Balanced Crystalloids Compared to Saline in Patients with Diabetic Ketoacidosis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

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- Supplemental Materials:

Supplemental file 1: Predefined protocol designed on July 19 2019.
Supplemental file 2: Search Strategy.
Supplemental table 1: Definitions used for DKA resolution.
Supplemental table 2: Predefined data abstraction sheet.
Supplemental table 3: Details of the eligible trials.
Supplemental table 4: Risk of bias assessment of the included studies.
Supplemental table 5: Evidence profile including GRADE certainty assessments.
Supplemental table 6: Adverse events reported in the included RCTs.
Supplemental figure 1: Effect of using either saline or balanced crystalloids (BC) on mortality. df= degree of freedom.
Supplemental figure 2: Effect of using either saline or balanced crystalloids (BC) on DKA resolution. df= degree of freedom
Supplemental Figure 3. Sensitivity analysis limited to adults for time to DKA resolution
Supplemental Figure 4. Forest plot for Post resuscitation chloride levels.

Supplemental File 1: Predefined protocol designed on July 19 2019.

TITLE OF REVIEW:

Balanced crystalloids compared to saline in patients with diabetic ketoacidosis: A systematic review and meta-analysis of randomized controlled trials.

REVIEW TEAM MEMBERS:

Naif Alghamdi, Paityn Major, Dipayan Chaudhuri, Janice Tsui, Brent Brown, Wesley H. Self, Matthew W. Semler and Bram Rochwerg.

CONFLICT OF INTEREST:

Dr. Self received funding in May 2019 from Baxter Healthcare Corporation to speak at an educational conference on intravenous fluid use.

QUESTION OF INTEREST:

In patients with diabetic ketoacidosis (DKA), is there a benefit in using balanced crystalloids as compared to saline?

BACKGROUND:

DKA is a common complication that occurs due to metabolic compensation triggered by either absolute or relative insulin deficiency. It is a unique condition owing to the presence of mild to severe metabolic acidosis in addition to severe fluid deficits at baseline. Current guidelines recommend using crystalloids rather than colloids but it is unclear if there is a favour to consider saline versus balanced like Ringer's Lactate.

Saline has been used historically as the main crystalloid for fluid resuscitation in DKA. Recently some concerns were unmasked due to potential adverse events as hyperchloremia with worsening metabolic acidosis especially in DKA.

Moreover, recent randomized controlled trials (RCTs) demonstrated reduction in a composite outcome that included death, need for renal replacement therapy or persistent acute kidney injury at 30 days in patients receiving balanced versus unbalanced crystalloids.

As a result, our goal from this systematic review is to examine the role of balanced crystalloids versus saline in the resuscitation of patients with DKA.

METHODS:

We will conduct this systematic review and meta-analysis by following the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

- Data Sources and Searches:
  We will perform a comprehensive search of MEDLINE, EMBASE and the Cochrane trial registry from inception. We will not apply any language or quality restriction. An experienced health science librarian will assist in developing the search strategy. Keyword search terms will include: DKA, fluid resuscitation, saline and balanced crystalloids.

- Study Selection:
  Two reviewers (NA, PM) will screen all citations independently and in in duplicate in two stages, first titles and abstracts, then full texts to identify eligible studies. A citation identified as potentially eligible by either reviewer at the first stage will be advanced to the second stage. In the second stage, disagreements will be resolved by discussion or third person (BR) adjudication if necessary. Reasons for exclusion at the second stage will be stated.
  We will include all RCTs that compared balanced crystalloids versus saline for fluid resuscitation among patients with DKA. Studies in both children and adults will be included in both critical and non-critical care settings. Case reports, case series and observational studies will be excluded.
  The following outcomes will be included: Mortality (at the longest time point reported), DKA resolution (as defined by study authors), time to DKA resolution, post resuscitation chloride and bicarbonate levels and length of stay in intensive care unit or stepdown. For post resuscitation electrolyte levels, if there are multiple time points reports, we will use the longest follow up post resuscitation level.

- Data Extraction and Quality Assessment:
  Using a predefined data abstraction form, two reviewers (NA and PM) will complete data extraction independently and in duplicate. A third reviewer (BR) will resolve disagreements if necessary. The following will be abstracted: study characteristics, demographic data, interventions details and outcome data. A graph analyzer (http://plotdigitizer.sourceforge.net) will be used to extract data if needed. We will contact individual study authors in cases of missing study date.
  Risk of bias will be assessed independently by 2 reviewers (NA and DC) and in duplicate for each study using a modified Cochrane risk of bias tool that classifies risk of bias as: “low”, “probably low”, “probably high” or “high” for each of the following items: randomization and sequence generation, allocation sequence concealment, blinding, incomplete data, selective outcome reporting and other risk of bias. We will evaluate the overall risk of bias as the highest risk attributed to any criterion.

- Data Synthesis and Analysis

  We will perform all analyses using RevMan 5.3 (Cochrane Collaboration, Oxford) software. We will be generating study weights using the inverse variance method and we will use random effects model. Results will be presented as relative risks for dichotomous outcomes and as mean differences for continuous outcomes, both with 95% confidence intervals. For continuous outcomes, we will assume a normal distribution and we will convert inter-quartile range to standard deviation using the methods suggested by Cochrane handbook for systematic reviews of interventions. For cluster randomized controlled trials that meet the inclusion criteria, we will use the intra-cluster correlation coefficient to calculate the design effect to reduce the sample size based on the cluster design. We will assess for publication bias if the included RCTs are equal to or more than 10 studies.

  Heterogeneity will be assessed between studies using the χ^2 tests for homogeneity, the I^2 statistic and the visual inspection of the forest plots. The magnitude and direction of heterogeneity will be considered when deciding whether to rate down our certainty in the evidence for inconsistency. Based on the characteristics of the included studies, a decision will be made regarding the need for performing subgroup or sensitivity analysis.

- Assessment of Certainty of Evidence:

  We will appraise the overall certainty of evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation approach (GRADE).

Supplemental File 2: Search Strategy.

Database: As an example: Embase Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)
Search Strategy:

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1 diabetic ketoacidosis/
2 diabet* acidos*.mp.
3 diabet* ketoacidos*.mp.
4 diabet* ketos*.mp.
5 KTA.ti,ab.
6 or/1-5
7 isotonic solution/
8 isotonic solution*.mp.
9 crystalloid/
10 crystalloid.mp.
11 electrolyte/
12 electrolyte solution/
13 Electrolyte*.mp.
14 or/7-13
15 balanced solution*.mp.
16 acetic acid plus gluconate sodium plus magnesium chloride plus potassium chloride plus sodium chloride/
17 plasma-lyte.mp.
18 plasmalyte.mp.
19 acetic acid/
20 Sodium Acetate.mp.
21 potassium chloride/
22 Potassium Chloride.mp.
23 magnesium chloride/
24 Magnesium Chloride.mp.
25 Ringer acetate/
26 Ringer lactate solution/
27 Ringer solution/

28 ringer*.mp.
29 Hartmann solution/
30 Hartman* solution.mp.
31 or/15-30
32 sodium chloride/
33 (sodium chloride or saline).mp.
34 or/32-33
35 31 and 34
36 14 or 35
37 fluid therapy/
38 fluid therap*.mp.
39 fluid resuscitation/
40 fluid resuscitation.mp.
41 resuscitation/
42 Water-Electrolyte Imbalance/
43 Water-Electrolyte Imbalance.mp.
44 or/37-43
45 6 and 36 and 44
46 diabetic ketoacidosis/th [Therapy]
47 45 or 46 (2086)

Supplemental Table 1: Definitions used for DKA resolution.

Study	DKA resolution definition
Mahler(24)	Not used
Van Zyl(25)	HCO^3 equal and >15 and pH equal and > 7.30
Aditianingsih(26)	Not reported
Tsui(27)	Serum glucose< 200 mg/dl and 2/3 (HCO^3 equal and>15, venous pH>7.3 or anion gap< 12 mEq/L)
Self(28)	Serum glucose< 200 mg/dl and 2/3 (HCO^3 equal and>15, venous pH>7.3 or anion gap equal or < 12 mEq/L)
Yung(29)	HCO^3 equal and >15 or pH>7.30
Williams(30)	HCO^3 equal and >15, pH equal and > 7.30 and normal sensorium

Supplemental Table 2: Predefined data abstraction sheet.

Basic Study Information	
Study Title	
Journal/Conference	
Year of Publication	
Author	List first author only
Correspondence Email	
Information requested from the author? If yes when?	
Number of Sites	
Country/Countries of Study	
Ethics and conflict of interest	
Study Sponsor	
Research ethic service approval	
Population Description	
Inclusion Criteria	
Exclusion Criteria	
Median/Mean age	
Number of Patients Fulfilling Criteria and approached?	
Number of patients randomized?	
Intervention (Types of fluid)	
Fluid type used in both arms	
Duration of Intervention	
Volume of Intravenous fluid	
Average duration of follow up	
Risk of Bias Assessment	
Randomization and sequence generation?	
Concealment of the intervention?	
Blinding of the intervention?	
Were there any missing data?	
Was there a concern of selective reporting?	
Any other bias noted?	
Risk of bias overall?	
Outcome #1	
Outcome being evaluated	e.g. DKA resolution
Dichotomous or continuous outcome?	

Intervention 1: Number analyzed	
Intervention 1: Number of Events/Mean	
Intervention 2: Number analyzed	
Intervention 2: Number of Events/Mean	
Intervention 3: Number analyzed	
Intervention 3: Number of Events/Mean	
Comments	
Outcome #2	
Outcome being evaluated	e.g. Time to DKA resolution
Dichotomous or continuous outcome?	
Intervention 1: Number analyzed	
Intervention 1: Number of Events/Mean	
Intervention 2: Number analyzed	
Intervention 2: Number of Events/Mean	
Intervention 3: Number analyzed	
Intervention 3: Number of Events/Mean	
Comments	

Supplemental Table 3: Details of the eligible trials.

Author	Mahler(24)	Van zyl(25)	Aditianingsih(26)	Tsui(27)	Self(28)	Yung(29)	Williams(30)
Site	Louisiana State University Health Sciences Center – Shreveport. Single site.	University of Pretoria. Kalafong (secondary) hospital and Steve Biko Academic (tertiary) hospital. Multi-site.	Emergency department of Cipto Mangunkusumo Hospital Jakarta. Single site.	The Emergency department of the University of Oklahoma Medical Center, an academic tertiary hospital. Single site.	Emergency and Intensive Care Unit departments at Vanderbilt University in Nashville in Tennessee. Single site.	North Adelaide, Australia. Single site	Emergency department and Intensive Care Unit departments in a large tertiary Hospital in Chandigarh. Single site.
Country	USA	South Africa	Indonesia	USA	USA	Australia	India
Design	Randomized controlled trial (RCT). Double blind.	RCT. Double blind...	RCT. Single blind.	RCT. Open label.	Subgroup analysis of cluster RCTs. Not blinded. .	RCT. Double blind.	RCT. Double blind.
Definition of Diabetic ketoacidosis (DKA)	Moderate to severe DKA defined by serum glucose greater than 200 mg/dL, serum bicarbonate (HCO3) less than or equal to 15 mmol/L, and anion gap greater than or equal to 16 mmol/L.	Venous pH at presentation 6.9–7.2, presence of at least two plus ketones on urine dipstick test at presentation and a capillary blood glucose of >13 mmol/l.	Blood sugar >250 mg/dl, positive ketone bodies in the blood and arterial pH <7.35	Blood glucose >250 mg/dl, pH < 7.3, serum HCO3 < 18 mEq/L and anion gap >10.	DKA defined as plasma glucose concentration greater than 250mg/dL, plasma HCO3 less than or equal to 18 mEq/L and calculated anion gap greater than 10 mEq/L.	Hyperglycemia (blood glucose >11 mmol/L), venous pH <7.3 and/or HCO3 <15 mmol/L and ketonemia or ketonuria and glycosuria.	Blood glucose> 11 mmol/L or 200 mg/dL, venous pH <7.3 and a serum beta hydroxybutyrate >3 mmol/L.
Inclusion criteria	Patients aged 18-65 with moderate to severe DKA.	Age >18 years with DKA in either newly diagnosed or previously known to have diabetes mellitus, type 1 or type 2 diabetes	Patients aged 18-65 with DKA.	Adult DKA patients.	Age 18 years or older, presentation to the Emergency department during the 15-month period when both the ED and ICUs were participating in the	Children with moderate to severe DKA were eligible. Criteria for the diagnosis of moderate to severe DKA are hyperglycemia (blood glucose >11	Children aged > 1 month to < 12 years who presented to the pediatric emergency room with DKA were enrolled into the study.

		and should have received <1L of resuscitation fluid prior to enrolment.			SALT-ED and SMART trials (January 1, 2016, to March 31, 2017), a clinical diagnosis of DKA in the ED.	mmol/L), venous pH <7.3 and/or HCO3 <15 mmol/L and ketonemia or ketonuria and glycosuria. Moderate DKA was determined as pH ≥7.1, HCO3 ≥ 5 mmol/L and severe DKA as pH <7.1, HCO3 <5 mmol/L. If HCO3 did not correlate with pH, the pH determined the severity.	
Exclusion criteria	Patients with hyperosmotic hyperglycemic nonketotic syndrome, hyperglycemia without signs of DKA, mild DKA, and patients receiving greater than 500mL of crystalloid or an Insulin bolus before enrollment in the study. Also, evidence of myocardial infarction, sepsis, respiratory failure, cerebral edema, and age less than 18 or greater than 65.	If another cause for acidosis was present, if severely ill and in need of inotropic or ventilatory support and if more than 1L of resuscitation fluid was administered before enrolment.	Patients with respiratory failure requiring mechanical ventilation, end-stage renal disease on hemodialysis, congestive heart failure, corrected sodium >158 or <120 mmol/L, myocardial infarction with signs of heart failure, traumatic brain injury with cerebral edema signs, and liver failure.	Age< 18 years, pregnancy, end stage renal disease or dialysis dependent, a condition for which aggressive fluid resuscitation is contra-indicated, corrected Na < 115 mmol/L, the patient does not understand English or intubated.	Transfer from an outside hospital to the study Emergency department, admission to the cardiac or neurologic Intensive Care Unit and presentation to the Emergency department within 24 hours prior to a planned crossover in the trial.	Patients with: Glasgow coma score (<11, mechanical ventilation, hyponatremia, potassium >5.5 mmol/L or previous enrolment.	Children with symptomatic cerebral edema (Glasgow coma score < 8 at presentation), known chronic kidney disease or liver disease or who had received pre-referral fluids and/or Insulin at the time of hospital presentation.

Number of patients	45	54	30	42	172> 106 after sample size reduction using intra-cluster correlation coefficient given cluster design.	77	66
Comparison	Saline vs Plasma-Lyte	Saline vs Ringer's Lactate	Saline vs Ringerfundin (Type of balanced crystalloids)	Saline vs Ringer's Lactate or Plasma-Lyte.	Saline vs Ringer's Lactate or Plasma-Lyte	Saline vs Hartmann's Solution	Saline vs Plasma-Lyte
Total fluid given (mean or median)	Not mentioned.	Not mentioned.	Saline: 6.23 L. Ringerfundin: 6.23 L	Saline: 2.585 L. Ringer's Lactate or Plasma- Lyte: 2.265 L	Saline: 4694 mL. Ringer's Lactate or Plasma-Lyte: 4000 mL.	Saline: 2167 mL. Hartmann's Solution: 1771 mL	Saline: 1190 mL. Plasma-Lyte: 1200 mL
Outcome	Post-resuscitation HCO3 and chloride (Cl) level.	Time to reach a venous pH of 7.32, to achieve serum glucose of 14 mmol/l and time to resolution of DKA defined as fulfilment of the following three criteria: venous pH > 7.3, serum HCO3 equal and more than 18 mmol/l and blood glucose <11.1 mmol/	Standard base excess and strong ion difference.	Primary outcome was time to resolution of DKA in hours.	The primary outcome was time to DKA resolution. Secondary outcomes were: time to Intravenous Insulin discontinuation and other outcomes as per the study supplement that include: total amount of Intravenous Insulin, Intensive Care Unit admission, in-hospital mortality and changes in plasma electrolyte concentrations.	Primary: Time to reach HCO3 equal and more than 15 mmol/L. Secondary outcomes: time to reach venous pH of 7.3; time to start subcutaneous Insulin; time to start oral intake; time to change in fluid type, either/or 0.45% saline or the addition of glucose to study fluid; total Insulin requirement per kilogram; length of stay in high dependency unit; time to normalisation of anion gap.	Primary outcome was incidence of new onset or progressive acute kidney injury as defined in the trial. Secondary outcomes were rate of resolution of acute kidney injury, time to resolution of DKA (pH > 7.3, HCO3 > 15mEq/L and normal sensorium), change in chloride, pH and HCO3 levels (baseline, 24 h), proportion of in-hospital all-cause mortality, proportion of children requiring renal replacement therapy, length of ICU and hospital stay.

Supplemental Table 4: Risk of bias assessment of the included studies.

Study	Randomization generation sequence	Allocation concealment	Blinding	Incomplete data	Selective reporting	others	Risk of bias overall
Mahler(24)	Low	Low	Low	Low	Low	Low	Low
Van Zyl(25)	Low	Low	Low	Low	Low	Low	Low
Aditianingsih(26)	Probably Low	Low	Low	Low	Low	Low	Low
Tsui(27)	High	High	High	Low	Low	Low	High
Self(28)	Low	Low	Low	Low	Low	Low	Low
Williams(29)	Low	Low	Low	Low	Low	Low	Low
Yung(30)	Low	Low	Low	Low	Low	Low	Low

Supplemental Table 5: Evidence profile including GRADE certainty assessments.

Certainty assessment							№ of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Balanced Crystalloids	Saline	Relative (95% CI)	Absolute (95% CI)	
DKA resolution.											
6	Randomised trials	not serious	not serious	not serious	serious [a]	none	200/212 (94.3%)	180/195 (92.3%)	**RR 1.00** (0.97 to 1.03)	**0 fewer per 1,000** (from 28 fewer to 28 more)	⨁⨁⨁◯ MODERATE
Time to DKA resolution. (assessed with: hours.)											
6	Randomised trials	not serious	not serious	not serious	serious [b]	none	202	183	-	MD **3.51 Hours higher** (0.9 higher to 6.12 higher)	⨁⨁⨁◯ MODERATE
Post treat HCO3 (assessed with: mmol/L)											
5	Randomised trials	not serious	not serious	not serious	serious [c]	none	174	159	-	MD **1.5 mmol/L lower** (2.33 lower to 0.67 lower)	⨁⨁⨁◯ MODERATE
Duration of hospital days. (assessed with: days.)											
4	Randomised trials	not serious	not serious	not serious	serious [d]	none	116	108	-	MD **0.89 days higher** (0.34 higher to 1.43 higher)	⨁⨁⨁◯ MODERATE
Post treat Cl (assessed with: mmol/L)											
6	Randomised trials	not serious	serious [e]	not serious	serious [f]	none	212	197	-	MD **1.62 mmol/L higher** (0.4 lower to 3.64 higher)	⨁⨁◯◯ LOW
Mortality											
6	Randomised trials	not serious	not serious	not serious	very serious [f]	none	4/189 (2.1%)	4/171 (2.1%)	**RR 1.13** (0.32 to 4.08)	**3 fewer per 1,000** (from 16 fewer to 72 more)	⨁◯◯◯ VERY LOW

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

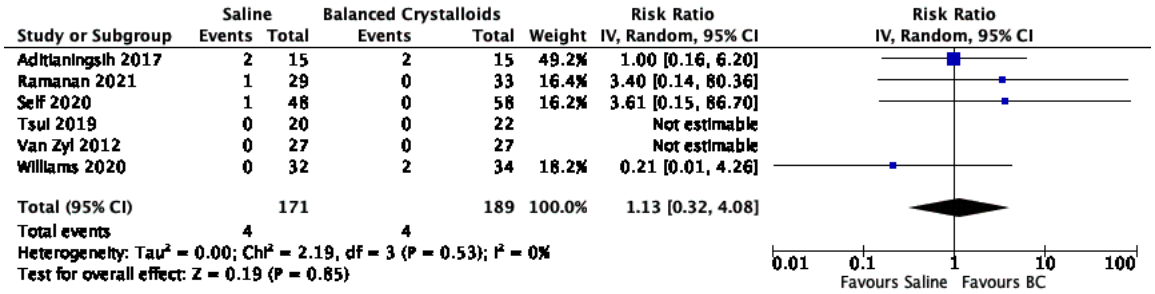
Explanations

a. Despite point estimate that suggests no effect, 95% confidence intervals do not rule out important benefit or harm. Also, low event number contributes to imprecision.
b. Point estimate suggests longer time to DKA resolution with saline, however lower end of the 95% CI suggests no effect thereby contributing to imprecision.
c. Point estimate suggests lower bicarbonate level with saline, however low patients number contributes to imprecision.
d. Point estimate demonstrates higher length of stay in saline, however low number of patients contributes to imprecision.
e. Important statistical heterogeneity given high I squared and significant Chi-squared test.
f. Very wide confidence intervals which do not exclude significant benefit or significant harm.

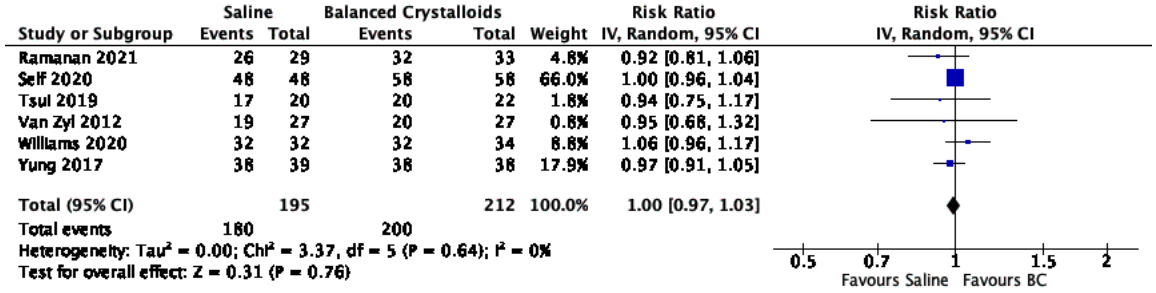
Supplemental Table 6: Adverse events reported in the included RCTs.

	Electrolyte disturbances		Cerebral edema		Hypoglycemia	
	Balanced crystalloids	Saline	Balanced crystalloids	Saline	Balanced crystalloids	Saline
Mahler(24)	Not reported	Not reported	None	None	None	None
Van Zyl(25)	Not reported	Not reported	Not reported	Not reported	4 patients	None
Aditianingsih(26)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Tsui(27)	None	None	None	None	None	None
Self(28)	11 patients with hyperkalemia 9 patients with hypokalemia	18 patients with hyperkalemia 15 patients with hypokalemia	Not reported	Not reported	Not reported	Not reported
Williams(29)	9 patients with hypokalemia	13 hypokalemia	1 patient	None	2 patients	3 patients
Yung(30)	1 patient with hypernatremia patients with hypokalemia	None	Not reported	Not reported	Not reported	Not reported

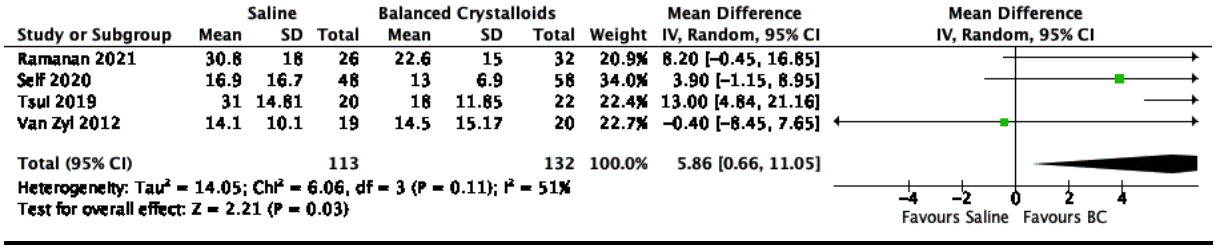
Supplemental Figure 1. Effect of using either saline or balanced crystalloids (BC) on mortality.



Supplemental Figure 2. Outcome = DKA resolution.



Supplemental Figure 3. Sensitivity analysis limited to adults for time to DKA resolution



Supplemental Figure 4. Outcome = Post resuscitation chloride level