Review Article

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Is Plasmalyte beneficial in resuscitation of diabetic ketoacidosis patients? A narrative review

Running title: Role of Plasmalyte In Diabetic Ketoacidosis Patients

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ABSTRACT:

Fluid resuscitation is vital in the resuscitation of diabetic ketoacidosis patients. The purpose of this narrative review is to analyze the role of Plasmalyte in fluid resuscitation of adult diabetic ketoacidosis patients. A thorough search was conducted in PUBMED, EMBASE and MEDLINE. Studies conducted between 1st January 2010 and 31st March 2023 were collected. Of 123 results, 5 pertinent randomized controlled trials were included. The close resemblance of Plasmalyte’s electrolyte composition to human plasma and its role in the prevention of hyperchloremic metabolic acidosis are some of its vital benefits in patients with diabetic ketoacidosis. Results on the role of Plasmalyte in length of stay, time to resolution of diabetic ketoacidosis and mortality in diabetic ketoacidosis patients are varied. Hence, further research on these topics is needed.

Keywords: Diabetic ketoacidosis, Sodium chloride, Balanced crystalloid, Plasma lyte, Plasmalyte

Capsule summary:

What is already known?
Plasmalyte plays a beneficial role in prevention of hyperchloremic metabolic acidosis among diabetic ketoacidosis (DKA) patients. Its magnesium and potassium concentrations make it particularly useful for DKA patients with hypokalemia or hypomagnesemia. However, it should be used cautiously in patients with or at risk of hyperkalemia, such as those with rhabdomyolysis, severe burns, renal failure, or adrenocortical insufficiency.

What is new in the current study?
This review provides an overview of Plasmalyte's electrolyte composition and its role in preventing hyperchloremic metabolic acidosis, as well as its impact on hospital stay and DKA resolution. Studies on the effects of Plasmalyte on DKA patients' length of hospital stay, time to DKA resolution, and mortality have yielded mixed results. Further research is needed to explore whether acetate in Plasmalyte induces ketogenesis in DKA patients and the relationship between Plasmalyte and acute kidney injury.
INTRODUCTION

Diabetic ketoacidosis is characterized by a combination of hyperglycemia, ketonemia and acidosis. Diabetic ketoacidosis is a severe form of poor glycemic control in diabetes, caused by an absolute or relative lack of insulin and an increase in stress hormones that act as counter-regulators, such as glucagon, catecholamines, cortisol, and growth hormone.¹

Osmotic diuresis is brought on by hyperglycemia, which causes substantial fluid and electrolyte losses. Therefore, fluid resuscitation is essential in treating diabetic ketoacidosis.² In diabetic ketoacidosis, the most recent research suggests using crystalloids rather than colloids.³,⁴ Additional treatments include insulin and electrolyte replacement.⁵

Normal saline has been shown to cause reduced smooth muscle contraction, metabolic acidosis and reduced renal perfusion (in pre-clinical studies).⁶⁷⁸⁹ Compared to both Hartmann's solution and normal saline, Plasmalyte's electrolyte composition more closely mimics the components of human plasma.¹⁰

This narrative review aims to investigate the role of Plasmalyte in resuscitating adult diabetic ketoacidosis patients. It emphasizes the distinctiveness of Plasmalyte in managing diabetic ketoacidosis by preventing hyperchloremic metabolic acidosis, attributed to its similarity to human plasma electrolyte composition. The review also discusses and underscores the necessity for additional research to investigate the effects of Plasmalyte on hospital stay duration, resolution time of diabetic ketoacidosis, and mortality rates among diabetic ketoacidosis patients.

LITERATURE SEARCH:
A thorough exploration was conducted in PUBMED, MEDLINE and EMBASE, covering the period from 1\textsuperscript{st} January 2010 to 31\textsuperscript{st} March 2023. All the studies that were retrieved were critically assessed by four authors, who then chose the trials they felt were most pertinent. The search encompassed specific keywords, namely diabetic ketoacidosis, sodium chloride, balanced crystalloid, Plasma lyte and Plasmalyte.

Out of the 123 studies obtained from the search results, 10 randomized controlled trials were retrieved, of which 5 randomized controlled trials were relevant to our outcomes (Fig1), (Table 1). Our inclusion criteria were randomized control trials assessing the role of Plasmalyte versus normal saline in adult patients with diabetic ketoacidosis published between 1\textsuperscript{st} January 2010 and 31\textsuperscript{st} March 2023. We evaluated the impact of Plasmalyte on the prevention of hyperchloremic metabolic acidosis and other associated complications, as well as analyzed its effect on the time needed for diabetic ketoacidosis resolution, duration of hospital stay and mortality rates.

The process of data extraction involved gathering pertinent details such as study type and location, author information, publication date and other specific information relevant to our designated outcomes. The total number of patients involved in all the studies together was 414, of which patients 404 patients were assigned to either normal saline or balanced electrolyte solutions group (mostly Lactated Ringer or Plasmalyte).

The study by Attokaran et Al. and Ramanan et Al. purely compared the role of normal saline and Plasmalyte in patients with diabetic ketoacidosis.\textsuperscript{11} The study by Weinberg et al. compared the roles of Plasmalyte and normal saline and their effects on the treatment of diabetic ketoacidosis. According to the review, both solutions have unique electrolyte compositions that may have an impact on the acid-base balance, electrolyte homeostasis and the prognosis of diabetic ketoacidosis patients.\textsuperscript{10}

**Electrolyte contents of Plasmalyte, normal saline and Ringer’s lactate**
For choosing the best fluid therapy for diabetic ketoacidosis, a thorough understanding of the electrolyte contents of crystalloid solutions is essential.

The composition of plasma is similar to Plasmalyte, with a pH range of 6 to 7.4 and an osmolarity of 294 mOsmol/L. It contains sodium, potassium, chloride, magnesium, acetate, and gluconate. The concentrations are as follows: potassium 5 mmol/L, sodium 140 mmol/L, chloride 98 mmol/L, magnesium 1.5 mmol/L, acetate 27 mmol/L, and gluconate 23 mmol/L.\textsuperscript{11,12}

Normal saline is an isotonic crystalloid solution which has an osmolarity of 308 mOsmol/L and a pH range of 4.5 to 7. Furthermore, it has an equal amount of both sodium and chloride ions (154 mmol/L). Potassium, magnesium, and bicarbonate are absent, which can have an impact on electrolyte imbalances and acid-base state in diabetic ketoacidosis.\textsuperscript{11,13}

Ringer’s lactate solution is an isotonic balanced crystalloid solution containing various essential electrolytes like sodium, chloride, potassium, calcium, and lactate. It has an osmolarity of 273 mOsm/L and a slightly acidic pH of approximately 6.5. The solution consists of specific amounts of these electrolytes: 130.5 mmol/L of sodium, 4.02 mmol/L of potassium, 0.67 mmol/L of calcium, 109.6 mmol/L of chloride, and 28 mmol/L of lactate.\textsuperscript{14,15}

In a randomized controlled trial, Ringer lactate and 0.9% sodium chloride were compared for managing diabetic ketoacidosis. The group receiving 0.9% sodium chloride took 683 minutes to reach a pH of 7.32, while the Ringer’s lactate group took 540 minutes. The duration for Ringer’s lactate to reach a blood glucose level of 14 mmol/L was notably longer than that of 0.9% sodium chloride. Both groups had comparable median hospital stays of 7 days and no fatalities. According to the study, Ringer’s lactate did not outperform 0.9% sodium chloride in resolving acidosis in diabetic ketoacidosis patients and even led to delayed glycemic recovery.\textsuperscript{16}
Role of Plasmalyte in the prevention of hyperchloremic metabolic acidosis and acute kidney injury in diabetic ketoacidosis management

Plasmalyte is a well-balanced intravenous fluid comprising of sodium, potassium, magnesium, calcium ions and anions like acetate. Large administration of chloride-containing fluids such as normal saline leads to hyperchloremic metabolic acidosis. The ability of a balanced electrolyte solution to prevent hyperchloremic metabolic acidosis can be understood by examining the differences in PH and chloride content between serum, normal saline and balanced electrolyte solution. Normal saline has a PH of around 5.5 and a chloride content of 154 mmol/L while balanced electrolyte solution (specifically plasma-lyte A) has a PH of 7.4 and chloride content of 98 mmol/L, which is more similar to human plasma (94-111 mmol/L).\textsuperscript{17,18} The electrical neutrality of serum is maintained by balancing positive and negative ions. When normal saline is used in larger quantities, serum chloride increases leading to the loss of an equivalent amount of bicarbonate ions to maintain electrical neutrality which causes hyperchloremic metabolic acidosis. Plasmalyte doesn’t cause a decrease in bicarbonate levels.\textsuperscript{17}

A study conducted by Mahler et al. investigated the effects of resuscitating diabetic ketoacidosis patients with a balanced electrolyte solution compared to normal saline. The findings indicated that patients who received balanced electrolyte solution showed lower serum chloride levels and high serum bicarbonate levels after resuscitation, which suggests a potential preventive effect against hyperchloremic metabolic acidosis. In contrast, the normal saline group exhibited higher post-resuscitation serum chloride levels, aligning with existing literature that suggests normal saline administration can contribute to hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis.\textsuperscript{17}

The study conducted by Mahler et al. reinforced the idea that the use of balanced crystalloids is effective in preventing hyperchloremic metabolic acidosis, showcasing its strength. However, the
small sample size, single-center study and lower baseline serum chloride in the sodium chloride group were its limitations. 17

Emerging evidence from recent preclinical and early clinical investigations has raised concerns about the potential adverse effects associated with the administration of normal saline. 19,20 Several reports have put forth the hypothesis of a potential connection between hyperchloremia and acute kidney injury. 20 Studies conducted on critically ill adults have consistently shown an increased risk of acute kidney injury and a greater need for renal replacement therapy when chloride liberal fluids are utilized. 20,21 In contrast, studies have consistently indicated a lower prevalence of hyperchloremic acidosis and renal injury, leading to improved patient outcomes with the adoption of balanced chloride-restrictive fluids. While the precise clinical implications of normal saline infusion are not yet fully understood, there is growing evidence indicating that its use may heighten the risk of kidney injury and hinder recovery from severe illness, potentially due to the induction of metabolic acidosis. 19 The definitive establishment of a link between hyperchloremia and acute kidney injury is still pending.

Existing literature indicates that hyperchloremic metabolic acidosis can cause disruptions that potentially have negative effects on patient outcomes. Animal studies on sepsis have shown less metabolic acidosis, reduced inflammatory cytokines and improved survival rates with balanced electrolyte solution compared to normal saline. Hyperchloremic metabolic acidosis has also been associated with increased blood product transfusion in postoperative patients and impaired renal function. 17

While Plasmalyte has demonstrated effectiveness in treating diabetic ketoacidosis, the assessment of its safety in patients with severe diabetic ketoacidosis has not been conducted formally. 21 Plasmalyte contains acetate with a concentration of 27 mmol/L. Acetate acts as a precursor for acetoacetate, one of the ketone bodies involved in diabetic ketoacidosis. In canines, acetate infusions have been
observed to raise acetoacetate levels and studies done on rats have indicated that liver mitochondria can convert acetate into acetoacetate. In humans, there is some evidence suggesting that acetate might contribute to ketogenesis, particularly in the context of hemodialysis. Nevertheless, it remains unknown whether a similar metabolically significant process occurs in patients with diabetic ketoacidosis and warrants further investigations.\textsuperscript{11}

Nonetheless, it is important to acknowledge that balanced crystalloids carry theoretical risks in diabetic ketoacidosis treatment, including the potential for alkalosis and hyperkalemia.\textsuperscript{18,19} Additionally, the comparative effects of balanced crystalloids and saline in this context are not well comprehended.

**Comparison of time of resolution, mortality and hospital stay in patients with diabetic ketoacidosis receiving Plasmalyte vs. normal saline**

Homogenous endpoints were found in 2 studies: (Time to diabetic ketoacidosis resolution in studies by Self et al. and Tsui et al. and median hospital length of stay in studies by Attokaran et al. and Ramanan et al.).

According to the SCOPE DKA trial by Ramanan et al., although the length of stay was shorter in patients receiving Plasmalyte as compared to normal saline, the rate of re-admission was higher in patients receiving Plasmalyte (4%) as compared to normal saline (2%) (Table 2). It was a randomized control trial involving adult patients admitted to ICU with severe diabetic ketoacidosis in seven hospitals with randomization of either Plasmalyte or normal saline as the intravenous fluid management. The study also showed quicker resolution of diabetic ketoacidosis among patients receiving Plasmalyte as compared to normal saline. Their criteria to consider diabetic ketoacidosis resolution was a shift of base excess to more than or equal to \(-3\) mEq/l at 48 hours. The study reported one death in a patient from the sodium chloride group due to mucormycosis.\textsuperscript{11}
Attokaran et al. in their cohort study involving two hospitals within a randomized control trial reported similar duration of hospital stay among patients receiving Plasmalyte-148 and normal saline after correcting for diabetes type, PH and blood glucose level (Table 2 and Table 4). However, compliance was low with assigned fluid in the Plasmalyte group which might have likely led to a chance of undervaluing the benefits of Plasmalyte. Mortality in either group was nil.  

As the study by Attokaran et al. and Ramanan et al. was conducted in more than one healthcare facility, one strength of the studies is that its results could be generalizable in tertiary centers’ emergency departments and intensive care units. However, one limitation of the study was the decreased compliance to study fluid in the Plasmalyte group.  

Self et al. in their analysis of two randomized controlled trials concluded earlier resolution of diabetic ketoacidosis in patients receiving balanced crystalloid solution (13 hours) as compared to normal saline (16.9 hours) (Table 3). In-patient mortality associated with balanced crystalloid solution was lower (0 patients) as compared to normal saline (1 patient). Their criteria for diabetic ketoacidosis resolution was obtained from the American Diabetes Association Consensus Statement on Hyperglycemic Crisis which included two of these criteria (plasma bicarbonate more than or equal to 15 mEq/L, venous PH more than 7.3, anion gap less than or equal to 12 mEq/L) and plasma glucose less than 200 mg/dL.  

Immediate assignment of patients to sodium chloride versus balanced crystalloids group soon upon presenting to the emergency department, strong fluid group compliance and implementation of study intervention into clinical practice are the strengths of the Self et al. study. Some limitations of the study include a single-center study, a subgroup analysis of previous clinical trials and a non-blinded study.  

The study by Tsui et al. comparing time to diabetic ketoacidosis resolution in adult intensive care unit patients receiving normal saline or balanced crystalloid (Lactated ringer or Plasmalyte) provided an
important finding of a faster time to raised serum bicarbonate and PH with balanced crystalloid as compared to sodium chloride. However, a non-statistically significant result of time to diabetic ketoacidosis resolution, small sample size and preliminary study results were some of its limitations.

In another retrospective study, diabetic ketoacidosis was observed to resolve at a comparable rate in patients who received normal saline (18.05 hours) and Plasmalyte (19.74 hours) as treatment. The criteria for resolving diabetic ketoacidosis were adopted from the American Diabetes Association Consensus Statement on Hyperglycemic Crisis. Plasmalyte exhibited a greater increase in pH during the 4-6 hour and 6–12-hour time frames.

CONCLUSION:

Plasmalyte has a positive role in preventing hyperchloremic metabolic acidosis in diabetic ketoacidosis patients. Due to the concentrations of magnesium and potassium in Plasmalyte, it can be helpful in diabetic ketoacidosis patients with hypokalemia or hypomagnesemia. At the same time, it should be used cautiously in patients with or at risk of hyperkalemia like rhabdomyolysis, severe burns, renal failure, and adrenocortical insufficiency. Results regarding the role of Plasmalyte in the length of stay, time to resolution of diabetic ketoacidosis and mortality in diabetic ketoacidosis patients are varied. Hence, further research on these topics is needed. Furthermore, studies are required in the following fields: whether the presence of acetate in Plasmalyte induces ketogenesis in diabetic ketoacidosis patients and the relation between Plasmalyte and acute kidney injury.

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REFERENCES:


9. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 1-L infusions of 6% hydroxyethyl starch suspended in 0.9% saline (voluven)


### TABLE 1: STUDY METHOD AND SAMPLE SIZE DISTRIBUTION

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Method</th>
<th>Sample size</th>
<th>Sodium chloride (SC)</th>
<th>Plasmalyte (PL)</th>
<th>Balanced Crystalloids (BC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attokaran et Al.</td>
<td>27th March 2023</td>
<td>Cluster, cross-over, open-label, randomized control trial (nested cohort study within SCOPE-DKA trial)</td>
<td>84</td>
<td>38</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Ramanan et Al.</td>
<td>5th October 2021</td>
<td>Cluster, crossover, open-label, randomized, controlled Phase 2 trial</td>
<td>93 enrolled (90 included)</td>
<td>42</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Self et al.</td>
<td>16th November 2020</td>
<td>A subgroup analysis of multiple cross-over cluster randomized clinical trial (SALT-ED and SMART)</td>
<td>172</td>
<td>78</td>
<td></td>
<td>94</td>
</tr>
<tr>
<td>Tsui et Al.</td>
<td>Jan-19</td>
<td>Prospective pilot study: cluster randomisation approach</td>
<td>Target sample size: 42, preliminary results of 13 presented</td>
<td>9</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Mahler et Al.</td>
<td>5th February 2010</td>
<td>Prospective, randomized, double-blind study</td>
<td>52 enrolled, 45 included</td>
<td>23</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>Study</td>
<td>Sodium chloride (SC)</td>
<td>Plasmalyte (PL)</td>
<td></td>
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<tr>
<td>Attokaran et Al.\textsuperscript{21}</td>
<td>3 days</td>
<td>3.1 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramanan et Al.\textsuperscript{11}</td>
<td>4.083 days</td>
<td>3.375 days</td>
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### TABLE 3
**TIME TO DKA RESOLUTION**

<table>
<thead>
<tr>
<th>Study</th>
<th>Time to DKA resolution</th>
<th>Time to DKA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sodium chloride (SC)</td>
<td>Balanced Crystalloid (PL/Lactated Ringer)</td>
</tr>
<tr>
<td>Self et al.</td>
<td>16.9 hr (IQR (Interquartile Range): 11.9-34.5 hours)</td>
<td>13 hr (IQR: 9.5-18.8 hours)</td>
</tr>
<tr>
<td>Tsui et Al.</td>
<td>26 hr (IQR 13–20 hours)</td>
<td>13.5 hr (IQR 10–24.5 hours)</td>
</tr>
<tr>
<td>Study</td>
<td>Patients admitted to ICU</td>
<td>Study</td>
</tr>
<tr>
<td>---------------------</td>
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<tr>
<td>Attokaran et al.</td>
<td>Plasmalyte (PL) 39.10%</td>
<td>Self et al.</td>
</tr>
<tr>
<td></td>
<td>Sodium chloride (SC) 50%</td>
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</table>
Figure 1: Flow Diagram Illustrating the Selection Process of Randomized Controlled Trials for Inclusion in the Study

Figure 1: Flow Diagram Illustrating the Selection Process of Randomized Controlled Trials for Inclusion in the Study. The diagram depicts the initial 123 results identified through database searches in PUBMED, MEDLINE, and EMBASE using specific keywords (diabetic ketoacidosis, Plasmalyte, normal saline, balanced crystalloid). Of these, 113 results were excluded based on title and abstract screening (as they were not randomized controlled trials), and an additional 5 randomized controlled trials were excluded after full-text assessment (not relevant to our study’s outcomes). Finally, 5 randomized controlled trials that were relevant to our study’s outcomes were included in the final analysis.