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Comparing the clinical effects of balanced electrolyte solutions versus normal saline in managing diabetic ketoacidosis: A systematic review and meta-analyses

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Abstract:

The first-line treatment of diabetes ketoacidosis (DKA) involves fluid resuscitation with normal saline infusion to correct hypovolemia. Hyperchloremic metabolic acidosis from aggressive normal saline administration was associated with worse clinical outcomes in managing DKA. Other choices for normal saline include balanced electrolyte solutions (BESs). This study aimed to compare the clinical effects between BESs and normal saline in managing DKA. This study was a systematic review of probing articles published from inception to October 2021 in Cochrane Central Register of Controlled Trials, Medical Literature Analysis and Retrieval System Online, Google Scholar, and Scopus. Eight randomized controlled trials with a total of 595 individuals were included. The data were analyzed at 95% confidence level using random-effects models. For the primary outcomes, there was no difference in the duration of DKA resolution. (Mean difference [MD] −4.73, 95% confidence interval [CI] −2.72–4.92; I^2 = 92%; P = 0.180). However, there was a significantly lower postresuscitation chloride concentration in the BES (MD 2.96 95% CI − 4.86 to − 1.06; I^2 = 59%; P = 0.002). For the secondary outcomes, there was a significant reduction in duration for normalization of bicarbonate in the BES group (MD 3.11 95% CI − 3.98-2.23; I^2 = 5%; P = 0.0004). There were no significant differences between groups in duration for recovery of pH, intensive unit admission, and adverse events (mortality and acute renal failure). Resuscitation with BES was associated with decreased chloride and increased bicarbonate values in DKA patients. It suggests that BES prevents DKA patients from hyperchloremic metabolic acidosis.

Keywords:

Balanced electrolyte solutions, diabetes ketoacidosis, meta-analysis, normal saline, systematic review

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Introduction

Diabetes ketoacidosis (DKA) continues to be one of the most significant complications of diabetes mellitus, accounting for approximately 30 admissions per 1000 people, at an average annual rate of 6.3%.[1] DKA is characterized by hyperglycemia, metabolic acidosis, and elevated serum ketone. There are no definite criteria for the diagnosis of DKA. Generally, the arterial pH is ≤7.3, and serum bicarbonate is ≤15 mmol/l with

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BOX-ED section

What is already known on the study topic?

- DKA is one of the most significant complications of diabetes mellitus and is characterized by hyperglycemia, metabolic acidosis, and elevated serum ketone
- The mainstay therapy includes vigorous normal saline administration to correct hypovolemia
- What is the conflict on the issue? Has its importance for readers?
- Administration of a large amount of normal saline contributes to a hyperchloremic metabolic acidosis that associated with worse clinical outcomes
- Balanced electrolyte solutions are intravenous fluids with electrolytes composition similar to plasma composition should have a minimal impact on acid-base equilibrium
- How is this study structured?
- This was a systematic review and meta-analysis of a randomized-control trial.
- What does this study tell us?
- There was no difference in the duration of DKA resolution between balanced electrolyte solutions and normal saline
- However, resuscitations with balanced electrolyte solutions were associated with lower chloride and higher bicarbonate concentrations that can prevent hyperchloremic metabolic acidosis.

positive serum or urine ketones.[2] The first-line therapy involves vigorous normal saline infusion to correct hypovolemia, administer insulin, and thoroughly monitor electrolytes with replacement. The sodium shortage typically ranges from 7 to 10 mmol/kg and is associated with water deficits (100 mL/kg), resulting in decreased extracellular fluid volume.[2] A recent study suggests that the administration of high quantities of crystalloids contributes to a nonanion gap hyperchloremic metabolic acidosis caused by high physiological chloride concentration and a substantial ion difference of zero.[3]

Balanced electrolyte solutions (BESs) such as lactated ringer's solution, Hartmann's solution, sterofundin, and plasma-Lyte are alternatives to normal saline. BES are intravenous fluids with an electrolyte composition analogous to plasma composition. By exchanging a portion of the chloride content with bicarbonate or rapidly metabolized and excreted organic anions such as lactate, acetate, or gluconate, it has a higher physiological chloride concentration. Hence, BES should have a minimal impact on acid-base equilibrium juxtaposed to the commonly reported normal saline-related hyperchloremic metabolic acidosis.[4] Hyperchloremic metabolic acidosis was explicitly associated with worse clinical outcomes, including a higher degree of renal injury and a more extended time resolution of DKA.[5]

Several recent meta-analyses assessed the clinical effects of BES with normal saline and other fluids in critically ill patients, sepsis patients, and patients in operation theatres and intensive care units (ICUs).[6-9] We performed a systematic review bolstered by its up-to-date literature review to assess the clinical effects of BES compared with normal saline in managing DKA. The primary outcomes included the duration of DKA resolution and postresuscitation chloride concentrations.

Methods

Study design

This systematic review and meta-analyses were implemented according to the protocol formerly published in the PROSPERO register. This review's protocol is registered with PROSPERO (ID CRD42021234611). The analyses were carried out in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines for conducting and reporting meta-analyses of randomized controlled trials (RCTs).

Search strategies

The Cochrane Central Register of Controlled Trials (1996 to October 2021), Medical Literature Analysis and Retrieval System Online (1960 to October 2021), Google Scholar (1960 to October 2021), and Scopus (1960 to October 2021) were searched for relevant literature.

We searched the reference lists of known RCTs and reviewed papers to identify unpublished trials or trials that were not found through electronic searches. We looked for ongoing trials on the World Health Organization International Clinical Trials Registry Platform (http:/www.who.int/ictrp/en/) and www.clinicaltrials.gov.

Study selection and data extraction

The study includes all RCTs comparing normal saline with BES in the treatment of DKA. We included blinded and open-labeled studies including patients over 1 month of age who had been hospitalized with DKA. Three review authors (RT, NY, and KAB) independently scanned the titles and abstracts from the searches, obtaining full-text publications when they appeared to meet the eligibility criteria or when there was insufficient material to assess eligibility. We independently evaluated the trials' eligibility and documented the reasons for exclusion. Any disputes between the review authors were handled through discussion. We extracted data on the study setting, participant characteristics (age, sex, and ethnicity), methodology (number of participants randomized and analyzed), method for diagnosing

DKA, time of resolution of DKA, changes in biochemical parameters (chloride, bicarbonate, and pH), duration of ICU stay, number of mortalities, the incidence of related adverse events such as acute renal failure. Primary outcomes were the duration of DKA resolution and postresuscitation chloride concentrations. Secondary outcomes included the duration for normalization of bicarbonate, the duration for recovery of pH, ICU admission, and adverse events (acute renal failure and mortality).

Assessment of risk of bias

We evaluated the likelihood of bias based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, and selective reporting of outcomes, and other biases.[10] Disagreements were settled through discussion. According to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology,[11] we graded the risk of bias, inconsistency, indirectness, imprecision, and publication bias as very low, low, moderate, or high for primary and secondary outcomes.

Statistical analysis

We used Review Manager 5.4 software (RevMan 2020) to conduct meta-analyses and pooled data using a random-effects model. The threshold for interpreting the I^2 statistic can be deceiving because the importance of inconsistency is dependent on several factors. We used the guide to interpret heterogeneity as outlined: 0%–40% might not be important, 30%–60% may represent moderate heterogeneity, 50%–90% may represent substantial heterogeneity, and 75%–100% may represent considerable heterogeneity.[10] We determined the presence of heterogeneity in two steps. First, we compared populations, settings, interventions, and outcomes to see if there was any noticeable heterogeneity. Second, we used the I^2 statistic to analyze statistical heterogeneity.[10] We calculated the treatment effect for dichotomous outcomes using risk ratios and absolute risk reduction, and mean differences for continuous outcomes, both with 95% confidence intervals. Continuous outcomes that were presented as the median with low-and high-end ranges/interquartile range were converted to the mean.[12,13]

Results

We retrieved 348 records from digital databases and two records from other references. We reviewed a total of 350 records. Due to duplication, 84 records were removed. 249 trials were removed because their abstracts did not meet the inclusion requirements. We screened 15 full texts for eligibility, of which nine publications possibly met the review inclusion criteria and six were ineligible for inclusion. We excluded six trials because five of them were observational studies,[14-18] and the remaining was a systematic review protocol.[19] Following the completion of the qualitative synthesis, one study[20] was excluded due to a lack of outcome interest. Therefore, eight trials involving 595 participants were embraced in the meta-analysis and systematic review [Figure 1 and Table 1].

Risk of bias in included studies

The randomization method was described in five trials. Two studies used computer-generated randomization,[21,22] one trial utilized a table of random numbers generated by a statistician,[23] and the participants in two trials were assigned using stratified randomization.[24,25] The method of randomization was unreported in three trials, and hence, we postulate random sequence generation an unclear risk of bias.[26,27] One study was presumed to have a high risk of bias because patients were assigned to receive either BES or normal saline based on the month of the year.[26] Allocation concealment was low risk in four trials.[21,23,24,27] The method for allocation of concealment was not stated in three studies, and hence we postulate it as an unclear risk of bias.[22,25,28] The allocation of concealment was labeled as high in one trial, as the random sequence was known to the clinicians in advance.[26]

Three trials described all personnel, and participants were blinded to treatment assignment.[21,23,24] Blinding was not explained in three studies, and hence, we classified performance bias as unclear risk of bias.[22,25,27] Two trials described that the treatment team was aware of what fluid the patients were receiving.[26,28] Four studies were judged as having a low risk for detection bias.[21,22,24,27]

Seven trials were judged as low risk for attrition bias.[21,22,24-28] Three trials used an intention-to-treat analysis in which the participants were analyzed based on the groups to which they were initially assigned.[25-27] Yung 2016, reported data were missing for ketones in eight subjects at randomization (normal saline two, Hartmann Solution six) and 23 on day one (normal saline 10, Hartmann Solution 13). The risk of bias in each domain was generally reported to be low or unclear in the included studies.

Figure 2 depicts the proportion of studies classified as having a low, high, or unclear risk of bias for each risk of bias indicator.

Primary outcomes

1. Duration of DKA resolution
2. Four trials reported the duration of DKA resolution. The duration of DKA resolution did not differ between BES and normal saline[21,24,26,28] [Figure 3]

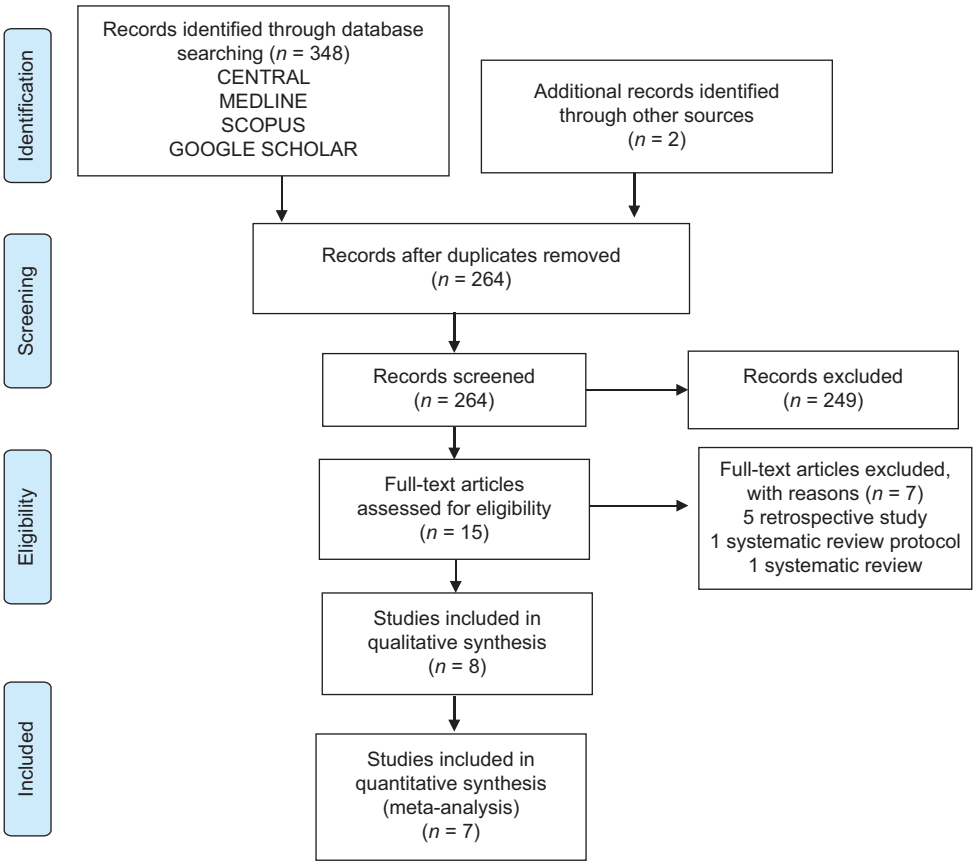

Figure 1: Study flow diagram (PRISMA flow). PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses

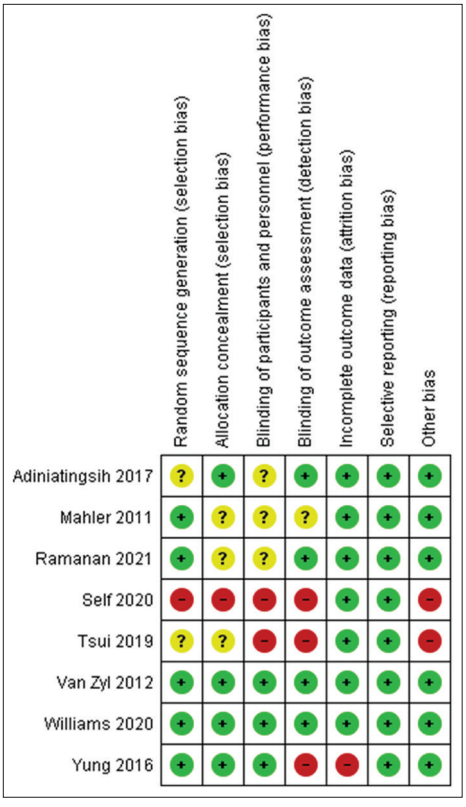

Figure 2: Risk of bias summary: Review authors' judgements about each risk of bias

3. Postresuscitation chloride concentrations
4. Four trials reported the primary outcomes of postresuscitation chloride concentrations.[22-25] In the BES group, there were significantly lower postresuscitation chloride concentrations than in the normal saline group, with considerable heterogeneity [Figure 4].

Secondary outcomes

Duration for normalization of bicarbonate

Three trials reported the duration for the normalization of bicarbonate.[23,24,28] There was a significant reduction in the duration of the normalization of bicarbonate in the BES group [Figure 5].

Duration for recovery of pH

This meta-analysis included three studies with a total of 176 participants for the outcome of duration for recovery of pH.[23,24,28] The results revealed no significant differences in the duration of recovery of pH between the BES and the normal saline group [Supplementary Figure 1].

Length of intensive care unit admission

Data from four studies were pooled to determine the length of ICU admission.[21-23,28] The results showed no

Table 1: Characteristics of included trials

Reference	Number of patients	Intervention (types of BES)	Control	Clinical setting	Outcomes
Adiniatingsih, 2017	30	Sterofundin	Normal saline	Patients with diabetic ketoacidosis aged 18–65 year old Blood sugar level during hospital admission >250 mg/dL Positive ketone bodies in the blood, and arterial blood pH <7.35	Mortality Adverse events: Acute renal failure
Ramanan, 2021	93	Plasmalyte - 148	Normal saline	Patients 16 years of age and over who presented with severe DKA Severe DKA defined as arterial pH ≤7.25 (or serum bicarbonate ≤15 mmol/L) and blood glucose ≥14 mmol/L	Mortality Length of ICU stay Postresuscitation chloride concentration
Self, 2020	172	Plasma Lyte A or ringer lactate	Normal saline	Age 18 years or older, presentation to the ED during the 15-month period when both the ED and ICUs were participating in the SALT-ED and SMART trials (January 1, 2016–March 31, 2017) A clinical diagnosis of DKA in the ED A medical record review confirming DKA was present at the time of ED evaluation rather than the delayed onset of DKA in the hospital after admission	Mortality Adverse events: Acute renal failure, deterioration of GCS Time of resolution of DKA
Tsui, 2019	42	Plasma Lyte A or ringer lactate	Normal saline	Age 18 years or older, diagnosed with DKA Blood glucose >250 mg/dL pH <7.3 Serum bicarbonate <18 mEq/L Serum and anion gap >10	The time resolution of DKA Length of ICU/PICU stay Duration of recovery of pH Duration for normalization of bicarbonate
Williams, 2020	66	Plasma Lyte A	Normal saline	Children >1 month to <12 years who presented to the pediatric emergency room with DKA as defined by the ISPAD-2014	Mortality Adverse events: Acute renal failure, hypoglycemia, patients requiring renal replacement therapy Time resolution of DKA Length of ICU/PICU stay
Yung, 2016	77	Hartmann solution	Normal saline	Children with moderate to severe DKA admitted to the PICU or high dependency unit biochemical criteria for the diagnosis of moderate to severe DKA are Hyperglycemia (blood glucose >11 mmol/L) Venous pH <7.3 and/or bicarbonate <15 mmol/L and ketonemia or ketonuria and glycosuria	Length of PICU stay Duration for recovery of pH Duration of normalization of bicarbonate Total fluid intake Postchloride concentration Adverse events: Acute renal failure, deterioration of GCS
Mahler, 2011	52	Plasma Lyte A	Normal saline	Patients aged 18–65 years old, with moderate to severe DKA. Moderate to severe DKA was defined by A serum glucose >200 mg/dL Serum bicarbonate ≤15 mmol/L and anion gap ≥16 mmol/L	Postresuscitation chloride concentration
Van Zyl, 2012	57	Ringer's lactate	Normal saline	Newly diagnosed or previously known to have diabetes mellitus, type 1 or type 2 diabetes Age ≥18 years A venous blood pH at presentation 6.9–7.2 Presence of at least two plus ketones on urine dipstick test at presentation A capillary blood glucose of >13 mmol/L at baseline and able to give verbal informed consent	Duration of DKA resolution Postresuscitation chloride concentration Duration for normalization of pH Duration of normalization of bicarbonate Adverse event: Hypoglycemia

DKA: Diabetes ketoacidosis, ISPAD-2014: International Society of Pediatric and Adolescent Diabetes Guidelines, ICU: Intensive care unit, PICU: Pediatric ICU, BES: Balanced electrolyte solutions, GCS: Glasgow coma scale, ED: Emergency department, SMART: Sequential, multiple assignment, randomized trial, SALT: Isotonic Solution Administration Logistic Testing

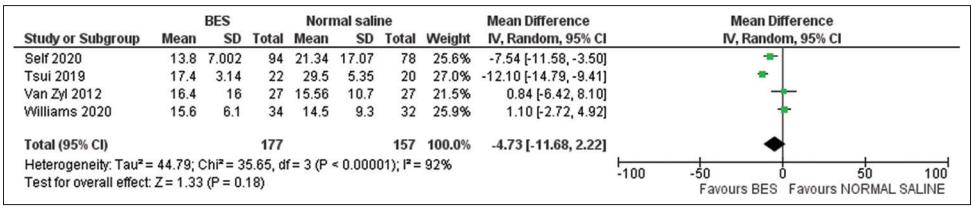

Figure 3: Forest plot for the outcome of DKA resolution. (MD [95% CI]–4.73 [−2.72, 4.92]; I^2 statistic = 92%, P = 0.180; four trials, 334 participants). DKA: Diabetes ketoacidosis, CI: Confidence interval, MD: Mean difference

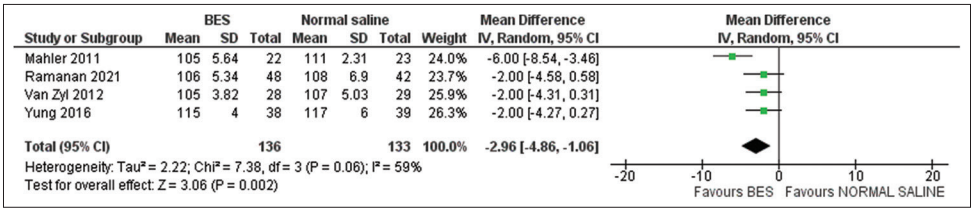

Figure 4: Forest plot for the outcome of postresuscitation chloride concentrations. (MD [95% CI] −2.96 [−4.86, −1.06]; I^2 statistic = 59% P = 0.002; four trials, 269 participants). CI: Confidence interval, MD: Mean difference

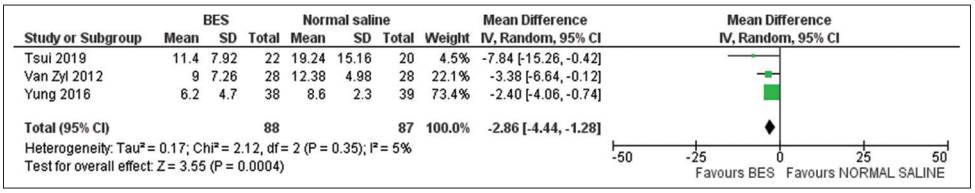

Figure 5: Forest plot for the outcome of duration for normalization of bicarbonate. (MD [95% CI] −3.11 [−3.98, 2.23]; I^2 statistic = 5% P = 0.0004; three trials, 175 participants). CI: Confidence interval, MD: Mean difference

statistically significant differences in the length of ICU/Pediatric ICU stay between the BES and normal saline groups [Supplementary Figure 2].

Adverse events: Mortality

Four trials reported mortality number.[21,22,26,27] However, there was no difference in the outcome between the BES and normal saline groups [Supplementary Figure 3].

Adverse events: Acute renal failure

Four studies have documented the number of patients with acute renal failure.[21,23,26,27] There was no difference between the BES and normal saline group for the adverse events of acute renal failure [Supplementary Figure 4].

Discussion

A recent meta-analysis evaluating BESs versus normal saline in DKA was published recently.[29] The study only focuses on the adult population, whereby our study combined both the adult and pediatric populations. The meta-analysis only discusses one single outcome, which is the resolution of DKA, thus excluding other potential trials[25,27] and affecting the analysis. Besides, one trial[28] was not included in the study even though the trial reported the outcome of interest.

This review focused on the effectiveness of BES in managing DKA compared to normal saline in all age groups. BES significantly lowered chloride concentrations compared to normal saline in managing DKA. However, there was no difference in the duration of DKA resolution between BES and normal saline in this review. There was a reduction in the duration for the normalization of bicarbonate in the BESs.

BES has a greater physiological chloride concentration and a strong ion difference when a portion of the chloride is replaced with bicarbonate or rapidly metabolized organic anions such as lactate, acetate, and gluconate.

Acute renal failure and higher mortality in critically ill patients have all been linked to high chloride loads from normal saline. Hyperchloremia could have resulted in renal vasoconstriction and a decrease in glomerular filtration, leading to acute renal failure. One large retrospective cohort study of 10,249 critically ill adults (cardiovascular 31%, infection 14%) revealed a reduction in mortality and acute renal failure as the percentages of Ringer's lactate solution increased and saline decreased.[30] According to a systematic review and network meta-analysis by Rochwerg *et al*.,[7] resuscitation with BES or albumin appears to be related to a lower mortality rate in sepsis patients when compared to other fluids. A recent systematic review comparing BES and normal saline in critically ill adult patients found that BESs had reduced hospital or 28/30-day mortality than

normal saline in critically ill adults, but not specifically those with sepsis.[8]

Although our meta-analysis disclosed no significant difference in the duration of pH recovery, the time of DKA resolution, the occurrence of acute renal failure, or the number of mortalities, this could be due to the small sample size, different criteria of DKA resolution used, or a lack of ketone or anion gap resolution measurements.

Our findings are based on studies identified through a comprehensive and systematic literature search. We included patients of all ages with different comorbidities or etiologies of DKA at baseline. Only two studies included the population of children.[21,23] Two studies included only patients with moderate to severe DKA as the inclusion criteria,[23,25] while the others included mild to severe DKA. Our findings should be taken with caution, even though the inclusion of all these studies allowed us to cover a wide range of patients. Criteria for the primary outcome of the duration of resolution of DKA varied substantially between studies. Two studies[26,28] used the American Diabetes Association Consensus Statement on hyperglycemic crises 2009 criteria for the resolution of DKA. One study[24] used the American Diabetes Association Consensus Statement 2006 criteria for the resolution of DKA, and another study[21] used criteria from the International Society of Pediatric and Adolescent Diabetes Guidelines 2014. Therefore, the diversity of criteria will influence the findings. In addition, the number of studies was insufficient to perform subgroup analyses, which would have allowed us to evaluate how our findings could be implemented in all patients.

Using the GRADE, the evidence quality for the measured outcomes ranged from low to high. We cannot rule out the possibility of a selective reporting bias, because none of the trials had published protocols. One study showed a high risk of performance bias due to its open-label trial, and another study considered a high risk of selection bias due to its cluster-randomized, multiple crossover design. For the primary outcome of the duration of DKA resolution, we downgraded the quality of evidence as low in view of inconsistency, as we noted substantial statistical heterogeneity. The substantial heterogeneity (92%) in the outcome of the duration of DKA resolution is possibly due to the differences in the criteria of DKA resolution used among studies. Subgroup analysis based on the population was unable to be carried out, as there were limited trials. However, the certainty of the evidence for postresuscitation chloride concentration was the high quality of evidence.

For secondary outcomes, the duration of normalization of bicarbonate and the recovery of pH are labeled as low quality of evidence. We downgraded two levels for the duration of normalization of bicarbonate in view of the small sample size, and there were two studies reported as having a high risk of bias for performance and detection bias. For the mortality outcome, the quality of the evidence was judged to be high. In this systematic review, we assessed the quality of all studies using Cochrane's risk of bias tool and GRADE to evaluate the quality of evidence for important outcomes.

Limitations

Our meta-analysis also acknowledges several limitations. Small sample sizes that ranged from 18 to 172 participants hindered our capability to conduct appropriate analyses. The analyses were limited due to the low number of randomized control trials that fulfilled all inclusion and exclusion criteria. Multiple factors contribute to the heterogeneity of our analysis, including the variation in population characteristics, etiologies of DKA, and different criteria of DKA resolution used among studies. Furthermore, there was a wide variation in the incidence of adverse events reported, such as acute renal failure, among the included studies, indicating variability in definitions used and challenges in detecting and reporting adverse events. Although a comprehensive search approach was performed to obtain potentially relevant trials, this review only included literature written in English.

Conclusions

Resuscitation with BES in DKA patients was associated with lower chloride and higher bicarbonate concentrations. This suggests that BES prevents hyperchloremic metabolic acidosis in DKA patients. Our analyses also suggest that, on the basis of mostly low-to-moderate-quality evidence, there is no difference when comparing the duration of DKA resolution between BES and normal saline. High-quality trials with a larger sample size are required to assess if the use of BESs compared with normal saline is associated with better clinical outcomes in managing DKA.

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Author contributions statement

- Designing the review: Rozinadya Tamzil (RT). Normalinda Yaacob (NY), Norhayati Mohd Noor (NMN). Kamaru Aryffin Baharuddin (KAB)
- Co-ordinating the review: RT, NY, NMN
- Literature search: RT, NY, NMN, KAB
- Quality assessment: RT, NY, KAB
- Entering data into RevMan: RT
- Data analysis: RT, NY, NMN, KAB
- Data interpretation: RT, NY, NMN. KAB
- Writing the review: RT, NY, NMN, KAB.

Conflicts of interest

None Declared.

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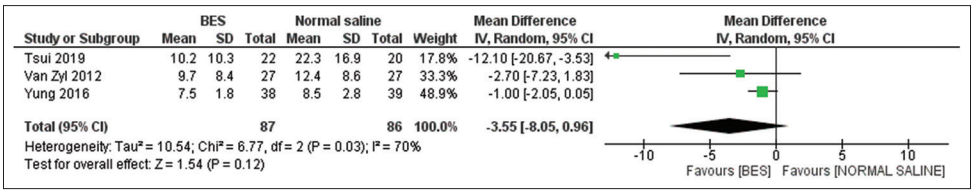
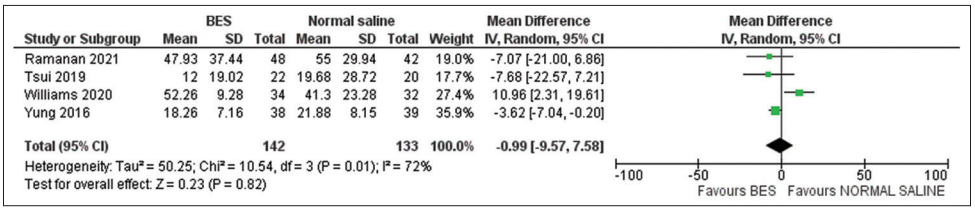
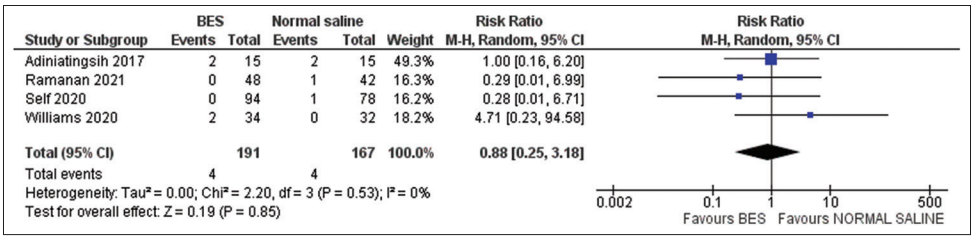


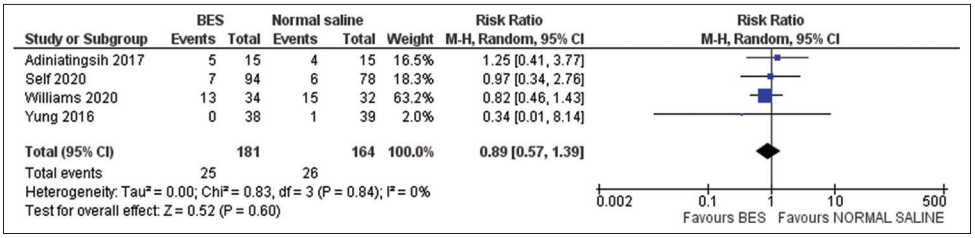
Supplementary Figure 1: Forest plot for the outcome of duration for recovery of pH. (MD [95% CI] −3.55 [−8.05, 0.96]; I^2 statistic = 70% P = 0.120; three trials, 177 participants). CI: Confidence interval, MD: Mean difference



Supplementary Figure 2: Forest Plot for the outcome of Length of ICU admission. (MD [95% CI] −1.00 (−9.57, 7.57); I^2 statistic = 72% P = 0.820; four trials, 275 participants). CI: Confidence interval, MD: Mean difference



Supplementary Figure 3: Forest Plot for the outcome of Adverse events: Mortality. (RR [95% CI] 0.88 (0.25, 3.18); I^2 statistic = 0%; P = 0.530; four trials, 358 participants). CI: Confidence interval, MD: Mean difference, RR: Risk ratio



Supplementary Figure 4: Forest plot for the outcome of adverse events: Acute renal failure. (RR [95% CI] 0.89 (0.57, 1.39); I^2 statistic = 0%; P = 0.600; four trials, 181 participants). CI: Confidence interval, MD: Mean difference, RR: Risk ratio