Balanced Versus Unbalanced Fluid in Critically Ill Children: Systematic Review and Meta-Analysis*

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OBJECTIVES: The ideal crystalloid fluid bolus therapy for fluid resuscitation in children remains unclear, but pediatric data are limited. Administration of 0.9% saline has been associated with hyperchloremic metabolic acidosis and acute kidney injury. The primary objective of this systematic review was to compare the effect of balanced versus unbalanced fluid bolus therapy on the mean change in serum bicarbonate or pH within 24 hours in critically ill children.

DATA SOURCES: We searched MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase, CENTRAL Trials Registry of the Cochrane Collaboration, ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform.

STUDY SELECTION: Using the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols guidelines, we retrieved all controlled trials and observational cohort studies comparing balanced and unbalanced resuscitative fluids in critically ill children. The primary outcome was the change in serum bicarbonate or blood pH. Secondary outcomes included the prevalence of hyperchloremia, acute kidney injury, renal replacement therapy, and mortality.

DATA EXTRACTION: Study screening, inclusion, data extraction, and risk of bias assessments were performed independently by two authors.

DATA SYNTHESIS: Among 481 references identified, 13 met inclusion criteria. In the meta-analysis of three randomized controlled trials with a population of 162 patients, we found a greater mean change in serum bicarbonate level (pooled estimate 1.60 mmol/L; 95% CI, 0.04–3.16; $p = 0.04$) and pH level (pooled mean difference 0.03; 95% CI, 0.00–0.06; $p = 0.03$) after 4–12 hours of rehydration with balanced versus unbalanced fluids. No differences were found in chloride serum level, acute kidney injury, renal replacement therapy, or mortality.

CONCLUSIONS: Our systematic review found some evidence of improvement in blood pH and bicarbonate values in critically ill children after 4–12 hours of fluid bolus therapy with balanced fluid compared with the unbalanced fluid. However, a randomized controlled trial is needed to establish whether these findings have an impact on clinical outcomes before recommendations can be generated.

KEY WORDS: balanced fluid; critically ill children; crystalloid fluid; normal saline; Ringer's lactate; resuscitation

BACKGROUND

IV crystalloid fluid bolus therapy is one of the most frequently administered therapies for replacement of intravascular volume and restoration of hemodynamic stability in critically ill children (1–3). However, the ideal composition of crystalloid solution remains unclear (4–9). Historically, 0.9% saline has been the most commonly used solution and is the most widely available (10). However, due to its high sodium (154 mmol/L) and chloride (154 mmol/L) concentration, 0.9% saline administration has been associated with hyperchloremic metabolic

acidosis (11, 12) and may therefore lead to the development or worsening of metabolic acidosis. In addition, normal 0.9% normal saline has been associated with decreased renal perfusion, acute kidney injury (AKI), increased proinflammatory state, and hemodynamic instability leading to concerns regarding its use in critically ill patients (13–17). In pediatric septic shock, hyperchloremic metabolic acidosis was associated with the amount of fluid received, and hyperchloremia (minimum serum chloride ≥ 110 mmol/L) was found to be an independent risk factor for 28-day mortality or persistence of organ failure (18, 19).

As a result, balanced solutions were developed with a decreased chloride load and added buffers making their composition and pH closer to human whole blood (see Additional file 1 in the protocol: type and composition of different isotonic crystalloids solution compared to human plasma [https://systematicreviewsjournal. biomedcentral.com/articles/10.1186/s13643-019-1109-2]). Ringer's lactate (RL), the most commonly used balanced solution, contains only 109 mmol/L compared with 154 mmol/L of chloride. RL, however, has decreased availability, higher cost (C$1.80 per liter vs C$1.41 per liter of 0.9% saline), and a lack of convincing data proving its superiority to 0.9% saline (10).

Numerous randomized trials, systematic reviews, and meta-analyses in perioperative and critically ill adults have demonstrated a decreased prevalence of hyperchloremia and metabolic acidosis with balanced fluid compared with unbalanced crystalloid fluids although benefits on clinical outcomes such as AKI, renal replacement therapy (RRT), and mortality remain uncertain (20–24). In critically ill children, data are more limited with a few small and inadequately powered studies (25–34). In a recent systematic review and meta-analysis, no benefits were found from balanced fluids on in-hospital mortality or AKI in critically ill adults and children or in the pediatric subgroup mortality analysis (odds ratio [OR], 0.97; 95% CI, 0.10–9.80; $p = 0.98$) (35). However, this meta-analysis only included four pediatric trials with a total of 258 patients, representing 0.2% of the weight of the mortality analysis. As mortality in critically ill children is significantly lower than in critically ill adults (36), we believe metabolic acidosis is a more appropriate outcome to study.

Although more convincing pediatric data are still needed before guidelines can be firmly generated, the Canadian Pediatric Society and Pediatric Surviving Sepsis Campaign guidelines already suggest the use of balanced over unbalanced fluids (37). Therefore, the objective of this systematic review and meta-analysis was to compare the effect of balanced versus unbalanced fluid bolus therapy on serum bicarbonate or blood pH in critically ill children.

MATERIAL AND METHODS

Our study was designed according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines and registered on PROSPERO (CRD42019134240) (see Additional file 2 in the protocol: PRISMA-P 2015 checklist) (9, 38–40). A more detailed description of the methods has been previously published (9).

Study Selection

Randomized controlled trials (RCTs) and observational cohort studies evaluating the effect of administration of balanced versus unbalanced fluid bolus therapy on laboratory and/or clinical outcomes were eligible. The population of interest was critically ill children, from 28 days old to 18 years old (41), who require active fluid bolus therapy in any setting: emergency department, ICU, operating room, or inpatient step-down units. Unbalanced fluids were defined as 0.9% saline, and balanced fluids were defined as sodium-based fluids with chloride content less than 154 mmol/L and the addition of buffers (10, 42). Fluid bolus therapy was defined as a minimum of 20 mL/kg or 1 L cumulative, and studies assessing only maintenance fluids were excluded (43–45). The primary outcome was the mean change in serum bicarbonate or serum pH within 24 hours of fluid bolus therapy compared with baseline levels. The primary outcome in our published protocol was intended to be the prevalence and/or time to resolution of metabolic acidosis; however, these data were unavailable for most studies. Secondary outcomes were time to resolution of metabolic acidosis, prevalence of hyperchloremia (defined as chloride > 106 mmol/L), AKI as defined by pediatric Risk, Injury, Failure, Loss End Stage Renal Disease (pRIFLE) or AKI Network or Kidney Disease Improving Global Outcomes (KDIGO) within 48 hours of the fluid bolus therapy (46–48), need and/or duration of RRT, duration of vasopressors, duration of mechanical ventilation, total volume of rehydration needed per day, need

for extracorporeal membrane oxygenation (ECMO), ICU and hospital length of stay (LOS), and mortality at any time point.

Data Sources and Search Strategy

In collaboration with an experienced clinical research librarian, we developed and validated an electronic search strategy (49–51) using the following databases: MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase, CENTRAL Trials Registry of the Cochrane Collaboration using the Ovid interface as well as ClinicalTrials.gov (52), and the World Health Organization International Clinical Trials Registry Platform (53) (see Additional file 3 in the protocol: search strategy and Additional file 4 in the protocol: data extraction) (9). References of relevant studies, review articles, and included studies were also reviewed (54). The search included all published studies with no restriction of language or journal of publication up to November 2020.

Screening and Data Extraction

Studies were screened, selected, and data extracted by two independent authors (S.R.A., A.R.L.) using a standardized and calibrated form detailed in the published protocol (9). Disagreements were resolved by consensus and/or a third independent reviewer (K.M.). If insufficient data were provided to assess study eligibility or extract relevant data, corresponding authors were contacted.

Evidence Synthesis

Descriptive statistics were provided on all included studies. Data on study characteristics, interventions, outcomes, and important covariates were summarized using frequencies and percentages for dichotomous outcomes and means and SDs or medians and interquartile ranges (IQRs), as appropriate, for continuous outcomes. For comparison purposes, when medians, ranges, or IQRs were reported, they were converted to means and SDs according to the method proposed by Wan et al (55). Individual participant data were available for serum bicarbonate in one study (28), which allowed us to calculate the correlation between bicarbonate levels pre and post bolus so as to compute the SE of the change. The effect measure used was mean difference for continuous outcomes and OR for dichotomous outcomes.

For the observational studies included in our systematic review, there was significant heterogeneity and a high level of bias as per the risk-of-bias tool for randomized trial (RoB 2). Therefore, we elected to conduct the meta-analysis only on the available RCT pooled data and only provide individual study results and descriptive statistics for the observational studies. We pooled results of included RCTs using a random effects model after excluding high risk of bias trials. Statistical heterogeneity among studies was examined using the I^2 statistic, and observed heterogeneity was elucidated by examining various sources including patient populations, settings, and interventions. Statistical significance was determined at a level α less than or equal to 0.05 and p value used to inform on the strength of the evidence (56). Analysis was performed using the R statistical software Version 3.5.1 (57). Forest plots were created using the R package Metafor (58). Subgroup analysis was not performed due to the small numbers of studies, patients, and population heterogeneity.

Risk of Bias Assessment

Two authors independently assessed the risk of bias for each included study using Risk Of Bias in Nonrandomized Studies – of Interventions (ROBINS-I) tool (59) for non-RCTs and the revised Cochrane RoB 2 (60, 61).

RESULTS

Studies Characteristics

A total of 481 references were identified by our search. After exclusion of duplicates and abstract screening, 42 full-text articles were assessed for eligibility (**Fig. 1**). The Kappa score was 0.75. Characteristics of included studies are summarized in **Supplemental Table 1** (http://links.lww.com/PCC/B935). Thirteen studies with a total of 11,848 patients met eligibility criteria, including nine RCTs enrolling 557 patients and four observational studies. Three RCTs with a total of 162 patients were included in the meta-analysis of our primary outcome. Overall study populations included patients with severe gastroenteritis (27–30), severe sepsis and septic shock (31–33, 62, 63), dengue shock (25, 26), and diabetic ketoacidosis (34, 64). The majority of studies (10/13) were single center, whereas one RCT (30) and two observational studies (31, 32) were multicenter. RL was the most commonly used balanced fluid (8/13), whereas 0.9% normal saline was
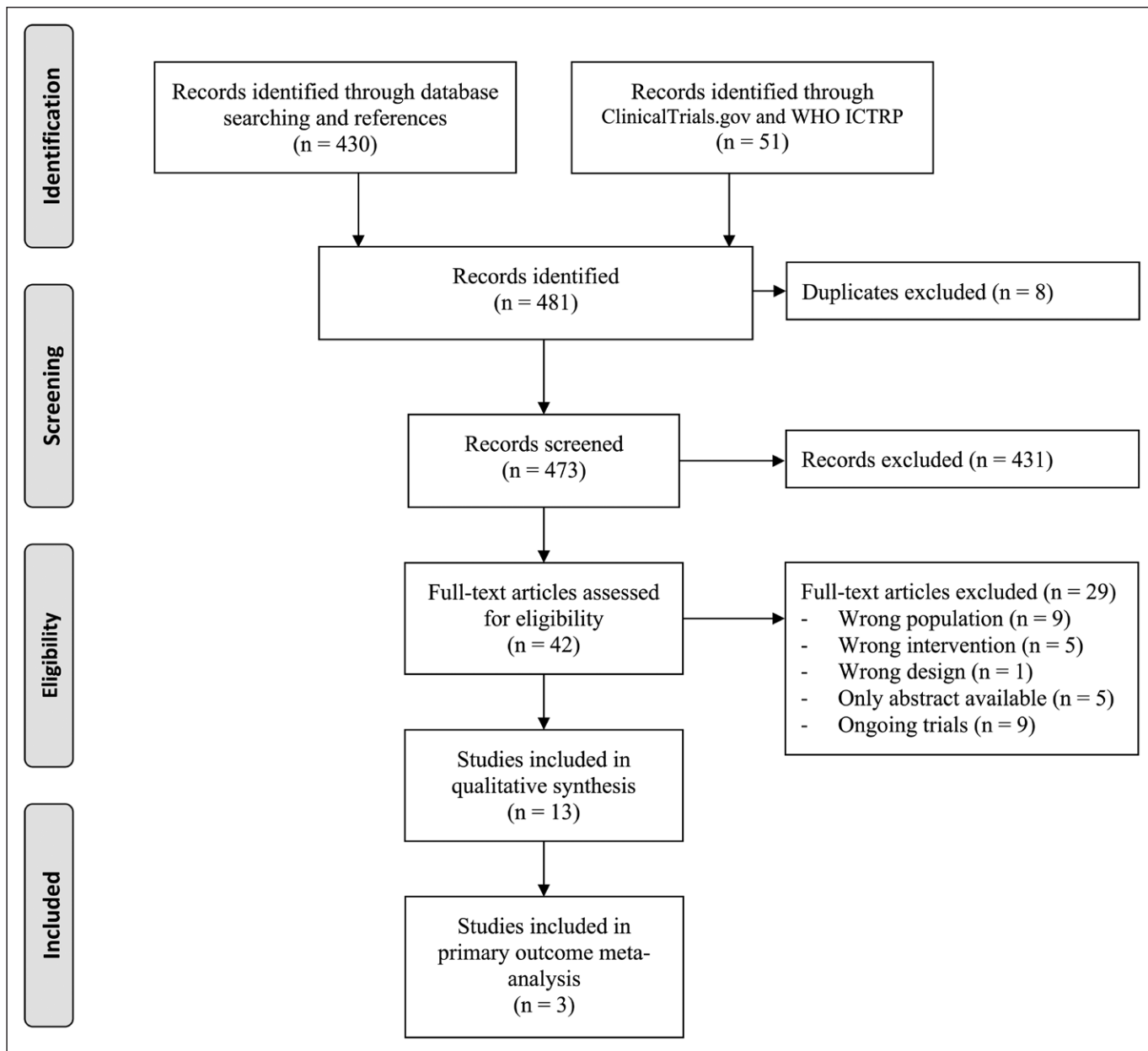
Figure 1. Preferred Reporting Items for Systematic Review and Meta-analysis 2009 flow diagram. ICTRP = International Clinical Trials Registry Platform, WHO = World Health Organization. From Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group: Preferred reporting items for systematic review and meta-analysis: The PRISMA Statement. *PLos Med* 21; 6:e1000097. For more information, visit http://www.consort-statement.org/.

the unbalanced fluid in all 13 studies. The bias assessment detailed in **Supplemental Table 2** (http://links.lww.com/PCC/B936): Risk of bias assessment reveals low-moderate risk of bias for seven of nine RCTs (26, 27, 29, 30, 34, 62, 63) and high risk of bias for two of nine RCTs (25, 64).

Primary Outcome

Three RCTs (27, 29, 30) provided adequate data to evaluate the primary outcome. In these trials, follow-up serum bicarbonate levels were measured at 4 (30), 6, (27) and 6–12 hours (29) post fluid administration. The pooled estimate of the three RCTs (27, 29, 30) with a total of 162 patients revealed a difference in mean change of 1.60 mmol/L in serum bicarbonate levels following fluid administration (95% CI, 0.04–3.16; $I^2 = 59.2\%$; $p = 0.04$) as shown in **Figure 2A**. Two of the three RCTs (27, 29) reported follow-up measures of pH with a pooled mean difference of 0.03 (95% CI, 0.00–0.06; $I^2 = 14.3\%$; $p = 0.03$) in favor of balanced fluid as presented in **Figure 2B**.

Secondary Outcomes

Different outcome measures for resolution of metabolic acidosis were reported. In a population of diabetic ketoacidosis, Williams et al (64) and Yung et al (34)
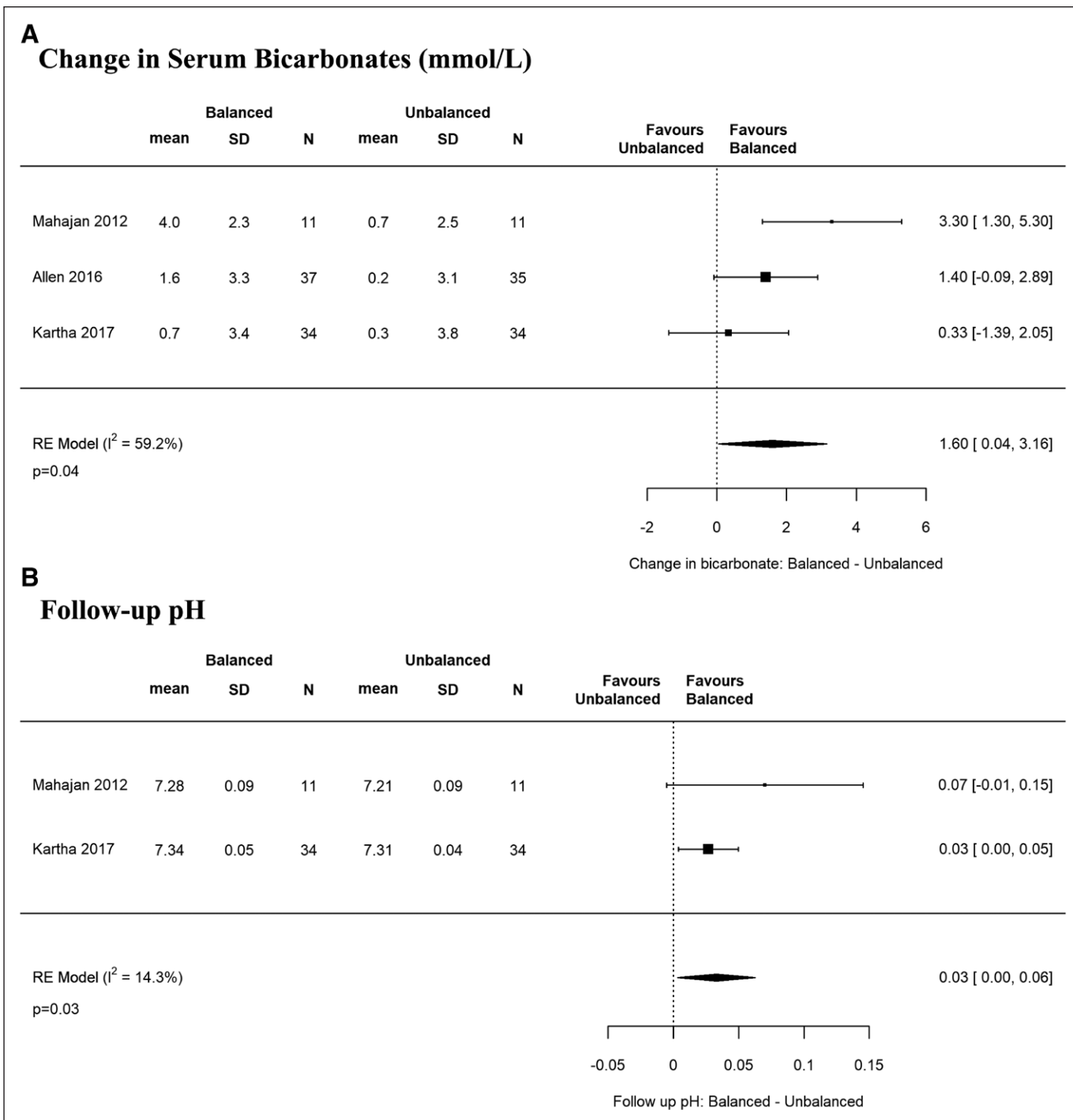
A

Change in Serum Bicarbonates (mmol/L)

	Balanced			Unbalanced				
	mean	SD	N	mean	SD	N		
Mahajan 2012	4.0	2.3	11	0.7	2.5	11		3.30 [1.30, 5.30]
Allen 2016	1.6	3.3	37	0.2	3.1	35		1.40 [-0.09, 2.89]
Kartha 2017	0.7	3.4	34	0.3	3.8	34		0.33 [-1.39, 2.05]
RE Model (I² = 59.2%) p=0.04								1.60 [0.04, 3.16]

B

Follow-up pH

	Balanced			Unbalanced				
	mean	SD	N	mean	SD	N		
Mahajan 2012	7.28	0.09	11	7.21	0.09	11		0.07 [-0.01, 0.15]
Kartha 2017	7.34	0.05	34	7.31	0.04	34		0.03 [0.00, 0.05]
RE Model (I² = 14.3%) p=0.03								0.03 [0.00, 0.06]

Figure 2. Acidosis forest plot: forest plot comparing change in serum bicarbonate from baseline to follow-up post exposition (**A**) and forest plot comparing follow-up pH (**B**) in critically ill children exposed to balanced versus unbalanced fluids. RE = random effect.

reported no significant difference in time to resolution of acidosis after fluid bolus therapy. In an observational study on patients with severe sepsis/septic shock, Samransamruajkit (33) showed a significant difference in base excess at 6 and 24 hours in the RL group compared with the 0.9% saline group (2.46 sd ± 4.07 vs –3.65 sd ± 4.14 in unbalanced; $p < 0.001$ at 6 hr and 3.36 sd ± 3. vs –1.18 sd ± 3.95; $p = 0.002$ at 24 hr),

whereas Anantasit et al (63) (RCT) did not find a significant difference in the prevalence of hyperchloremic metabolic acidosis.

Three RCTs reported serum chloride levels at 4 (30), 6 (27), and 6–12 hours (29), respectively, following fluid administration. Serum chloride levels were lower in the balanced compared with unbalanced group (**Fig. 3A**) but did not reach statistical significance
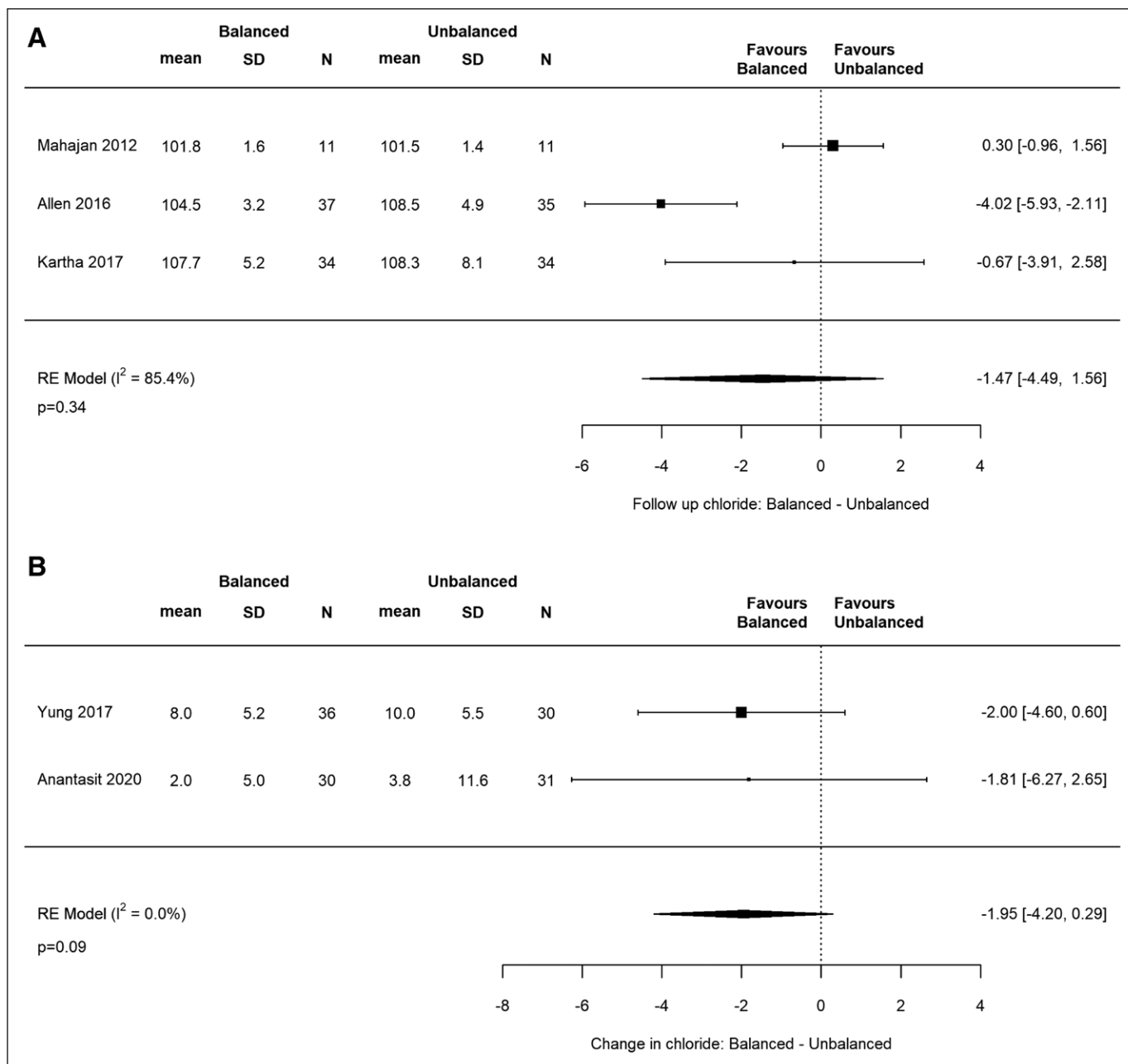
Figure 3. Chloride forest plot: forest plot comparing serum chloride level at baseline (**A**) and follow-up (**B**) in critically ill children exposed to balanced versus unbalanced fluids. RE = random effect.

with a pooled mean difference of –1.47 mmol/L (95% CI, –4.49 to 1.56; $I^2 = 85.4\%$; $p = 0.34$). Two RCTs (34, 63) reported a change in serum chloride levels from baseline and found a pooled estimate of the difference in mean change of –1.95 mmol/L in serum chloride levels (95% CI, –4.20 to 0.29; $I^2 = 0.0\%$; $p = 0.09$) measured at 6 hours (63) or unspecified time point (34) post intervention (**Fig. 3B**).

AKI was defined by pRIFLE classification, KDIGO classification, or an unspecified definition in RCTs (27, 34, 62–64) and *International Classification of*

Diseases, 9th Edition codes (31, 32). The pooled estimate of the four RCTs (27, 34) suggested no difference between both groups (OR, 0.97; 95% CI, 0.46–2.04; $I^2 = 0.0\%$; $p = 0.94$) as shown in **Figure 4A**. The two observational studies showed no significant differences in the prevalence of AKI within 24 hours (32) or during the hospital stay (31) in the balanced group. RRT was reported in three observational studies (31–33) and three RCTs (34, 62–64). The pooled estimate of three of those RCTs showed no difference between balanced and unbalanced fluid groups (OR, 0.63; 95% CI, 0.08–5.31;
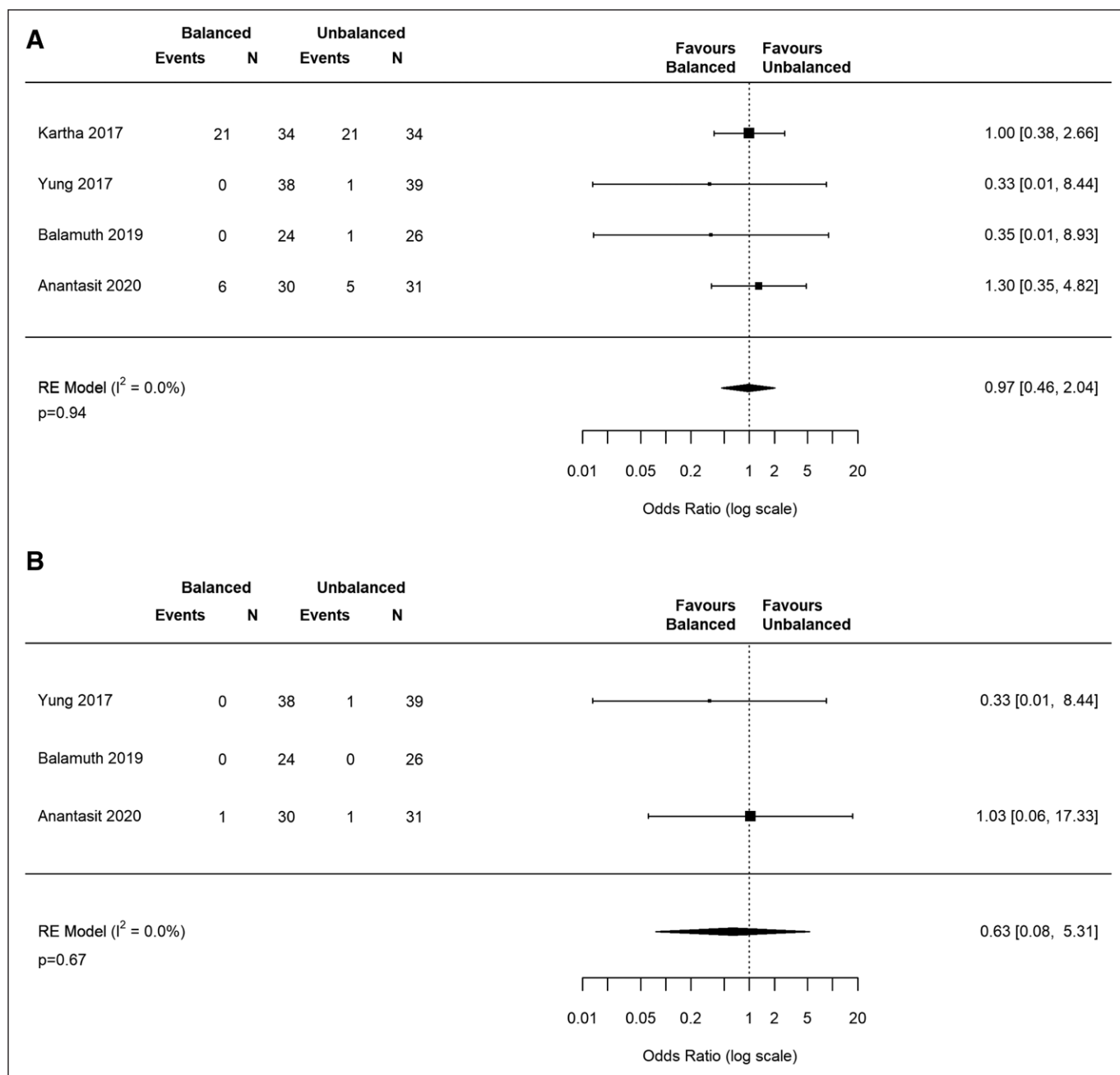
Figure 4. Renal forest plot: forest plot comparing prevalence of acute kidney injury (**A**) and renal replacement therapy (**B**) in critically ill children exposed to balanced versus unbalanced fluids. RE = random effect.

$I^2 = 0.0\%$; $p = 0.67$) as shown in **Figure 4B**. The duration of RRT was not specified in the studies.

Total volume of rehydration needed was reported in eight studies with means ranging from 33 to 541.33 mL/kg as shown in **Supplemental Table 3** (http://links.lww.com/PCC/B937). No meta-analysis was feasible because of significant heterogeneity in reported timing of fluid bolus therapy (25, 26, 28, 30, 33, 34, 62, 64) and inclusion by some of maintenance fluids and/or rehydration fluids in the total IV fluid received

(27, 29, 63). Overall, two of two observational studies and five of eight RCTs (27–30, 33, 34, 64) who reported volume of fluid administered showed evidence toward less volume of fluid bolus needed in the balanced groups when compared with unbalanced groups (Supplemental Table 3, http://links.lww.com/PCC/B937).

Vasopressor needs were assessed in two retrospective studies (32, 33) and suggested no differences between groups in inotropic score (mean 15.47 sᴅ ±

9.04 in balanced group vs mean of 23.7 SD ± 17.36 in the unbalanced group; $p = 0.1$) or vasoactive infusion days within 24 hours (mean 3.4; 95% CI, 3.1–3.9 in the balanced group vs mean of 3.4; 95% CI, 3.1–3.8 in the unbalanced group; $p = 0.897$). The meta-analysis of two RCTs revealed no differences in the need for vasopressors (OR, 1.07; 95% CI, 0.22–5.14; $I^2 = 0.0\%$; $p = 0.93$) (**Supplemental Fig. 1**, http://links.lww.com/PCC/B938). The frequency of mechanical ventilation, reported in one observational study (33), was similar between both groups with 40% in the balanced group (6/15) versus 50% in the unbalanced group (10/20) ($p = 0.4$). The need for ECMO support between groups was not reported in any studies.

Hospital LOS (27, 29, 62, 63) and PICU LOS (34, 63) were reported in four and two RCTs, respectively, but a meta-analysis was not feasible as the mean and SD were not reported. No differences in overall mortality were found between groups in the three RCTs (OR, 0.95; 95% CI, 0.33–2.70; $I^2 = 0.0\%$; $p = 0.92$) (**Fig. 5**). (29, 62, 63)

DISCUSSION

To our knowledge, this is the largest systematic review and meta-analysis to assess the effect of balanced versus unbalanced fluids on serum bicarbonate and blood pH and clinical outcomes in critically ill children. We identified 13 studies, including nine RCTs

with a total of 11,848 patients. Although only RCTs with a low-to-moderate risk of bias were included in this meta-analysis, these studies were limited by their small sample size (range 22–77 participants per studies) and significant clinical and statistical heterogeneity; therefore, our primary outcome included 162 patients.

We found higher serum bicarbonate levels (difference of 1.60 mmol/L) and higher blood pH levels (difference of 0.03) in critically ill children treated with balanced fluid bolus therapy compared with unbalanced fluids when compared with baseline levels. These findings are comparable with the systematic review of Antequera Martín (35) who found very low-certainty evidence of higher bicarbonate level (mean difference [MD], 2.26; 95% CI, 1.25–3.27; $I^2 = 72\%$; very low-certainty evidence) and higher pH level (MD, 0.04; 95% CI, 0.02–0.06; $I^2 = 59\%$; very low-certainty evidence) in the balanced solution group of critically ill patients. However, only 99 of 344 participants for the bicarbonate outcome and zero of 200 participants for the pH outcome represented pediatric populations.

Despite a growing body of evidence suggesting unbalanced fluids are associated with increased serum chloride (24, 35), we were unable to demonstrate evidence for this association. Furthermore, we reported no evidence of difference in the prevalence of AKI which is comparable with three other adult-based meta-analyses
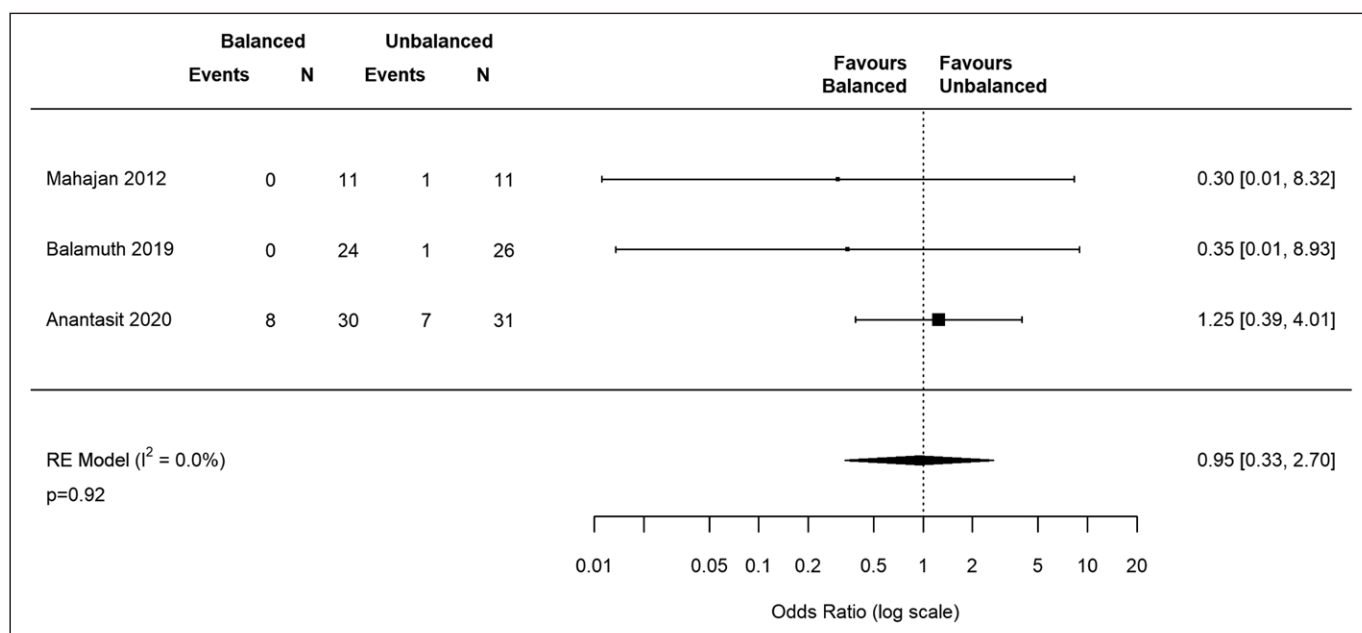

Figure 5. Total mortality: forest plot comparing prevalence of mortality in critically ill children exposed to balanced versus unbalanced fluids. RE = random effect.

(35, 65, 66). We found no differences in vasopressor need, PICU LOS, hospital LOS, or mortality.

Limitations of our meta-analysis included the small sample size and high risk of bias of some of the included studies which also precluded further subgroup analysis. Furthermore, our studies included variable diagnoses, illness severities, outcome measure, and time points which limit interpretation of the findings.

The clinical relevance of our findings on the statistical differences in serum bicarbonate levels and blood pH is unclear. However, these biochemical markers may serve as intermediate outcomes in the causal pathway to more relevant clinical benefits such as AKI, RRT, and LOS. Therefore, rigorous well-powered trials comparing the effect of balanced versus unbalanced fluids on clinical outcomes in critically ill children are needed to provide high-quality evidence and allow generation of clinical recommendations and guide clinical practice. If future studies can establish clinical benefits of balanced fluids, it would legitimize their use as first-line agents, whereas if no clinical benefits are found, their use would no longer be justified as they are more expensive and less accessible. Therefore, no matter the outcome, future studies would standardize practice and optimize resource utilization in the healthcare system.

CONCLUSIONS

Fluid bolus therapy is a widespread treatment in the resuscitation of critically ill children. However, there is no clear evidence to support the choice of balanced versus unbalanced fluid. The present systematic review suggests improved serum bicarbonate and blood pH values in critically ill children after fluid bolus therapy with balanced fluid compared with the unbalanced fluid although no clear benefits on clinical outcomes were demonstrated. Although no recommendation can be generated at this point, our systematic review provides background information for further robust methodical studies on the choice of fluid bolus therapy in critically ill children.

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