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Balanced electrolyte solutions versus isotonic saline in adult patients with diabetic ketoacidosis: A systematic review and meta-analysis

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ABSTRACT

Background: Current guidelines suggest the use of isotonic saline (IS) infusion as the preferred resuscitation fluid in the management of diabetic ketoacidosis (DKA). However, balanced electrolyte solutions (BES) have been proposed as an alternative due to a lower propensity to cause hyperchloremic metabolic acidosis. Evidence regarding the use of BES in DKA remains limited.
Objectives: To determine if the use of BES in fluid resuscitation leads to faster resolution of DKA compared to IS.
Methods: The study involves a comprehensive search of literature from PubMed, Cochrane CENTRAL, Google Scholar, and Science Direct of clinical trials addressing the use of BES vs IS in fluid resuscitation in DKA. The time to resolution of DKA was examined as the primary endpoint. Pooled hazard ratios (HR) and Mean Difference (MD) in hours with their 95% confidence intervals (CI) were calculated using a random-effects model.
Results: The literature search included 464 studies that were screened individually. A total of 9 studies were identified but 6 studies were excluded due to irrelevance in the outcome of interest and target population. The pooled hazard ratio HR significantly revealed 1.46 [1.10 to 1.94] ($p = 0.009$) with 12% heterogeneity while MD was -3.02 (95% CI -6.78–0.74; $p = 0.12$) with heterogeneity of 85%.
Conclusion: Considering the evidence from pooled small randomized trials with moderate overall certainty of evidence, the use of BES in DKA was associated with faster rates of DKA resolution compared to IS.

Introduction

Although mortality rates for diabetic ketoacidosis (DKA) have been steadily declining in the USA with a current in-hospital case fatality rate of 0.4%, trends have shown that DKA hospitalization rates have dramatically increased by 54.9%.[1] This reflects significant healthcare burden not only to the patients but also to the healthcare system.[1] Despite this, research to improve outcomes in the management of DKA has lagged behind, there is still contention with regards to the preferred intravenous (IV) fluid for use in DKA therapy.

There are two types of IV fluids commonly used for general fluid replacement in hospitalized patients, Balanced Electrolyte Solutions and Isotonic (0.9%) NaCl. Balanced Electrolyte Solutions (BES) are isotonic crystalloids that have a more similar composition to convalescent plasma in comparison to saline. It is commonly used as a fluid replacement in dehydrated or volume-depleted patients. Examples of BES fluids commonly utilized in medical practice are Lactated Ringers (LR) solution and Plasma-Lyte 148 (PL).[2] Isotonic (0.9%) NaCl or isotonic saline (IS) is another isotonic crystalloid often used for fluid volume replacement. It is notable as being the most common IV fluid in use for medical purposes. Although IS and BES are both isotonic,[3,4] there exists a significant difference between the two. For instance, IS has a slightly higher osmolality (308 mOsm/L vs LR 273 mOsm/L), lower pH (5.5 vs LR 6.6), and a higher chloride content (154 vs LR 109) which often associates IS with the development of hyperchloremic metabolic acidosis in comparison to BES.[3,4]

In light of these fundamental differences, the rationale to use BES which has the tendency to contribute less to the already acidotic state

Abbreviation: ADA, American Diabetes Association; BES, Balanced Electrolyte Solutions; CI, Confidence Interval; DKA, Diabetic Ketoacidosis; HHNK, hyperglycemic hyperosmolar nonketotic coma; IS, Isotonic saline; LR, Lactated Ringers; NSS, Normal Saline Solution; PL, PlasmaLyte Solution; RCT, Randomized Control Trial; MD, Mean difference

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in DKA has been brought up. Current guidelines still suggest the use of 0.9% NaCl or isotonic saline infusion as the preferred maintenance fluid in the management of DKA.[5] However, BES is proposed as a superior alternative and has gained recent interest in the management of DKA.[6] Unfortunately, there seems to be no clear answer on which is more efficacious in the treatment of adult DKA patients. Thus, this study aims to perform a comprehensive systematic review and meta-analysis to determine if the use of balanced electrolyte solutions (BES) in fluid resuscitation leads to faster resolution of DKA compared to isotonic saline (IS).

Methods

Eligibility criteria

Randomized controlled trials comparing the use of balanced electrolyte solutions (BES) compared to a control group of isotonic saline (IS) in the management of DKA among adult patients were included in the study. BES include Plasma-Lyte, Lactated Ringer's solutions, or any intravenous fluid with a similar composition to plasma, used in individual studies. A control group composed of patients with DKA managed with IS must be present. The studies included must have a sample population of only adult patients with DKA. Related conditions such as hyperglycemic hyperosmolar non-ketotic coma (HHNK) were excluded since the objective is to look at the resolution of acidosis among patients. Retrospective studies, case reports or case series and studies with pediatric patients, were excluded given innate differences in physiology. Furthermore, the studies included must also look at the resolution of DKA included and must provide either the actual counts or hazard ratios.

Search methods for identification of studies

The search was not restricted by language, date, publication status, or any other trial characteristics. The following electronic databases were utilized for the search: PubMed, Cochrane CENTRAL, Google Scholar, and ScienceDirect. Specific search criteria used were: "DKA" OR "diabetic ketoacidosis" AND "saline" OR "NSS" OR "normal saline", OR "balanced solutions" OR "Lactated Ringer's" to search for the studies. The PICO question was "Among patients with diabetic ketoacidosis, what was the effect of balanced electrolyte solutions compared to isotonic saline in the resolution of acidosis". References within the primary selected studies reviewed in the full text and gray literature were screened. Efforts were made to contact some of the study authors for additional relevant study information but only 1 reply was received.

Selection of studies

Two authors (JAC and ETP) independently screened each title and abstract of each study. For studies with uncertainties evaluated in the title and abstract, the full text was reviewed. All screened studies were assessed for inclusion in accordance with the eligibility criteria. Disagreements were resolved by discussions between the two screening authors. A third author (MC) was consulted when a consensus could not be met.

Data extraction

From the included studies, data were independently extracted such as the type of study design, year of publication, country of origin, sample size, criteria for the diagnosis, classification, and resolution of diabetic ketoacidosis, baseline and change in biochemical parameters post-resuscitation, reported outcomes, follow-up period, and types of fluids used. From this, the inclusion and exclusion criteria as well as the nature of intervention were derived.

Outcomes

The primary outcome measure is the time to resolution of DKA both in the form of hazard ratios and the actual mean difference in hours. We define time to resolution of DKA as the mean time (in hours) from diagnosis or treatment up to its resolution, as defined by the ADA 2009 criteria. The ADA 2009 definition was used by all meta-analyzed studies to define DKA resolution (venous pH $>$ 7.3, serum bicarbonate $>$ 15 mEq/l, blood glucose $<$11.1 mmol/l or $<$200 mg/dL, anion gap $\leq$12 mEq/L) with the exception for Van Zyl et al. 2012 as it did not include anion gap due to lack of reported values for electrolytes needed for its computation, as part of their criteria.[7] Pooled hazard ratios (HR) and Mean differences using 95% confidence intervals (CI) were calculated using a random-effects model.

Risk of bias

Two authors (JAC and ETP) independently assessed the risk of systematic errors (bias) in the included studies using the Cochrane collaboration's risk of bias tool for randomized studies.[8] The criteria to appraise the studies included: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases were assessed.

Data synthesis

Pooled hazard ratios and confidence interval estimates, as well as the mean differences, were calculated using Review Manager version 5.4.1.[9] Pooled hazard ratios were chosen to help account for any adjustments for potential confounders made by individual studies and the time to event analysis. Studies were weighted according to their standard errors to produce the final pooled hazard ratios using the DerSimonian-Laird random-effects model (to account for potential differences in study inclusion criteria, nature of the balanced solutions used, and outcomes based on the nature of DKA with different cutoff values). A p-value of 0.05 or less was considered statistically significant. In addition, when necessary, the authors also utilized the method established by Hozo et al. 2005 to convert median (interquartile ranges) to mean (standard deviation), to enable the calculation of mean differences.[10]

Assessment of heterogeneity

Heterogeneity of the included studies was assessed using I^2 with Low, moderate, and high levels of heterogeneity corresponding to I^2 values of 25%, 50%, and 75% respectively.[11]

Results

The literature search included 464 published articles that were screened individually (Supplemental Figure 1) using the search terms reflected in Supplemental Table 1. 454 were excluded based on title and abstract not fulfilling inclusion criteria. Out of 9 qualifying studies that were identified, the studies by Bergmann et al. 2021, Yung et al. 2017, and Williams et al. 2020 were also excluded since they used the pediatric population instead of adult subjects in their studies.[12-14] Additionally, Mahler et al. 2010, Aditianingsih et al. 2017 were excluded since they did not report on the outcome of interest.[15,16] Tsui et al. 2020 was excluded as only the abstract was available and not the full text.[17] No sample size counts, number of events or hazards, or odds ratios were also available.

A total of three studies with a total population of N = 316 were included in the final meta-analysis.[7,18,19] All factors considered, the studies pooled exhibited a low risk in all parameters appraised except for the absence of blinding in the studies of Ramanan et al. 2021 and

Self et al. 2020.[18,19] Hence, the major limitation being the aforementioned open-label protocol employed by two out of three studies. Fig. 1 describes the risk of bias assessment. Supplemental Table 2 describes the parameters observed in this review including inclusion and exclusion criteria used, volume of fluids infused, baseline and change in biochemical parameters post-resuscitation, time to DKA resolution (hours), hazard ratio, mean difference, the follow-up period for the outcome, and criteria used for DKA classification and resolution. Supplemental Table 3 shows the differences in electrolyte contents comparing isotonic saline, lactated ringer solution (LRS), and Plasma Lyte-148 as the type of fluid administered differed with Van Zyl et al. 2012 and Self et al. 2020 using primarily LRS and Ramanan et al. 2021 using Plasma Lyte-148.

With regards to the total fluid infused, Ramanan et al. 2021 reported the mean volume of fluid administered as 6798 mL (SD 4850) in the BES group and 6574 mL (SD 3123) IS group.[18] Whereas Self et al. 2020 reported the median IQR of total fluids administered as 4267 (3000–7090) in the BES group and 4927 (3324–6026) in the IS group.[19] On the other hand, Van Zyl et al. 2012 made no mention of the total administered fluids in their study.[7]

Other outcomes including post-resuscitation electrolytes such as chloride, potassium, and sodium, as well as bicarbonate, and creatinine were reported differently among the studies and were difficult to pool together. Although higher in the IS arm, Van Zyl et al. 2012 reported that there is no significant increase of serum chloride 1-hour post-resuscitation (BES**:** 109.54 mmol/L vs IS**:** 111.36 mmol/L, $p = 0.421$) and no difference was evident at the time of resolution of ketoacidosis. On the other hand, Ramanan et al. 2021 reported the repeated-measures mixed-effects model for change in serum chloride, showing the BES group with significantly lower serum chloride concentrations at 24 h (−3.5 mmol/L, 95% CI −6.4 to −0.5, $p = 0.021$) but similar serum chloride concentrations at 48 h (−2.9 mmol/L, 95% CI −6.5 to −0.6, $p = 0.106$). Self et al. 2020 had a graphical representation showing that patients with BES had lower chloride and higher bicarbonate concentrations over time. Meanwhile, differences in bicarbonate concentrations were also reported in the study of

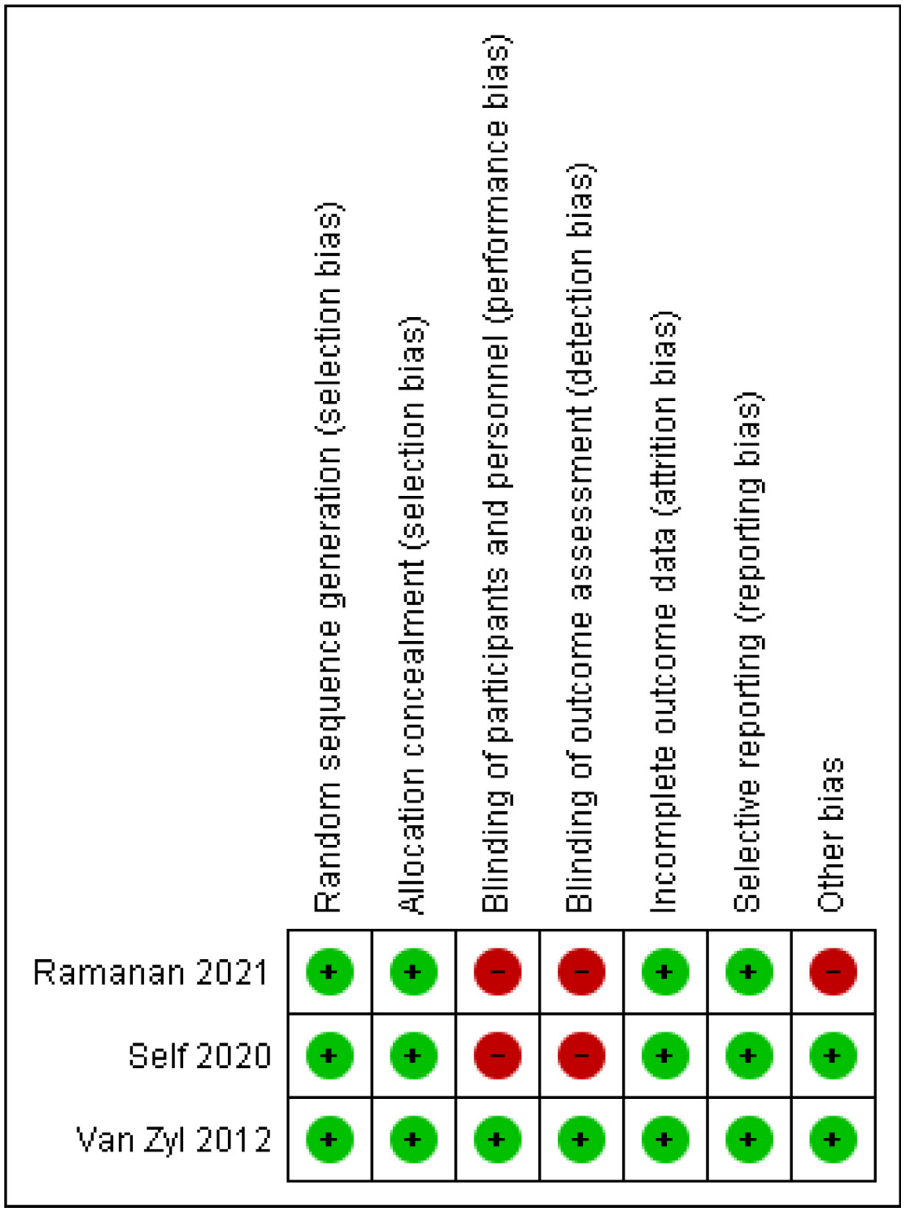

Fig. 1. Risk of bias summary among the included randomized controlled trials. Note. The figure shows the review authors' judgments about each risk of bias item in the column for each included study in the rows. A green dot with a plus symbol indicates presence of a bias item in a corresponding study. A red dot with a minus symbol indicates absence of a bias item in a corresponding study.

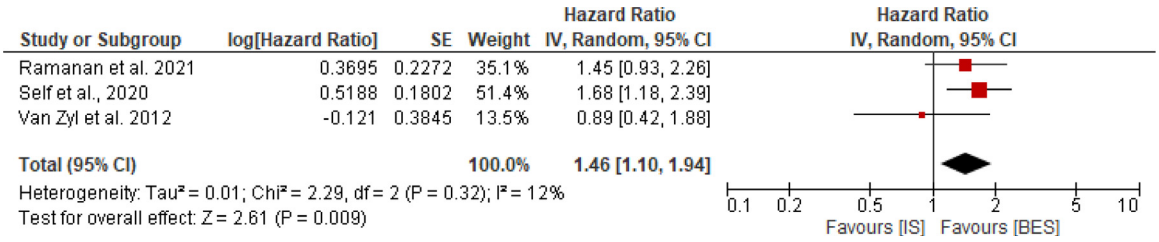

Fig. 2. Forest plot for time to DKA resolution HR. Note. This figure shows the forest plot for the time to DKA resolution among the included RCTs. The red square represents the individual study effect. The size varies to reflect the weight a particular RCT has in the overall analysis. Conversely, the study by Van Zyl et al. 2012 contributes the least weight, followed by Ramanan et al. 2021 while the study by Self et al. 2020 contributes the most weight overall. The black horizontal line represents the confidence interval (CI) of a study; studies with smaller squares generally have larger CIs than the larger squares. The black diamond represents the overall summary effect. The outer edges of the diamond repesent the CIs.

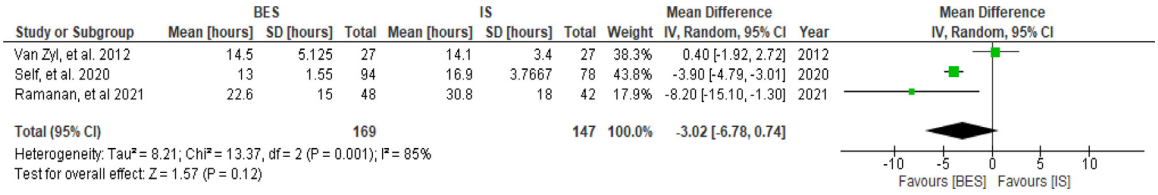

Fig. 3. Forest plot Time to DKA resolution Mean Difference. *Note*. This figure shows the forest plot for the time to DKA resolution mean difference among the included RCTs. The green square represents the individual study effect. The size varies to reflect the weight a particular RCT has in the overall analysis. Conversely, the study by Ramanan et al. 2021 contributes the least weight while the study by Self et al. 2020 contributes the most weight overall. The black horizontal line represents the confidence interval (CI) of a study; studies with smaller squares generally have larger CIs than the larger squares. The black diamond represents the overall summary effect. The outer edges of the diamond repesent the CIs.

Ramanan et al. 2021 in the form of base excess which was significantly higher in the BES group at 24-hr (+3.6 mEq/L, 95% CI 1.1–6.2, $p = 0.005$) and 48-hr (+3.5 mEq/L, 95%CI 0.4–6.7, $p = 0.026$) with an OR of 1.47 (95% CI 0.61–3.52, $p = 0.390$) using the ADA criteria. On the other hand, Van Zyl et al. 2012 did not provide the differences in bicarbonate concentration but did adjust for it in their analysis of the primary outcome.

For the primary outcome of this study, the authors pooled both the Mean difference in time and Hazard ratios. Meta-analysis on three studies showed that the pooled hazard ratio HR (95%CI) for the resolution of DKA was 1.46 [1.10 to 1.94] ($p = 0.009$) with low 12% heterogeneity in favor of BES as depicted in Fig. 2 while the pooled mean Difference for time (in hours) to DKA resolution was calculated as shown in Fig. 3, illustrating an MD −3.02 (95% CI [−6.78, 0.74]; $p = 0.12$) with significant heterogeneity of 85%.

Discussion

To the best of our knowledge, this is the first meta-analysis that tackles the topic of isotonic saline (IS) and balanced electrolyte solutions (BES) as fluid therapy in adult DKA patients taking into account time-to-event analysis. All three studies enrolled patients with at least moderate to severe DKA based on the ADA 2009 criteria. Although there have been meta-analyses that focus on the effects of BES vs IS in different populations, particularly in critically ill patients, studies focusing on adults with DKA have not been systematically reviewed or meta-analyzed.[20-22]

The pooled analysis of this study shows that BES results in faster DKA resolution (in hours) in comparison to IS. When examined individually, the studies by Van Zyl et al. 2012 and Ramanan et al. 2021 showed insignificant results due to the smaller sample size used (suggesting a type 2 error) as compared to that of the study by Self et al. 2020, which involved a larger sample size (as it was a combination of subgroups of 2 trials) and otherwise significant results.[7,18,19] Nonetheless, the three studies collectively summate a sample size of 316, wherein 261 patients (83%) achieved resolution of their DKA, which is significant enough when combined together to produce the pooled hazard ratio.

This study examined both mean difference and adjusted (hazard ratio) analysis to look at the primary outcome. Since DKA resolution is a time-dependent outcome and could be affected by confounders such as baseline bicarbonate concentration, baseline capillary glucose concentration, baseline capillary hydroxy-buterate concentration, diabetes type, amount of study fluid administered, diabetes type, time of follow-up, and GCS level on presentation,[7,18,19] ignoring these factors may underestimate or overestimate the true association between exposure and outcome. To overcome this heterogeneity, the Hazard ratio is utilized as it is an effective tool in comparing and producing a more reliable analysis since it is estimated via a Cox proportional hazards model[23] which addresses potential confounders as covariates together with looking at time to event analysis which is advantageous over using mean difference alone.[23-25] Looking at the mean difference alone, we found that there was no statistically significant difference between BES and IS in time to DKA resolution. However, it should be noted that pooling together mean differences has its limitations including the process of conversion from median (interquartile ranges) to mean (standard deviation) and conversion from minutes to hours therefore having more assumptions to consider. The mean differences also do not take into account adjustment for confounders as opposed to hazards ratios obtained by cox regression.[23-25]

Across all studies, the results are consistent with the existing mechanistic and pathophysiological evidence in the use of BES and IS in DKA. Although stated differently, it is noticeable that there is comparatively lower serum chloride levels post-resuscitation in the BES arm from both studies of Van Zyl et al. 2012 and Ramanan et al. 2021 than the IS arm, leading to a relatively lower risk of hyperchloremia. This lower serum chloride level in BES arm is according to their lower amount of chloride as these solutions mimics the plasma concentration of electrolytes.[18,19] The higher serum chloride level in IS arm post-resuscitation relates to its baseline higher chloride concentration with strong ion difference of zero, leading to risk of hyperchloremia worsening the metabolic acidosis and acute kidney injury that may result to prolonged hospital stay due to worsening of acidosis in DKA.[7,18,19]

Meanwhile, the change in bicarbonate post-resuscitation corroborates with the higher bicarbonate content found in BES.[18] These

bicarbonate differences are due to the fact that BES contain additional anions, such as lactate, acetate, malate, and gluconate, which act as physiological buffers to generate bicarbonate, resulting in a more neutralizing or alkalizing effect to the high anion gap acidosis secondary to the accumulation of ketone bodies in DKA, leading to its faster resolution.[7,16,18,19] Moreover, volume resuscitation is significant in DKA resolution as it helps restore volume loss and in its ability to decrease hyperglycemia by stimulating osmotic diuresis and enhancing the peripheral action of insulin.[26,27] However, the amount and type of fluid administered were also different as presented in this study. Interestingly, studies by Gosmanov et al. 2014 and Caputo et al. 1997 indicate that regardless of the fluid therapy rate (as affected by volume and time), no significant difference in any of the metabolic parameters (anion gap, chloride, sodium or potassium), morbidity and mortality were observed in DKA.[26,27] Fluid types whether Plasma-Lyte 148 or Lactated Ringer's Solution also insignificantly impacts the overall alkalinizing effects according to the studies of Noritomi et al. 2011, Hadimioglu et al. 2008, and Weinberg et al. 2015.[28-30]

Finally, we recommend further investigation into the topic of BES vs IS in adult DKA patients as there are currently very few clinical trials in publication to conclusively make a decision on the verdict. There should ideally be more blinded studies as the majority of those in publication utilized an open-label approach which increases their chances for bias. The consistent collection of other clinical indicators of recovery such as length-of-hospital stay, length-of-ICU stay, time-to-discontinuation of insulin, and total insulin infusion should also be done. Additionally, collecting data on the difference in the development of complications in this population could further help elucidate whether the choice of BES or IS on these fronts has any benefit after controlling for confounders. Further clinical trials on whether there is a difference in outcome between the types of BES used on adult DKA patients would also be a good addition in future studies to show whether the difference in composition between BES types would exhibit superiority or non-inferiority in patient outcomes when compared. We suggest that another pooled analysis of RCTs be done in the future. As of the time of this writing, there are two RCTs in the process of publication relevant to our population and intervention, namely the PLUS (NCT02721654) and BRISK-ED (NCT04926740) clinical trials. The addition of these studies would help improve the power of any future meta-analysis done on this matter.

Limitations

The meta-analysis was limited by the number of available studies and relatively smaller sample sizes. Of the pooled studies, only Van Zyl et al. 2012 utilized blinding while both Self et al. 2020 and Ramanan et al. 2021 were both open-label clinical trials.[7,18,19] This renders the latter two studies at high risk for performance bias due to lack of blinding of participants and personnel, and detection bias due to lack of blinding of outcome assessment (see Fig. 1).

In terms of fluid compliance, Ramanan et al. 2021 reported poor compliance in the BES arm at 66% (IQR 38–85%) in the BES (Plasma-Lyte) group but a 100% (IQR 75–100%) in the IS (Sodium Chloride) group while Self et al. 2020 had a compliance of 85.3% in the BES and 96.7% in the IS.[18,19] However, there was no mention of the level of compliance to the assigned treatment groups in the study by Van Zyl et al. 2012.[7] This poor compliance actually biases the pooled effect size towards the null with contamination of the treatment group with normal saline potentially diminishing the effect size for the benefit for BES - despite this, there was still a significant difference in favor of BES. Additionally, the poor compliance of the BES arm in adhering to their designated treatment seen in Ramanan et al. 2021 constitutes contamination bias and the heterogeneity of balanced electrolyte solutions across all studies limit the analysis.

This study pooled together hazard ratios to take into account the time to event analysis and potential confounders. Nonetheless, since the studies included were all small randomized controlled trials which are currently the best evidence available at the present, the level of certainty of evidence is placed at moderate based on the GRADE criteria.[31,32] This was after being downrated for both risk of bias and imprecision, it was uprated as all the perceived biases or confounding including from using different balanced solutions to the poor compliance in some studies (with treatment group also getting saline) - all these confoundings tend to bias the results towards the null. Despite this, we are still seeing a significant effect in favor of BES.

All of the three studies only took into account the type of fluid intervention and baseline patient characteristics into account and did not consider differences in other aspects of management of DKA such as the insulin protocol followed or parameters for renal function such as serum creatinine post-resuscitation. Thus, assessment[1–32] of the primary outcomes in relation to chloride levels, change in insulin requirement or renal status could not be accounted for directly in this meta-analysis. Some studies did account for these potential confounders in their cox regression analysis of their primary outcomes.

The follow-up period in determining time to DKA resolution also differed for each study. There might be some slight differences in inclusion criteria but after examining closely the patient characteristics of the included studies, all of the studies included at least moderate to severe DKA according to the ADA criteria 2009 (see Supplemental Table 2). Most of the studies included also had relatively narrow confidence intervals and heterogeneity was low with most of the hazards ratio favoring BES. The study by Van Zyl et al. 2012 was different as it included an incomplete 2009 ADA criteria but it was included in the study nonetheless, taking a conservative approach to this analysis favoring bias towards a negative result. In their separate analysis using complete 2006 ADA criteria, the hazards ratio pointed towards in favor of balanced solutions.[7]

Conclusion

Considering the evidence from pooled small randomized trials with moderate overall certainty of evidence, the use of BES in DKA was associated with faster rates of DKA resolution compared to IS.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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