Study protocol

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**Augmented-Medication CardioPulmonary Resuscitation (AMCPR) trial:**

Study protocol for a randomized controlled trial

**Abbreviated title:** AMCPR trial

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ABSTRACT

Background: Because most previous studies about the usefulness of vasopressin during resuscitation had been physician-oriented, it is necessary to evaluate with patient-centered. The aim of this study is to investigate whether Augmented-Medication CardioPulmonary Resuscitation (AMCPR) would enhance chance to return of spontaneous circulation (ROSC) in patients with out-of-hospital cardiac arrest.

Methods: This is a double-blind, single-center, randomized placebo-controlled trial conducted in the emergency department in tertiary, university-affiliated hospital in Seoul, Korea. A total of 148 adult patients with non-traumatic, non-shockable, out-of-hospital cardiac arrest those who have initial diastolic blood pressure above 20 mmHg will be randomly assigned to two groups of 74 patients (1:1 ratio). Patients will receive intravenously a dose of 40 IU of vasopressin with epinephrine, or a placebo with epinephrine. The primary endpoint is a sustained ROSC (over 20 minutes). Secondary endpoints are enhancing diastolic blood pressures, end-tidal carbon dioxide levels, acidosis, and lactate levels during resuscitation.

Discussion: AMCPR is a trial about tailor made medication for selected patients during resuscitation. This is a first randomized control trial to find patients who will be help to ROSC by vasopressin. This study will provide evidence about the effect of additional administration of vasopressin with epinephrine to increase the ROSC rate.

Keywords: Out-of-hospital cardiac arrest; Vasopressin; Cardiopulmonary resuscitation; Epinephrine

CAPSULE SUMMARY

What is already known

* A combination of vasopressin and epinephrine for patients with out-of-hospital cardiac arrest
has shown not to improve outcomes.

What is new in the current study

Although the routine combination of vasopressors has not been shown effective, individualizing resuscitation to the appropriate hemodynamic goal would be necessary for adult patients with non-shockable, non-traumatic out-of-hospital cardiac arrest.
BACKGROUND

Out-of-hospital cardiac arrest is a major public burden contributing to morbidity and mortality worldwide\(^1\)\(^-\)\(^3\). Recent epidemiological study reported that over 1 in 10,000 patients suffered from cardiac arrest and survival rates were lower than 20\%\(^4\). To improve outcome, guidelines of the American Heart Association and European Resuscitation Council have strengthened the chain of survival, including early recognition, effective chest compression, timely defibrillation, and prompt use of vasopressors\(^5\)\(^-\)\(^7\). Among various vasopressors, epinephrine and vasopressin had been considered as the candidates to improve chance of return of spontaneous circulation (ROSC)\(^8\),\(^9\). Especially since vasopressin stimulate smooth muscles to vasoconstriction without catecholamine effect, it can be used by different way with epinephrine\(^10\). However, current guidelines did not recommended vasopressin can be able to replace with epinephrine (class III, LOE) based on the previous research that the additional use of vasopressin did not prove any outcome benefit compared to epinephrine alone\(^11\)\(^-\)\(^13\). However, previous controlled trials did not get any real-time change of diastolic blood pressure or end-tidal carbon dioxide levels which had been considered as the surrogate marker of organ perfusion\(^11\),\(^12\). Moreover, the use of vasopressin for all patients with cardiac arrest could mask little advantage of the combination therapy especially in patient with using epinephrine only would be enough to increase vital-organ perfusion\(^13\),\(^14\).

Although resuscitation guidelines remain uniform across all cardiac arrest patients, individualizing resuscitation to the appropriate hemodynamic goal rather than a standard “one-size-fits-all” CPR seems a promising in highly monitored patients. Until now, previous randomized-controlled animal studies have established that hemodynamic-directed targeted CPR results in superior outcomes compared to standard CPR\(^15\)\(^-\)\(^17\). However clinical trials about hemodynamic-directed CPR are limited. Therefore, individualization strategy such as blood pressure-directed CPR which for the administration of additional vasopressors in refractory
cardiac arrest patients who could not maintain diastolic blood pressure from epinephrine injection alone during CPR is worthwhile.

**Aim of the study**

To understand whether there was an improvement in the ROSC rate when vasopressin added in refractory cardiac arrest patients during CPR, we designed the “Augmented-Medication CardioPulmonary Resuscitation trial” (AMCPR). We hypothesized that the additive administration of vasopressin when the patients cannot achieve diastolic blood pressure over 20 mmHg with epinephrine during CPR would improve outcomes.

**METHODS/DESIGN**

**Study design**

We conducted randomized, double-blind, placebo-controlled, single-center trial among patients with non-traumatic OHCA in the emergency department of urban, tertiary hospital, located in Seoul, South Korea. The trial protocol has been approved by the Institutional Review Board of the study facility (number: 2017-0669) and the Ministry of Food and Drug Safety in Korea. Waiver of informed consent was confirmed by the ethic committee because of the emergent need for treatment of cardiac arrest. The patients’ legal representatives were informed about the trial later. Figures 1 and 2 show the study flow chart and the schedule, respectively. A Standard Protocol Items: Recommendations for Clinical Interventional Trials (SPIRIT) checklist is also available (Additional file 1).

**Eligibility criteria**

Adult patients (above 18 years old) with non-traumatic, non-shockable OHCA and with diastolic blood pressure below 20 mmHg measured by invasive radial or femoral arterial line
at presentation will be included. The following exclusion criteria apply: patients with traumatic cardiac arrests; patients with a signed do-not-resuscitate order; patients with an underlying terminal-state disease without an active treatment plan; patients with failed arterial line insertion within 6 minutes; patients with applying extracorporeal membrane oxygenation; patients with pre-hospital down-time longer than 60 minutes; patients with successful ROSC before hospital arrival or ROSC within 6 minutes; patients who have diastolic blood pressure above 20 mmHg for 6 minutes during resuscitation.

**Randomization and study medication**

The patients will be randomly assigned in a 1:1 ratio via a random number generator to either the intervention group or the placebo group. Random number with written words of vasopressin or placebo will be secured in a predetermined box and will be opened by trial administration nurse and only he/she will be able to know drugs. Then, he/she will prepare the vasopressin (40 IU) or saline placebo. During the entire trial, all emergency physicians, nurses, and interns will be unaware of which drugs will be used. Unblinding will only take place in case of a suspected unexpected serious adverse reaction. After randomization, the patients will be received either 1 mg of epinephrine and 40 IU of vasopressin or 1 mg of epinephrine and saline placebo in separate injections less than 10 seconds separately. If ROSC would not achieved within the following 3 minutes, patients will be administered one more vasopressin (40 IU) or placebo with epinephrine. After then, only 1 mg of epinephrine will be administrated every 3 minutes for both groups. Other conventional drugs, including amiodarone, calcium, or bicarbonate will be also administered on clinicians’ decisions and no other drugs will be administered.

**Clinical management**
Advanced Cardiac Life Support will be performed in accordance with last international guidelines and local procedures\textsuperscript{5,6}. In brief, all cardiac arrests presenting to emergency department would have resuscitation initiated while being assessed for eligibility. Defibrillation will be performed for patients with shockable rhythms. Eligible patients will be tried to get arterial line for continuous monitoring via radial or femoral arteries. Confirmation of the adequate placement of the catheter will be performed by an experienced emergency physician on duty using bedside ultrasonography. Moreover, arterial line square wave test will be conducted for confirming adequate function of invasive catheters. Survivors who will be successfully resuscitated will be admitted to the intensive care units for further post-cardiac arrest care, including targeted temperature management, percutaneous coronary intervention, mechanical ventilation, and renal replacement therapy.

**Data and laboratory measurements**

All data will be anonymized and collected according to Utstein guidelines using database designed with Microsoft access software (Microsoft Inc., Redmond, WA) by independent blinded researchers\textsuperscript{18}. Baseline characteristics and other laboratory variables will be fill in from electronic medical records of the study facility. We also collected prehospital information, including prehospital total no-flow, low-flow time, presence of shockable rhythm, administration time of epinephrine, and amount of epinephrine. In addition, arterial blood pressure and end-tidal carbon dioxide levels during resuscitation will be recorded on video and rewritten in electronic database every 10 seconds. Arterial blood gases will be performed at initial, 10 minutes, 20 minutes, and end of resuscitation. All case-record data will be subsequently collected in database, where a random sample of 10% of the data will be assessed by the data and safety monitoring committee.
Outcome measures

The primary outcome will be the sustained ROSC defined as a spontaneous return of a palpable pulse and measurable blood pressure longer than 20 minutes. Secondary outcomes are (1) survival discharge; (2) good neurologic recovery at discharge (Cerebral Performance Category 1 or 2); (3) escalation of diastolic blood pressure; (4) elevation of end-tidal carbon dioxide levels; and (5) improvement of acidosis and lactate levels. Diastolic blood pressure and end-tidal carbon dioxide levels will be extracted every 10 seconds from recording during entire resuscitation period. Then, trends and median values will be compared between groups. Acidosis and lactate levels will be obtained initial, 10, and 20 minutes from arterial line, and compared median values.

Adverse events

Risks to participants in this study may be minimal. There are no previous reports about harmful effects of administration of vasopressin up to 80 IU for patients with out-of-hospital cardiac arrest during resuscitation. Therefore, we have no predefined adverse events for this trial.

Statistical analysis

Data analyses will be performed with the intention-to-treat set, the full analysis set, and the per-protocol analysis set, and missing data will not be assigned. The sample size was calculated based on an expected difference of 25%. We assumed that 30% of patients in the control group would achieve ROSC. For $a = .05$ and statistical power = 0.80, a total sample size of 74 patients will be required in each group. With 15% of drop rate, we will enroll 174 patients. All collected data will be analyzed using descriptive methods according to intervention and control group. For continuous variables, mean with standard deviation (SD) or median with interquartile range (IQR) will be presented depends on normality. For binary variables, number with percentage
will be reported. Using t test or the Mann-Whitney U test for continuous variables and the chi-square test or Fisher’s exact test for categorical variables will be conducted. Statistically significance was considered as P-value < 0.05. All statistical analysis will be conducted by using SPSS (IBM SPSS, Version 27.0; IBM Corporation, Armonk, New York).

DISCUSSION

Vasopressors have been considered as key elements during cardiopulmonary resuscitation. Despite vasopressin was more effective than that of epinephrine in animal studies, past meta-analysis of clinical studies of cardiopulmonary resuscitation showed no evident benefit of vasopressin over epinephrine 20,21. While the main focus of previous trials was universal administration of vasopressin during resuscitation, the key goal of this trial is to assess the effects of augmentation of vasopressin to improve the outcome among patients with cardiac arrest who do not maintain diastolic blood pressure above 20 mmHg only. Because diastolic pressure is associated with coronary perfusion pressure and vasopressin is another vasopressor which has different mechanism from epinephrine 22. Therefore, for the patients who is severe vasoplegic state during CPR, vasopressin may have a synergic effect with epinephrine.

The current guidelines have requested that monitoring diastolic blood pressures and tried to improve quality of resuscitation when the level of diastolic blood pressures is keeping lower than 20 mmHg 5,6. Although insertion of an arterial line during chest compressions can be technically difficult, it is worth trying not only hemodynamic-directed CPR but also dynamic changes of acid-base metabolism 23,24. We will try to access radial or femoral artery with catheters and adequate placement and function of the catheters will be confirmed by bedside sonography, and square wave test. Failed insertion of the arterial line is one of exclusion criteria, and withdrawal due to fail of arterial line can be higher than our thoughts. However,
experienced at least two emergency physicians on duty will be tried to insert catheter for reducing exclusion cases.

The patients will receive a 40 IU of vasopressin just after administration of epinephrine 1 mg and receive one more dose with same dose if ROSC will not be achieved. The applied dose of vasopressin has been proven to be safe and no serious adverse outcomes were reported in past clinical trials. Furthermore, we will exclude the patients with shockable rhythms (i.e. ventricular fibrillation and ventricular tachycardia) because it needs an immediate defibrillation and defibrillation is more important than arterial catheterization which is a time dependent procedure in this trial.

The enrollments of the patients were started from August 2017. Along with the recent trial with in-hospital cardiac arrest patients, this study will provide valuable evidence about the effectiveness of augmented administration of vasopressin to epinephrine among patients with refractory low organ perfusion pressure in resuscitation of out-of-hospital cardiac arrest. If this treatment is shown to be effective, our strategy to get an arterial line for monitoring diastolic blood pressure and deciding to administrate additional vasopressors would be applicable for patients with out-of-hospital cardiac arrest.

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CONFLICT OF INTEREST
The authors have no conflicts of interest to disclose of any funding.

TRIAL REGISTRATION
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REFERENCES


**FIGURE LEGENDS**

**Fig. 1.** Trial flow chart

Abbreviations: DNR, do-not-resuscitation; ED, emergency department; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.
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<th>Enrolment</th>
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* Terminations of cardiopulmonary resuscitation were decided by emergency medicine physicians on duty after return of spontaneous circulation or declaration of death.

** Assessment of survival discharge, favorable neurologic outcome (Cerebral Performance Category 1 or 2).

Fig. 2. Trial schedule