothesis and your primary outcome measure.

2) **Methods:**

- The methods should include subsections with contents that detail the study design (include human subject or animal use committee review), study setting and population, study protocol, measurements or key outcome measures, and data analysis (include sample size determinations and other relevant information, the names of statistical tests, and the software used).
- The role of funding organizations and sponsors in the conduct and reporting of the study should be included here.
- When equipment is used in a study, provide in parentheses the model number, name, and location of the manufacturer.
- If citing an in-press paper for the description of methods (i.e., when referencing methods used in a prior study, which is currently in press), please upload a copy of the in-press paper for the editor and reviewers. This in-press material will be handled with appropriate confidentiality.
- Research involving human subjects or animals must meet local legal and institutional requirements and generally accepted ethical principles such as those set out in the Nuremberg Code, the Belmont Report, or the Declaration of Helsinki.
- Manuscripts reporting data involving human subjects must indicate a positive review by an IRB or equivalent. This requirement includes studies that qualify for IRB expedited status. Most institutions require IRB review of studies that qualify for exempt status and that this determination be made by the IRB, not by the authors. The "Methods" section of the manuscript must explicitly state that IRB approval was obtained (including IRB number), that the IRB determined the study was exempt, or that the study did not involve human subjects (e.g., publicly available and previously de-identified information from national data sets, or other studies not meeting the definition of human subjects research as set forth in US Code of Federal Regulations, Title 45, Part 46; additional information available at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/research-involving-coded-private-information/index.html). The "Methods" section should also indicate the type of consent used (written, verbal, or waived), and confirm that consent was obtained from all subjects (unless waived by the IRB).
- Manuscripts reporting the results of investigations of live vertebrate animals must indicate approval by an Animal Care and Use Committee or equivalent. We reserve the right to request submission of IRB or Animal Care and Use Committee documentation at any time.
- When working with administrative databases, authors should be diligent in checking the validity of variables

(e.g., by cross-checking with other variables in the dataset) and patterns of missing data. Both factors can bias results. Authors should also recognize that causal inferences are generally limited when interpreting results from administrative data sources. For analyses using probability samples, care should be taken to use clusters, strata and weights in analyses and that substantially restricting such samples (e.g., to small age groups) may create bias and unusual associations between variables.

- All papers involving surveys are screened by one of two Editorial Board members with formal training in survey science; well over half are declined at this screening phase due to weak methodology. Authors considering performing survey projects and submitting survey manuscript should review the following commentary, which discusses some of the key features of survey methodology: Mello MJ, Merchant RC, Clark MA. Surveying emergency medicine. Acad Emerg Med 2013;20(4):409-12.

3) **Results:** Results should be concisely stated and include the statistical analysis of the data presented. Results presented in tabular or graphic form should be referred to in the text, but the material should not be presented again. In addition to the data collected in the study, the results should also indicate the success of protocol implementation (e.g., was blinding successful, was there a high interater reliability?). In keeping with the recommendations of the Institute of Medicine regarding gender-specific research, we ask that all papers reporting the outcomes of clinical trials report on men and women separately unless a trial is of a sex-specific condition (such as endometrial or prostatic cancer).

4) **Discussion:** Briefly summarize the results and how they relate to your area of investigation. Consider only those published articles directly relevant to interpreting your results and placing them in context. Do not stress statistical significance over clinical importance. Do not use a separate conclusion section, but instead append it as the last paragraph of the Discussion beginning with something like: "In summary, ..." Take care that the conclusion is restricted to what can be justified by your experimental results. Discuss shortcomings and biases related to study design and execution. Highlight areas where future investigations and/or different methods of analysis might prove fruitful.

4. References

- References should be numbered consecutively in the order in which they are first mentioned in the text. Every reference must be cited at least once in the text. Each reference should be cited as [1], [1,4], or [1-3], at the end of the related sentence in the text.
- The abbreviated journal title should be used according to the NLM Catalog: Journals referenced in the NCBI Databases (https://www.ncbi.nlm.nih.gov/nlmcatalog/journals) and the Korean Medical Journal Information (https://journals.koreamed.org/).
- If there are six or fewer authors in a reference, then all the names of the authors should be listed. If the number of authors is greater than six, list the initial three authors, and then abbreviate the rest of the authors with by "et al."
- Personal communications and unpublished data should be cited in the body of the paper in parentheses, not listed in the references section. Manuscripts that have been accepted for publication may be listed as "In press." Manuscripts that have been submitted or are under revision but have not been accepted may not be cited as references.
- The use of abstracts that have not been published as full manuscripts is discouraged.
- Authors are responsible for the accuracy and completeness of the references and text citations.
- The style and punctuation for references should follow the format illustrated in the following examples. For types not addressed in these examples, the author is referred to the Citing Medicine: The NLM Style Guide for Authors, Editors, and Publishers (https://www.ncbi.nlm.nih.gov/books/NBK7256/).

Journal Article

1. Kang BH, Jung K, Huh Y. Suicidal intent as a risk factor for mortality in high-level falls: a comparative study of suicidal and accidental falls. Clin Exp Emerg Med 2021;8:16-20.
2. Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000;343:230-8.
3. Turner CH, Robling AG. Mechanisms by which exercise improves bone strength. J Bone Miner Metab 2005;23 Suppl:16-22.

Book and Book Chapter

4. Buchman A. Clinical nutrition: a guide for gastroenterologists. Thorofare, NJ: Slack Incorporated; 2005.
5. Goadsby PJ. Pathophysiology of headache. In: Silberstein SD, Lipton RB, Dalessio DJ, ediors. Wolff's headache and other head pain. 7th ed. Oxford, UK: Oxford University Press; 2001.

p.57-72.

Online

6. Centers for Medicare & Medicaid Services, U.S. Department of Health and Human Services. CMS proposals to implement certain disclosure provisions of the Affordable Care Act [Internet]. Baltimore, MD: Centers for Medicare & Medicaid Services; 2011 [cited 2022 Jun 10]. Available from: https://www.cms.gov/newsroom/fact-sheets/cms-proposals-implement-certain-disclosure-provisions-affordable-care-act.

5. **Tables:** Tables should be created using the table tool in MS Word. Tables must be referenced in the text in sequential order. Each table should be submitted on a separate page with a descriptive title. Define all abbreviations in a footnote to the table. For special remarks, lower case letters in superscripts [a], [b], [c], [d], [e]…. should be used and should also be defined in a footnote. If a table has been previously published should be accompanied by the written consent of the copyright holder and the footnote must acknowledge the original source.
6. **Figures and Legends:** Figures must be referenced in the text in sequential order. Figures should clarify and augment the text. Put figure legends on a separate page. Figures in PDF are not of acceptable quality for publication. Photographs must be submitted electronically according to the following specifications: color photographs should be saved as TIF files in RGB at a minimum of 12.5 cm in width at 300 dpi; black and white photographs should be saved as TIF files in grayscale at a minimum of 12.5 cm in width at 300 dpi. Figure reproduction cannot improve on the quality of the originals. Any special instructions about sizing, placement, or color should be clearly noted. Symbols, arrows, or letters used to identify parts of the illustration must be explained clearly in the legend. The illustrations of pathological tissue should state clearly the type of stain (e.g., H&E, ×400), and the main contents should be marked by signs or arrows on the picture. If a figure has been previously published should be accompanied by the written consent of the copyright holder and the legend must acknowledge the original source. The ability to reproduce figures and photographs in color is limited, and at the discretion of the Editor-in-Chief. In some circumstances, color figures and photographs may be published.
7. **Video Clips:** Videos of interest to our readers are published in this online-only section of the journal. Each submission must be accompanied by a brief written description of the video contents. Examples of acceptable content include the demonstration of a procedure, an overview of a disease process, an interview with an author, and any other creative or professional presentation of useful emergency medicine-related content. Videos should not exceed 10 minutes in length, and will undergo peer review. The preferred formats are Apple QuickTime, MPEG, or Windows Media. Upload the video as "supplemental materials for online publication." The section editor will contact you if there are file size, quality, or compatibility issues with the video you submit.

V. Submitting Manuscripts to CEEM

To submit to CEEM, please first check the Checklist before Submission (https://www.ceemjournal.org/authors/checklist.php). When you are ready, submit according to the following instructions.

A. First Submission

Log in is required for the first-time user. If you do not have an account, click "Register" button and create your account. ID should be your e-mail address being actively used now. If you have an account but forgot your password, click the "Forgot Your Password?" button. Your password will be given to your e-mail address on your request. To begin, enter your User ID and password into the boxes provided, and click. At the welcome screen, click "Submit a Manuscript" button. After that, click "New Submissions" button to submit your new manuscript and follow steps 1-8.

- *Step 1.* Title, abstract, and corresponding author: Choose the manuscript type, and enter your title and abstract into the appropriate boxes. If you need to insert a special character, click the "Special Characters" button. If you are submitting a manuscript that does not require an Abstract, please type N/A in the Abstract box. Please click the check box if the corresponding author is the first author.
- *Step 2.* Authors: Enter the personal information for the first author in the boxes under "Add the First Author."
- *Step 3.* File upload: The manuscript file (main text) should not include the authors' names or affiliations. Upload and select the correct file designation for each.
- *Step 4.* PDF conversion: Merged file will be created in a PDF format.
- *Step 5.* Cover letter and additional Info: Please write down the additional notes to the Editor-in-Chief.
- *Step 6.* Suggest reviewers: This is particularly important when the manuscript deals with a highly specialized subject. Use the fields below to give us contact information

for each suggested reviewer. Please note that the journal may not use your suggestions, but your help is appreciated and may speed up the selection of appropriate reviewers.

- *Step 7.* Preview: Review the information in the Preview chart for correctness; make changes if needed. If you have not completed a required step, you will not be able to submit your manuscript.
- *Step 8.* Submit: Once it is submitted, you will be able to monitor the progress of your manuscript through the peer review process.

B. Following Submission

- A Major Revision and a Minor Revision should be submitted within 180 days and 60 days, respectively, of the decisions. Otherwise, the manuscript will be treated as a new submission.
- Please carefully read and follow the instructions written here and those included in the manuscript decision e-mail.
- To start the submission of a revised manuscript, log in at https://submit.ceemjournal.org/. Click the "Manuscripts in Revision" queue in the "My Manuscripts" area. Then, find the submission you wish to start the revision process for and click on the "Create Revision" link for that manuscript.
- To continue with a revised manuscript that has yet to be submitted, click on the "Revised Manuscripts in Draft" queue in the "My Manuscripts" area. Find the submission you wish to continue with and then click on the "Continue Submission" button.
- Please submit a point-by-point response to the editor/reviewer comments by directly pasting it in the box provided in "View and Response to Decision Letter" page as well as by uploading the same as a Microsoft Word document file (DOC/DOCX) on the "File Upload" page.
- Any changes in the authorship should be reported to the editor in the cover letter.
- For file uploading, if you have updated a file, please delete the original version and upload the revised file. To designate the order in which your files appear, use the dropdowns in the "order" column on the "File Upload" page.
- For a revision, we require two copies of the Main Document. Each should be a Microsoft Word document. The FIRST COPY should represent the final copy of the manuscript highlighting all changes.
- The SECOND "annotated" COPY should have changes tracked using the track changes function in Microsoft Word with marginal memos indicating changes, which is optional. (e.g., E-1 indicates a response to comment #1 of the Editor; R2-3 indicates a response to comment #3 of Reviewer #2).

VI. Review Process of CEEM

1. The submitted manuscript will first be evaluated at the Editorial Office regarding the completeness of the submitted materials and their suitability to CEEM. Modifications/corrections may be requested from the authors at this stage before starting the peer review.
2. Submitted manuscripts will generally be reviewed by the editors, as well as two to three peer reviewers who are experts in the submitted subject matter and the peer reviewers will make suggestions to the editor(s).
3. CEEM performs double-blinded peer review of the submitted manuscripts. Neither the peer reviewers nor the authors are revealed to each other. Authors may suggest preferred and non-preferred reviewers during manuscript submission. However, the ultimate selection of the reviewers will be determined by the editor(s).
4. The authors can monitor the progress of the manuscript throughout the review process at the submission site (https://submit.ceemjournal.org/).
5. Submitted manuscripts will be rendered one of the following decisions:
   - Accept: The manuscript is accepted for publication.
   - Minor Revisions: A revision needs to be submitted within 60 days of the decision. Otherwise, the manuscript will be treated as a new submission.
   - Major Revisions: A revision needs to be submitted within 180 days of the decision. Otherwise, the manuscript will be treated as a new submission.
   - Reject, Resubmission allowed: The authors are allowed to resubmit their work. However, it is effective only when they are able to respond to the various reviewer comments and make substantial changes to the study. The resubmitted manuscript will be treated as a new submission.
   - Reject, No further consideration: The paper will no longer be considered for publication.
6. The decision to accept a manuscript is not based solely on the scientific validity and originality of the study content;

other factors are considered, including the extent and importance of new information in the paper as compared with that in other papers being considered, the journal's need to represent a wide range of topics, and the overall suitability for CEEM.

7. Decision letters usually, but not always, convey all factors considered for a particular decision. Occasionally, the comments to the authors may appear to be inconsistent with the editorial decision, which takes into consideration reviewers' comments to the editor, as well as the additional factors listed above.
8. If the author(s) believe that the journal has rejected their article in error, perhaps because the reviewers have misunderstood its scientific content, an appeal may be submitted by e-mail to the Editorial Office (office@ceemjournal.org). However, appeals are ineffective in most cases and are discouraged.

VII. Article Processing Charges

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Checklist before Submission

☐ Authors have written the manuscript in compliance with Instructions to Authors and Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org) from the International Committee of Medical Journal Editors, and the Guideline of Committee on Publication Ethics (https://publicationethics.org).

☐ Authors have omitted names and organizations in the manuscript submitted for review.

☐ The title page should include a title; authors' names and academic degrees, affiliations; corresponding author(s)' name(s), contact information; ORCID; acknowledgments; COI/funding; running title; and capsule summary.

☐ A running title should be given in 50 characters or shorter including spaces.

☐ The abstract should be divided into Object, Methods, Results, and Conclusions; it is within 250 words for Original Articles. Reviews (including systematic reviews) and Case Reports have abstracts in a single paragraph whose structure is up to author's discretion within 200, 150 words, respectively.

☐ The abstract should be included in the manuscript, regardless of whether it is included in the submission system.

☐ Three to five keywords should be included (those recommended in MeSH; http://www.ncbi.nlm.nih.gov/mesh).

☐ Information regarding approval of an institutional review board and obtaining informed consent should be mentioned in the Method section.

☐ The number of references is limited to 50 (for original article), 60 (for study protocol) or 15 (for case report).

☐ Each figure should be uploaded as a separate file and should not be included in the main text. The file name of each figure should be the figure number.

☐ Figures must be prepared in no less than 300 dpi.

☐ All authors have completed the Copyright Transfer Agreement and COI Statement.

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