EDITORIAL

Intravenous Fluid Prescription in Diabetic Ketoacidosis: Where is the Evidence?

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Keyword: 0.9% saline, Balanced electrolyte solution, Diabetic ketoacidosis, Fluid resuscitation.
Indian Journal of Critical Care Medicine (2025): 10.5005/jp-journals-10071-24875

Patients with diabetic ketoacidosis (DKA) can have significant volume deficit, up to the tune 10–15% of body weight.[1] Volume deficit results from loss of fluid through osmotic diuresis related to hyperglycemia and vomiting, complicated further by poor oral intake. Restoration of both intravascular and whole-body volume is the key to the successful management of DKA. In fact, rehydration itself improves hyperglycemia; by reducing the level of counterregulatory hormones following intravascular volume restoration.[2] Insulin administration should be deferred till intravascular volume is restored, to avoid further worsening of hypovolemia. Insulin infusion facilitates the movement of glucose to the intracellular compartment dragging water along and thus reducing the intravascular volume further.[2]

A number of diabetes societies have provided guidelines recommending fluid type and volume to be infused in patients with DKA.[1,3,4] However, rationales for these recommendations are mostly limited to expert opinion with limited evidence supporting them. Guidelines recommend 0.9% Saline as the preferred choice of resuscitation fluid in DKA. However, in recent years, there has been a growing concern regarding the safety 0.9% Saline, especially when administered in large volumes as in DKA. Large volume of saline administration is associated with hyperchloremia and non-anion gap metabolic acidosis potentially delaying the resolution of DKA.[5] Saline may also be associated with a risk of acute kidney injury and the potential increase in mortality.[6,7] The adverse consequences of saline are shown to be dose-dependent.[7,8] Balanced electrolyte solutions (BES), with a composition closer to human plasma, have been suggested as alternative resuscitation fluids, which may avoid the adverse effects of saline and can potentially shorten duration of DKA.[9,10] However, the lower osmolarity of some BES may potentially increase the risk of cerebral edema and buffering substances present in a particular balanced solution may complicate DKA management further.[10–12]

Comparative effects of saline and BES, in resuscitation of adult patients with DKA, are so far limited to mostly single-center randomized control trials or observational studies with rather small sample size, or retrospective analysis of DKA subgroups from larger randomized studies. In the only multicenter randomized trial (SCOPE-DKA trial), in this setting, no difference was observed in the rate of DKA resolution (defined as base excess correction) at 48 hours between patients resuscitated with Plasmalyte-A (a BES available commercially) and those with saline.[10] In the secondary analysis of the data, more patients in the Plasmalyte-A group had DKA resolution at 24 hours. However, there was no between-group difference in terms of ketoacid and anion-gap correction, the strongest markers of DKA correction. There were also no differences in patient-centered clinical outcomes including mortality or ICU and hospital length-of-stay between groups. In this issue of the journal, Gupta et al. has reported a systematic review and meta-analysis of currently available evidence comparing the efficacy of saline and BES in DKA resuscitation in adult patients.[13] The authors looked into number of clinical outcomes including time to resolution of DKA (Primary outcome), hospital length of stay (Primary outcome), adverse events (hypokalemia, hyperkalemia, acute kidney injury), and mortality. They also looked into certain biochemical parameters including post-resuscitation chloride levels and post-resuscitation bicarbonate levels. Nine studies were included in the analysis, including six randomized studies, one subgroup analysis of two previously published randomized studies, and two retrospective studies. Primary outcomes including time to DKA resolution and hospital length of stay were not different between the saline group and BES group.[13] However, the BES group had significantly higher post-resuscitation bicarbonate and lower post-resuscitation chloride level. Incidences of hypo- and hyperkalemia, acute kidney injury, as well as the rate of mortality were not different between groups. The authors acknowledged several limitations of their study, including a small number of randomized studies, small sample size of individual studies, and wide variations in the reporting of adverse events. It is also important to note that clinical outcomes were defined somewhat differently in different studies included in the meta-analysis. For example, in the retrospective analysis of a subgroup of patients from SALT-ED and SMART studies, DKA resolution was defined using more rigorous criteria published by the American Diabetes Association (ADA) that includes plasma glucose less than 200 mg/dL and two of the following: plasma bicarbonate ≥15 mEq/L, venous pH >7.3, and anion gap ≤12 mEq/L.[3,9] In contrast, in the SCOPE-DKA trial, DKA resolution was

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How to cite this article: Ghosh S. Intravenous Fluid Prescription in Diabetic Ketoacidosis: Where is the Evidence? Indian J Crit Care Med 2025;29(1):10–11.

Source of support: Nil

Conflict of interest: None

broadly defined as change in base excess to ≥ – 3 mEq/L; although ADA criteria were also used in the sensitivity analysis at 24-hour post-ICU admission.[10]

Several questions remain unanswered. Perhaps future large multicenter studies would be able to provide answers to them.

- Favorable biochemical profiles were observed in DKA patients treated with BES compared to saline, including lower chloride and higher bicarbonate.[13] Similar profiles were observed in individual studies too.[9,10] However, do these favorable biochemical profiles transform into improved clinical outcome?
- As pointed out by Gupta et al., a volume of fluid infused may have a significant impact on patient's clinical outcome.[13] In a retrospective analysis of data from BaSICS trial, Zampieri et al. observed a significant increase in mortality in patients resuscitated with saline compared to BES (Plasmalyte-A) when used in larger volume.[8] Future studies should address this issue.
- Some of the BES solutions are hypo-osmolar (e.g., effective osmolarity Ringer's lactate 257 mOsmol/L, Plasmalyte-A 270 mOsmol/L). Does the osmolarity of individual solutions have an impact on risk of cerebral edema in adult patients with DKA? However, in a large clinical study in pediatric populations, osmolarity of resuscitation fluid was not found to have any impact on cerebral edema incidence or long-term cognitive outcome.[11]
- Can the buffering substances present in individual BES have an impact on the clinical outcome of DKA patients? In a small randomized study from South Africa, the time to lower glucose below 250 mg/dL was significantly longer in patients resuscitated with Ringer's lactate (RL) compared with Saline, which could potentially be explained by lactate present in RL.[12] Similarly, acetate present in Ringer's acetate, Plasmalyte-A, and Sterofundin can potentially delay the clearance of acetoacetate in DKA. However, in the SCOPE-DKA trial ketone levels at 48 hours were not different between saline and Plasmalyte-A groups.[10]
- Hyperchloremia seems to be associated with acute kidney injury. Whether large volume resuscitation with high chloride-containing saline (154 mEq/L) in DKA, needs to be established unequivocally.[14]

Till we get answers to these questions, it is safe to conclude that balanced crystalloids should be the preferred fluid for resuscitation of patients with DKA, based on strong physiological rationale against using 0.9% saline, none of the clinical studies showing any harm associated with these solutions and most studies showing quicker resolution of DKA with their use; especially when large volume of fluid is anticipated to be administered. The choice of balanced solution should be based on the osmolarity and buffering substance of a particular solution, the risk of cerebral edema in an individual patient, as well as cost and availability. However, 0.9% Saline may be considered when cost and availability issues are there or when the clinician is not anticipating a high volume of fluid infusion.

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References

1. Diabetes Canada Clinical Practice Guidelines Expert Committee, Goguen J, Gilbert J. Hyperglycaemic Emergencies in Adults. Can J Diabetes 2018;42 Suppl 1:S109–S114. DOI: 10.1016/j.jcjd.2017.10.013.
2. Ghosh S. Handbook of Intravenous Fluids. 1st ed. Singapore: Springer; 2022. Chapter 14, Fluid Management in Diabetic Ketoacidosis; pp. 279–295. DOI: 10.1007/978-981-19-0500-1_16.
3. Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycaemic crises in adult patients with diabetes. Diabetes Care 2009; 32:1335–1343. DOI: 10.2337/dc09-9032.
4. Dhatariya KK; Joint British Diabetes Societies for Inpatient Care. The management of diabetic ketoacidosis in adults-An updated guideline from the Joint British Diabetes Society for Inpatient Care. Diabet Med 2022;39(6): e14788. DOI: 10.1111/dme.14788.
5. Chua HR, Venkatesh B, Stachowski E, Schneider AG, Perkins K, Ladanyi S, et al. Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. J Crit Care 2012;27(2):138–145. DOI: 10.1016/j.jcrc.2012.01.007.
6. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 2012;256(1):18–24. DOI: 10.1097/SLA.0b013e318256be72.
7. Raghunathan K, Shaw A, Nathanson B, Stürmer T, Brookhart A, Stefan MS, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. Crit Care Med 2014;42(7):1585–1591. DOI: 10.1097/CCM.0000000000000305.
8. Zampieri FG, Machado FR, Veiga VC, Azevedo LCP, Bagshaw SM, Damiani LP, et al. Correction: Determinants of fluid use and the association between volume of fluid used and effect of balanced solutions on mortality in critically ill patients: A secondary analysis of the BaSICS trial. Intensive Care Med 2024;50(1):79–89. DOI: 10.1007/s00134-023-07264-9.
9. Self WH, Evans CS, Jenkins CA, Brown RM, Casey JD, Collins SP, et al. Clinical effects of balanced crystalloids vs saline in adults with diabetic ketoacidosis: A subgroup analysis of cluster randomized clinical trials. JAMA Netw Open 2020;3(11):e2024596. DOI: 10.1001/jamanetworkopen.2020.24596.
10. Ramanan M, Attokaran A, Murray L, Bhadange N, Stewart D, Rajendran G, et al. Sodium chloride or Plasmalyte-148 evaluation in severe diabetic ketoacidosis (SCOPE-DKA): A cluster, crossover, randomized, controlled trial. Intensive Care Med 2021;47(11):1248–1257. DOI: 10.1007/s00134-021-06480-5.
11. Kuppermann N, Ghetti S, Schunk JE, Stoner MJ, Rewers A, McManemy JK, et al. Clinical trial of fluid infusion rates for pediatric diabetic ketoacidosis. N Engl J Med 2018;378:2275–2287. DOI: 10.1056/NEJMoa1716816.
12. Van Zyl DG, Rheeder P, Delport E. Fluid management in diabetic-acidosis--Ringer's lactate versus normal saline: A randomized controlled trial. QJM 2012;105(4):337–343. DOI: 10.1093/qjmed/hcr226.
13. Gupta P, Nasa P, Shahabdeen SM. Effectiveness of balanced electrolyte solution vs normal saline in the resuscitation of adult patients with diabetic ketoacidosis: An updated systematic review and meta-analysis. Indian J Crit Care Med 2025;29(1):65–74.
14. Honore PM, Mugisha A, Kugener L, Redant S, Attou R, Gallerani A, et al. The causal link between hyperchloremia and acute kidney injury is yet to be conclusively established: We are not sure. Crit Care 2020; 24:271. DOI: 10.1186/s13054-020-02966-8.