Intensive Care Med
https://doi.org/10.1007/s00134-021-06527-7

EDITORIAL

Fluid management in diabetic ketoacidosis: new tricks for old dogs?

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Some treatment recommendations in medicine stem from guidelines based on expert opinion, anecdotal reports and pathophysiological rationale. In one such entity, diabetic ketoacidosis (DKA), pathophysiological rationale and expert opinion have guided treatment recommendations with limited experimental scrutiny in the form of randomized clinical trials. While fluid therapy is a cornerstone of the management of DKA, the recommendations on the volume, rate and of type of fluid to be administered are based on scarce experimental data. In this issue of Intensive Care Medicine, Ramanan et al. report the results of the SKOPE-DKA cluster-crossover phase 2 randomized clinical trial comparing Plasmalyte (PL) to 0.9% sodium chloride (SC) in the management of patients admitted to the intensive care unit (ICU) with DKA [1].

The current American Diabetes Association (ADA) guidance on the management of DKA recommends using 0.9% SC initially as a 15–20 mL/Kg bolus for hemodynamic resuscitation and then 250–500 mL/h of fluid until glucose is normalized (usually faster than DKA resolution) and then 150–250 mL/h until DKA resolution [2]. For the replenishment solution after the bolus, the guideline recommends using 0.45% SC unless hyperglycemia-corrected hyponatremia is present. For this recommendation, no clinical trial is referenced [2]. Actually, one reference suggests colloids should be the preferred fluid administered, while acknowledging 0.9% SC would be a good compromise to replenish the fluid losses of patients with DKA [3]. Another reference from prior guidance, which is based on descriptive information of 29 episodes on 26 subjects, suggests that the loss of water is greater than sodium, which is nevertheless greater than the chloride losses [4], which raises the intriguing question whether the use of balanced solutions might be beneficial. Surprisingly, these are a glimpse of the reports that have been guiding fluid management in DKA for decades.

Some authors have postulated that the use of balanced solutions instead of 0.9% SC in the management of DKA may avoid concurrent hyperchloremic acidosis (HA), a known side effect of unbalanced solutions, and shorten time to DKA resolution [5]. Though HA has been shown to be a common issue during the treatment of DKA [6], others argue that HA in DKA is not necessarily related to the type of fluid administered, but due to renal handling of bicarbonate and sodium and other issues [7]. A large pediatric multicenter factorial DKA trial studied the tonicity (0.45% vs. 0.9% SC) and volume/rate of administration of fluid [8]. The primary outcome was neurological deterioration, which was not different between groups, nor were there differences in medium to long term cognitive outcomes. However, HA was observed in the 0.9% SC (compared to 0.45%) and the fast treatment groups, suggesting these could be relevant issues during the treatment of DKA.

In adults, reports about fluid management in DKA include the recent sub analyses of the SALT-ED and SMART trials, which showed a hastened time to DKA resolution and time to cessation of insulin infusion when using any balanced crystalloid [9]. Another, albeit small, clinical trial published in 2012 demonstrated that ringer lactate did not lead to hastened correction of pH compared to 0.9% SC, but that there was a lower correction rate of glucose levels in spite of the same amount of insulin administered per hour [10]. Finally, another small clinical trial published in 2011 demonstrated that PL,

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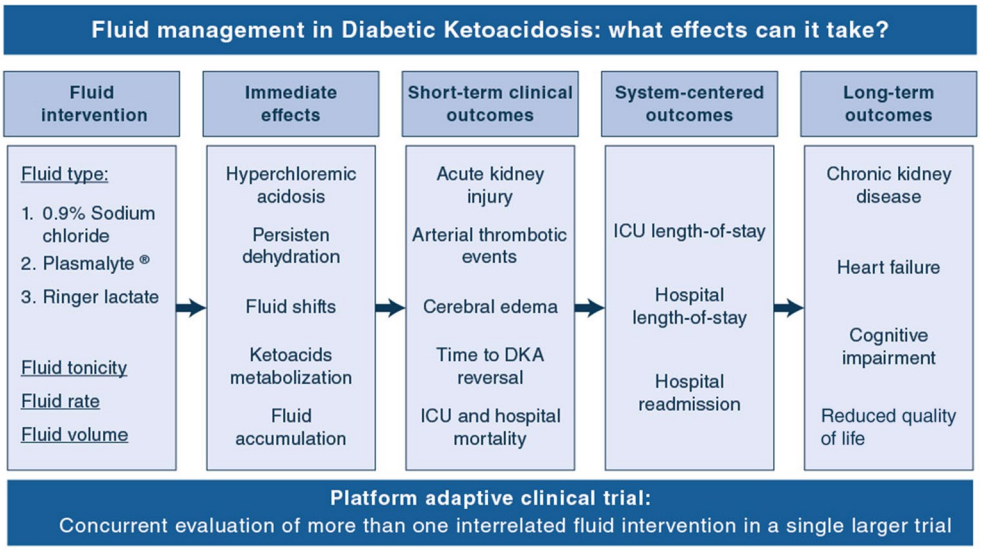

Fig. 1 How fluid type, tonicity, rate and volume may impact outcomes in patients with severe diabetic ketoacidosis. The fluid variables have short-lived physiological effects, such as hyperchloremic acidosis or fluid accumulation that may be associated to short-term clinical outcomes, such as acute kidney injury, thrombotic events, cerebral edema and the most commonly used outcome of DKA reversal. ICU and hospital mortality are unlikely events in DKA and probably are hardly modulated by different fluid strategies. Through these events, length-of-stay or readmissions may be shorter or less frequent. Finally, the impact on long term clinical outcomes of having a faster or slower resolution of DKA and a complicated or uncomplicated admission for DKA can also be studied. All these outcomes would probably be better scrutinized in a platform adaptive trial, where many interventions (fluid related or not) could be studied and patients followed-up for enough time after discharge to evaluate long-term outcomes. *DKA* diabetic ketoacidosis; *ICU* intensive care unit

compared to 0.9% SC, improved bicarbonate concentrations faster by avoiding an overlapping HA during treatment [11]. Unfortunately, this experimental evidence still has not been translated to guidelines and neither to clinical practice.

Ramanan et al. bring needed evidence in their report of the results of SKOPE-DKA cluster-crossover clinical trial [1]. The authors defined DKA resolution as base excess correction at 48 h. There was no difference at 48 h, but there was a difference at 24 h, with resolution in over two thirds in the PL group compared to just over a third in the SC group. Ketoacid and anion-gap correction—the strongest markers of DKA correction—were not different between groups and hospital length-of-stay was the same between groups. The immediate implications are that 0.9% SC has no deleterious effects on DKA resolution itself, but that SC fluid therapy does add HA during treatment [12]; and that acetoacetate from PL does not impair ketoacid elimination, although it is metabolized through this metabolic pathway. Whether these small physiological benefits translate into improved patient centered outcomes or at least to a shortened ICU and total hospitalization duration remains unclear, but the case for using balanced solutions, such as PL seems stronger. Nevertheless, the recently published BaSICS trial assessing PL against 0.9% SC on critically ill patients' 90-day mortality is a reminder of the need to randomize to accumulate enough evidence to have realistic expectations from fluid effects on critically ill patients overall and in important subgroups [13].

The trial has its limitations due to its small sample size and its open-label design. Adherence to the intervention was not adequate in the intervention (PL) group (only about 2/3 received PL in that group), especially in the emergency department before ICU admission, this despite a cluster trial design to enhance uptake of intervention and avoid contamination. Explanations may include the absence of blinding, unfamiliarity of ED physicians with PL and lack of training and education about the trial equipoise and procedures, which are important considerations in the design of a larger trial.

Future research in DKA fluid management should include not only the type of fluid, but also the total volume and rate of administration, important variables that may affect the speed of DKA resolution. Outcomes to be measured should include not only DKA resolution, but hospitalization duration (a system centered outcome), acute kidney injury incidence [14], neurological and coronary adverse events [15] and, if possible, more medium to long term outcomes, such as chronic kidney disease development due to concerns with chloride-rich solutions. Finally, modern approaches for

clinical trial design [16] should be considered to allow testing more than one intervention in a single platform and bring much needed robust experimental evidence to guidelines on fluid management during the treatment of DKA (Fig. 1).

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Funding
None.

Declarations

Conflicts of interest
BAMPB, PMH and WB report no conflicts of interest related with the content of this editorial.

Publisher's Note

Received: 8 August 2021 Accepted: 3 September 2021
Published online: 05 October 2021

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