



Care of the Critically Ill

Bicarbonate use and mortality outcome among critically ill patients with metabolic acidosis: A meta analysis

Kevin Bryan Lo^{a,*}, Veronica Garvia^a, Jessica M. Stempel^a, Pradhun Ram^a, Janani Rangaswami^{a,b}^a Department of Medicine, Einstein Medical Center, Philadelphia, 5501 Old York Road, Philadelphia, PA 19141, United States^b Sidney Kimmel College of Thomas Jefferson University, Philadelphia, PA, United States

ARTICLE INFO

Article History:

Received 24 June 2019

Revised 14 October 2019

Accepted 16 October 2019

Available online 14 November 2019

Keywords:

Bicarbonate

Mortality

ICU

Metabolic acidosis

Meta analysis

ABSTRACT

Background: The use of sodium bicarbonate in the treatment of metabolic acidosis in critically ill subjects has long been a subject of debate. Despite empiric use in the setting of severe acidemia in critically ill patients, there is little data looking into the role of sodium bicarbonate in the treatment of severe metabolic acidosis in the intensive care unit (ICU) setting.

Methods: We conducted a comprehensive search of Pubmed and Cochrane Central Register of Controlled Trials addressing bicarbonate use in the metabolic acidosis in the intensive care unit (ICU) setting. We examined mortality as end point. Pooled odds ratios (OR) and their 95% confidence intervals (CI) were calculated for all outcomes using a random-effect model.

Results: The final search yielded 202 articles of which all were screened individually. A total of 11 studies were identified but 6 studies were excluded due to irrelevance in mortality outcome and methodology. Analysis was done separately for observational studies and randomized controlled trials. The pooled OR [95% CI] for mortality with bicarbonate use in the observational studies was 1.5 [0.62–3.67] with heterogeneity of 67%, while pooled OR for mortality in the randomized trials was 0.72 [0.49–1.05] (figure 2). In combining all studies, the pooled odds ratio was 0.93 95% [0.69–1.25] but with heterogeneity of 63%. After sensitivity analysis with removing the study done by Kim et al. 2013, heterogeneity was 0% with OR 0.8 [0.59–1.10].

Conclusion: There is no significant difference in mortality in the use of bicarbonate among critically ill patients with high anion gap metabolic acidosis predominantly driven by lactic acidosis.

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Introduction

The use of sodium bicarbonate in the treatment of metabolic acidosis in critically ill subjects has long been a subject of debate. Metabolic acidosis is a common disorder in the critically ill population and the use of sodium bicarbonate as buffer in the treatment of acidosis is widespread. However, the evidence to support this common practice is weak. Some proponents may argue the use of bicarbonate to reverse acidosis in shock states because acidosis impairs myocardial and vascular responses to catecholamines as was seen in previous experimental studies.¹ However, some clinical studies have shown that bicarbonate administration did not improve hemodynamics in critically ill patients with acidosis.^{2,3} Current evidence supports the use of bicarbonate in settings of actual bicarbonate loss such as in renal tubular acidosis and diarrhea. This is rational as both these conditions are normal anion gap causes of metabolic acidosis which involve actual net

loss of bicarbonate through the urine and stool respectively.⁴ However, there is continued controversial use of sodium bicarbonate for conditions such as severe lactic acidosis and ketoacidosis which can be easily reversed once the underlying condition is treated.⁴ Sodium bicarbonate administration is not without potential side effects. Some of the notable side effects include electrolyte disturbances such as hypokalemia, hypocalcemia and hypernatremia, prolonged QTC interval, progression of vascular calcifications, rebound metabolic alkalosis and potentially increased lactate production.⁵ Another potentially deleterious side effect is the generation of carbon dioxide from bicarbonate which may lead to hypercapnia especially in patients with impending respiratory failure and decreased cardiac output who are unable to compensate adequately with hyperventilation.^{5,6} Because of this, other buffers such as tris-hydroxymethyl amino-methane (THAM) are sometimes used especially in the setting of respiratory failure as it is renally eliminated and does not cause hypercapnia.⁷ However, the use of alternative buffers has not caught on in current medical practice due to other concerns, mainly with anticoagulant effects of the medications. These

*Corresponding author.

E-mail address: LoKevinB@einstein.edu (K.B. Lo).

alternative buffers are not recommended in any major guidelines. In the setting of few alternatives, indiscriminate and empiric use of bicarbonate infusions in the setting of severe acidemia in critically ill patients is still common, which may be associated with adverse consequences. There is little data looking into the role of sodium bicarbonate in the treatment of severe metabolic acidosis in the intensive care unit (ICU) setting, with various studies yielding mixed results. More recently, a randomized trial was done showing mortality benefit specifically in the subset of patients with severe kidney injury and acidosis.⁸ The major question remains as to whether the use of bicarbonate can potentially lead to improved clinical outcomes specifically mortality. This study is therefore focused on the effect of sodium bicarbonate on mortality in critically ill patients with severe metabolic acidosis.

Methods

Eligibility criteria

We included any studies looking at bicarbonate infusion compared to a control group, a control group must be present. The studies included were required to have a sample population of only adult patients acidemia from predominantly anion gap metabolic acidosis in the ICU setting. This is because even though the main acid-base disturbance is anion gap metabolic acidosis other concomitant disturbances such as normal anion gap metabolic acidosis, metabolic

alkalosis and respiratory acidosis may coexist. Given the wide range of heterogeneity expected across included studies, critical illness was defined as requiring need for ICU admission in these studies. We included both randomized clinical trials, prospective and observational retrospective studies. Case reports or case series were excluded. We only included studies reported on mortality as an outcome, with availability of actual counts of mortality, and not just merely the ratios.

Search methods for identification of studies

We did not restrict the search by language, date, publication status or any other trial characteristics. We searched the following electronic databases: Cochrane Central Register of Controlled Trials in the Cochrane Library; Ovid MEDLINE and PubMed. Specific search terms used were “sodium bicarbonate” AND “acidosis” AND “mortality” to search for the studies. Our PICO question was “Among critically ill patients with metabolic acidosis, what was the effect of sodium bicarbonate compared to no sodium bicarbonate infusion on mortality”. References within the primary selected studies reviewed in full text were screened but no gray literature were included/screened.

Selection of studies

Two authors KBL and VG independently screened each title and abstract. If there was uncertainty with evaluation of title and abstract,

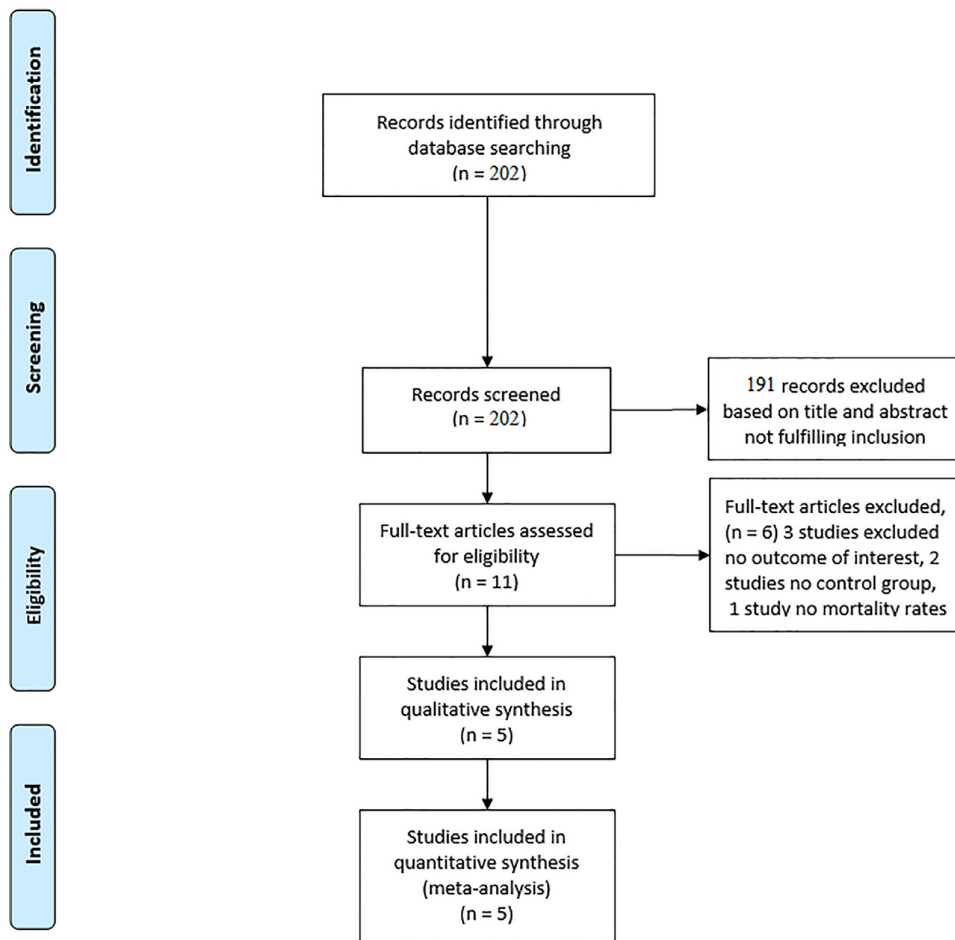


Fig. 1. Prisma Diagram for the meta analysis.

the full text was also reviewed. All screened studies were assessed for inclusion in accordance with the eligibility criteria. Disagreements were resolved by consensus between the two screening authors, and a third author PR was consulted when agreement could not be met.

Data extraction

The two above authors then independently extracted data of the included studies including country, date of publication, study design and number of samples. Inclusion and exclusion criteria, nature of intervention was also derived.

Outcomes

We examined mortality only as end point. Pooled odds ratios (OR) and their 95% confidence intervals (CI) were calculated it using a random-effects model.

Risk of bias

Two authors independently assessed the risk of systematic errors (bias) in the included studies using ROBINS-I tool for nonrandomized studies⁹ and Cochrane collaboration's risk of bias tool for randomized studies.¹⁰ For nonrandomized studies, 7 domains were assessed including confounding, selection of participants, classification of intervention, deviation from interventions, missing outcome data, measurement of outcomes, selection of reported result and overall risk of bias assessment. We used the following colors to rate the Risk of bias: Blue—No information; Green—Low; Yellow—Moderate; Orange—Serious; Red—Critical.⁹ For Randomized studies, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases were assessed.¹⁰ Non-randomized studies with critical risk of bias and those with no information available to assess risk of bias were excluded from the analysis as recommended in the ROBINS-I tool.⁹

Data synthesis

We calculated pooled Odds ratios and confidence interval estimates using Review Manager. Studies were weighted according to their sample size to produce the final pooled Odds ratios. We considered a P value of <0.05 or less as statistically significant. We analyzed nonrandomized and randomized studies separately and combined.

Assessment of heterogeneity

was done 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 total search included 202 studies all of which were screened. 191 were excluded based on title and abstract not fulfilling inclusion criteria. Out of 11 qualifying studies that were identified, the studies by Chen XF et al. 2013 and Su Mi Lee et al. 2015 were not included because they did not have a control group, and all subjects received intravenous bicarbonate.^{12,13} The studies by Cooper et al. 1990, Mathieu et al. 1991 and Noritomi et al. 2009 were excluded as they did not report on the outcome of interest.^{2,3,14} The study by Zhang et al. 2018 was excluded as it did not provide specific mortality rates to include in pooled odds ratios.¹⁵ Please see Fig. 1 for the PRISMA diagram¹⁶ and Table 1 for the summary of studies included in the meta-analysis.

A total of 5 studies were included in the final meta-analysis. Majority of the studies included had low to moderate risk of bias

with 1 study by Kim et al. 2013 with serious, but not critical risk of bias. The problems were predominantly in confounding as expected from nonrandomized ICU/critical care studies.^{8, 17–20} Please see Table 2 and Fig. 2 for risk of bias assessment for both nonrandomized and randomized trials respectively. Analysis was done separately for observational studies and randomized controlled trials. The pooled OR [95% CI] for mortality with bicarbonate use in the observational studies was 1.5 [0.62–3.67] with heterogeneity of 67%, while pooled OR for mortality in the randomized trials was 0.72 [0.49–1.05] with heterogeneity of 0% (Fig. 3). In combining all studies, the pooled odds ratio was 0.93 [0.69–1.25] but with heterogeneity of 63%. When we examined the possible causes of heterogeneity, we found that results from the study by Kim et al. in 2013 were far outlying compared to the results from the rest of the included studies. It was also this study which had the highest risk of bias during our assessment (see Table 2). Therefore, we conducted a sensitivity analysis by presenting pooled analysis for all studies both with the study of Kim et al., 2013 included and excluded, in accordance with the recommendations from the Cochrane Handbook for Systematic Reviews for Interventions.²¹ When we removed the study done by Kim et al. 2013, heterogeneity was 0% with OR 0.8 [0.59–1.10] (Fig. 4). We did not have enough data to pool results with regards to renal function/outcomes as only 1 study reported this in the form of rates of renal replacement therapy during the ICU stay⁸ (see Table 1).

Discussion

Current evidence supports the use of bicarbonate in the treatment of metabolic acidosis where actual bicarbonate losses are the primary mechanism such as in normal anion gap metabolic acidosis like renal tubular acidosis and diarrhea.⁴ However, the use of bicarbonate therapy in other settings has become more controversial especially when acidosis is brought about by lactic acidosis and ketoacidosis both of which can be converted back to bicarbonate once the underlying process has been addressed.⁴ The use of bicarbonate for the treatment of acidosis in setting of diabetic ketoacidosis is not supported when pH is above 6.9 and is controversial even when below this level as was seen in one meta-analysis.²² In lactic acidosis there is also evidence that the use of bicarbonate has not been shown to improve mortality and in fact, in the study conducted by Kim et al. 2013 showed association with increased mortality.²⁰ However, this study by Kim et al. 2013 might be affected by potential confounding due to the significantly higher Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scores potentially reflecting a sicker population in the bicarbonate group.²⁰ A more recent study showed that the use of bicarbonate was associated with improvement in mortality. The randomized controlled trial done by Jaber et al. in 2018 showed significantly less mortality in the subgroup analysis of patients with acute kidney injury (AKI). Although the incidence of hyperkalemia, hyponatremia and metabolic alkalosis were significantly more in the bicarbonate group, there were no associated life-threatening events.⁸ It should be noted that this study suffered from bias from its lack of blinding. We recognize that in the critically ill patient population, it might not be feasible for proper blinding to be done. Notwithstanding this bias, we decided to include this study as all other domains of possible bias were low.

There may be a role for sodium bicarbonate infusion in the setting of severe metabolic acidosis and AKI, but as of now the available literature does not support the broad use of sodium bicarbonate in severe metabolic acidosis. When dividing the patients by study design (randomized control trials and non-randomized control trials), the pooled OR of either group showed no significant changes in the primary outcome. These differences in results may be explained by the inherent nature of observational studies as these studies usually are subject to higher rates of biases especially confounding. Confounding factors may impact the results of mortality such as having a sicker sample

Table 1

Summary of studies included in the meta-analysis.

| Study, design and location | Inclusion criteria/ exclusion Bicarbonate dose and amount infused | baseline pH and lactate and bicarb (bicarbonate vs control group) | Anion gap electrolytes & clinical scores (bicarbonate vs control group) | Baseline pCO ₂ , PO ₂ & Other acid base disturbances (bicarbonate vs control group) | Mortality outcome (bicarbonate vs control group) | Secondary Outcome (bicarbonate vs control group) |
|--|--|---|---|---|--|---|
| El-Solh et al. 2010 (n = 72) Tertiary hospital USA Retrospective A control group was matched 1:1 for age, site of infection, and by (APACHE) II score | Included: Infection, SIRS, shock within 72 h. Excluded: pre-hosp cardiac arrest, emergent surgery, liver cirrhosis or failure, ESRD requiring HD, inappro- priate initial antibiotic intervention: bicarbon- ate infusion (0.15 M, 0.1–0.2 mmol/kg ideal body weight/h) started with increased lactate and pH < 7.3 discontinued when pH was 7.35 to 7.4 | pH 7.17 vs 7.19 (p = 0.17) lactate 4.87 vs 3.36 mmol/L (p = 0.02) | APACHE II score 23.3 ± 4.2 21.7 ± 3.5 0.64 no data available for anion gap and electrolytes | No data available | 10/36 (27.78%) vs 12/36 (33.33%) | After bicarb infusion pCO ₂ 44.3 vs control 43.8 (p = 0.68) more rapid normaliza- tion of pH on day 3 in bicarbonate group (p < 0.001) reversal of shock 78% vs 72% (p = 0.78) time to reversal of shock 44.5 h vs 55.0 h (p = 0.09) Median time to wean off mechanical ventilation (days) 10 vs 14 (p < 0.02) length of ICU stay(days) 11.5 vs 16 days (p = 0.01) |
| Jung et al. 2011 (n = 155) Multi-center France Prospective | Included: severe acidemia pH < 7.20, bicarbonate < 22 mmol/L, base excess less than or equal to 5 mmol/L and severe mixed acidemia Excluded: diabetic ketoacidosis intervention: sodium bicarbonate mean of 3–4 mmol/kg within the first 24 h | pH 7.07 vs 7.10 (p = 0.39) lactate 9.3 vs 7.8 mmol/L (p = 0.32) serum bicarb 12.6 vs 15.4 (p < 0.01) | Anion gap (mmol/L) 31 vs 26 (p = 0.02) SAPS II 71 vs 64 (p = 0.10) SOFA 11 vs 10 (p = 0.15) | pCO ₂ 41.6 vs 52.1 (p < 0.01) included patients with secondary respiratory acido- sis but unclear how many | 34/57 (59.65%) vs 55/98 (56.12%) | Length of vasopressor treatment (days) 3.9 vs 5.3 (p = 0.35) length of ICU stay (days) 10.1 vs 11.4 (p = 0.32) Length of mechanical ventilation (days) 6.6 vs 8.3 (p = 0.85) |
| Kim et al. 2013 (n = 103) Single center Korea Retrospective | Included: lactic acid level > 3.3 mmol/L with high anion gap metabolic aci- dosis Excluded: without high anion gap excluded intervention: no specific dose (retro- spective analysis) bicarbonate group = received >20 mEq sodium bicarbonate | pH 7.27 vs 7.37 (p = 0.002) lactate 9.36 vs 7.0 mmol/L (p = 0.016) | Anion gap (mmol/L) 20.7 vs 17.9 p = 0.053 SOFA 9.5 vs 7.0 (p < 0.0001) APACHE II 24.21 (p = 0.012) | No information but mean PaCO ₂ at baseline was 29.16 ± 12.0 mmHg, sodium bicarbon- ate not if with pCO ₂ > 50 mmHg | 61/69 (88.41%) vs 22/34 (64.71%) | Ventilator use 62.37 vs 20.6 (p < 0.0001) |
| Fang et al. 2008 (n = 64) Multi-center study china Randomized controlled trial | Included: systolic blood pressure < 90 mmHg or MAP < 70 mmHg, or a reduction of 40 mm Hg from baseline AND two of four SIRS, or a positive blood culture Excluded: myocardial infarction, hemorrhagic shock, trauma, preg- nancy, DNR orders, requirement for imme- diate surgery, or death imminent within 24 h Intervention: randomly assigned to three groups normal saline group (n = 32), 5 ml/kg normal saline; hypertonic saline group (n = 30), 5 ml/kg 3.5% sodium chloride; and bicarbonate group | pH 7.38 vs 7.33 lactate 4.30 vs 8.15 serum bicarb 20.84 vs 18.43 | SOFA 8.44 vs 8.97 (p > 0.05) APACHE II 18 vs 8.69 SAPS II 27.03 vs 29.31 (p > 0.05) K 3.77 vs 4.11 (p < 0.05) Ca 2.35 vs 2.12 (p > 0.05) | No information on mixed disturban- ces or pCO ₂ or O ₂ | 5/32 (15.63%) in both groups | sodium bicarbonate improved MAP (30 vs 60 min) and cardiac output (60 vs 120 min) more rapidly than normal saline |

(continued)

Table 1 (Continued)

| Study, design and location | Inclusion criteria/ exclusion Bicarbonate dose and amount infused | baseline pH and lactate and bicarb (bicarbonate vs control group) | Anion gap electrolytes & clinical scores (bicarbonate vs control group) | Baseline pCO ₂ , PO ₂ & Other acid base disturbances (bicarbonate vs control group) | Mortality outcome (bicarbonate vs control group) | Secondary Outcome (bicarbonate vs control group) |
|--|---|---|---|---|--|--|
| Jaber et al. 2018 (n = 389) Multi-center France Randomized controlled trial | (n = 32), 5 ml/kg 5% sodium bicarbonate Included: ≥18 years admitted to ICU with pH ≤7.20, PaCO ₂ ≤45 mm Hg, and sodium bicar- bonate concentration ≤20 mmol/L (SOFA) score of ≥4 or an arte- rial lactate concentra- tion of ≥2 mmol/L Excluded: respiratory acidosis, proven diges- tive or urinary tract loss of sodium bicarbonate (volume loss ≥1500 mL per day), stage IV chronic kidney disease, ketoacidosis, and sodium bicarbonate infusion (including renal-replacement ther- apy) within 24 h before screening Intervention: 4.2% sodium bicarbonate infusion of 125–250 mL in 30 min, with a maxi- mum of 1000 mL within 24 h after inclusion, measurement of arterial blood gas done 1–4 h after the end of each infusion, target pH of 7.3 or more | pH 7.15 vs 7.15 (p > 0.05) lactate 6.3 vs 5.3 serum bicarb 13 vs 13 (p>0.05) | SOFA 10 vs 10 (p > 0.05) SAPS II 59 vs 60 (p > 0.05) | Excluded respira- tory acidosis pCO ₂ 38 vs 37 (p > 0.05) | 87/195 (44.62%) vs 104/194 (53.61%) | Mortality in patients with acute kidney injury 42/ 92 (46%) vs 57/90 (63%) p < 0.0166 Renal replacement dur- ing the ICU stay 68 (35%) vs 100 (52%) p = 0.0009 length of ICU stay (days) 7 vs 4 (p = 0.06) Vasopressor-free days 19 vs 9 (p = 0.1) Mechanical ventilation free days Invasive mechanical ventilation- free days 4 vs 0 (p = 0.48) |

*SOFA: Sequential Organ Failure Assessment score, APACHE II: Acute Physiology And Chronic Health Evaluation score, SAPS II: Severity Acute Physiology Score II.

population, the presence/rates of AKI, the differences in route, dose and time of initiation of bicarbonate infusion, severity of infection and degree of lactic acidosis and concomitant respiratory acidosis. Including observational studies together with randomized trials is appealing to increase the number of studies available for calculating the summary effect, especially in this case where there are limited studies available.²³ This strategy might narrow the confidence interval (or credibility interval) and therefore potentially increase the precision of the effect estimate.^{21,23}

Implications for practice

Based on the findings of this systematic review and meta-analysis, the evidence for the use of sodium bicarbonate in critically ill patients is predominantly in setting of **high Anion-gap metabolic acidosis particularly lactic acidosis**. There is an overall trend of mortality benefit for this specific population subset that was not clinically significant. Likely, the beneficial effects are due to the mechanisms of reversal of acidosis and better sensitization to the effects of catecholamines.¹ This was apparent in the secondary outcomes of some studies which showed slightly faster although not statistically significant resolution of pH and blood pressure back to normal.^{17–19} Another important consideration here is that most of the studies excluded patients with concomitant respiratory acidosis. This is likely due to the deleterious effects of bicarbonate administration and resulting hypercapnia which might aggravate the already existing respiratory acidosis.^{5,6} This justifies avoidance of use of sodium bicarbonate in

patients unable to compensate due to poor respiratory function. There are signals of potential mortality benefits and better renal outcomes in terms of less need for renal replacement therapy in the subset of patients with AKI.⁸ This makes more sense as patients with AKI usually have concomitant normal anion gap metabolic acidosis for which bicarbonate therapy might be more appropriate as usually there is impaired net bicarbonate synthesis in these conditions.²⁴ In addition, administration of bicarbonate instead of normal saline initially might diminish the impact of chloride in contributing to the worsening normal anion gap metabolic acidosis.²⁴ However, these findings should be taken with caution as this is predominantly driven by a single randomized controlled study.⁸ Clearly more studies specifically looking at this subset of critically-ill patients with severe metabolic acidosis and concomitant renal dysfunction are needed to confirm these findings.

Limitations

This meta-analysis is limited by the small number of studies available. There were only a total of 5 studies included with a total sample size of 783 patients. No other outcomes such as AKI were formally assessed, given the non-uniformity with reporting of data across these studies. Studies included predominantly had metabolic acidosis from lactic acidemia. No studies looking at diabetic keto-acidosis qualified for inclusion in the meta-analysis. The concomitant occurrence of other mixed acid base disorders such as normal anion gap metabolic acidosis was not accounted for by any of the studies

Table 2
Risk of bias in non-randomized studies according to the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool.

| Study | Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | Domain 7 | Overall |
|---------------------|----------|----------|----------|----------|----------|----------|----------|---------|
| El-Solh et al. 2010 | Green | Green | Green | Green | Green | Green | Green | Green |
| Jung et al. 2011 | Yellow | Yellow | Yellow | Green | Green | Green | Green | Yellow |
| Kim et al. 2013 | Orange | Yellow | Green | Green | Green | Green | Green | Orange |

Domain 1: confounding; Domain 2: selection of participants; Domain 3: classification of intervention; Domain 4: deviation from interventions; Domain 5: missing outcome data; Domain 6: measurement of outcomes; Domain 7: selection of reported result; Overall. Risk of bias assessment: Blue—No information; Green—Low; Yellow—Moderate; Orange—Serious; Red—Critical.

which may influence the outcomes. Given the nature of the topic at hand, it is difficult to truly standardize the use of bicarbonate in the ICU setting especially in the critically ill population. We could not assess whether very early sodium bicarbonate administration (within the first six hours of acidemia), a different load of buffer (high vs low dose) or administration modalities (slow vs rapid infusion and/or concentrated vs diluted) bicarbonate had any different effects on outcome. The large randomized trial by Jaber et al., 2018 suffered from bias from lack of blinding. The contributions of this study with relatively large effect size and the tendency for bias must be considered especially that there is some evidence that trials with blinding tend to have a larger number needed to treat/harm and therefore absence of blinding may influence the effect size.²⁵ We were also unable to obtain mortality data from the study from Zhang et al., 2018 which had a large sample size, but had to be excluded for this reason.¹⁵ Another potential limitation is the substantial heterogeneity present

especially with inclusion of non-randomized studies such as those included in this meta-analysis. Different population characteristics, different disease conditions leading to metabolic acidosis and differences in the manner of treatment such as vasopressors and antibiotics for these conditions may substantially influence outcomes especially in studies involving critically ill patients. These various factors mentioned above were not controlled for in the setting of observational studies which comprised more than half of the studies included in our meta-analysis.

Conclusion

There is no significant difference in mortality in the use of bicarbonate among critically ill patients with high anion gap metabolic acidosis predominantly driven by lactic acidosis. However, there is weak evidence showing possible mortality benefit and improved

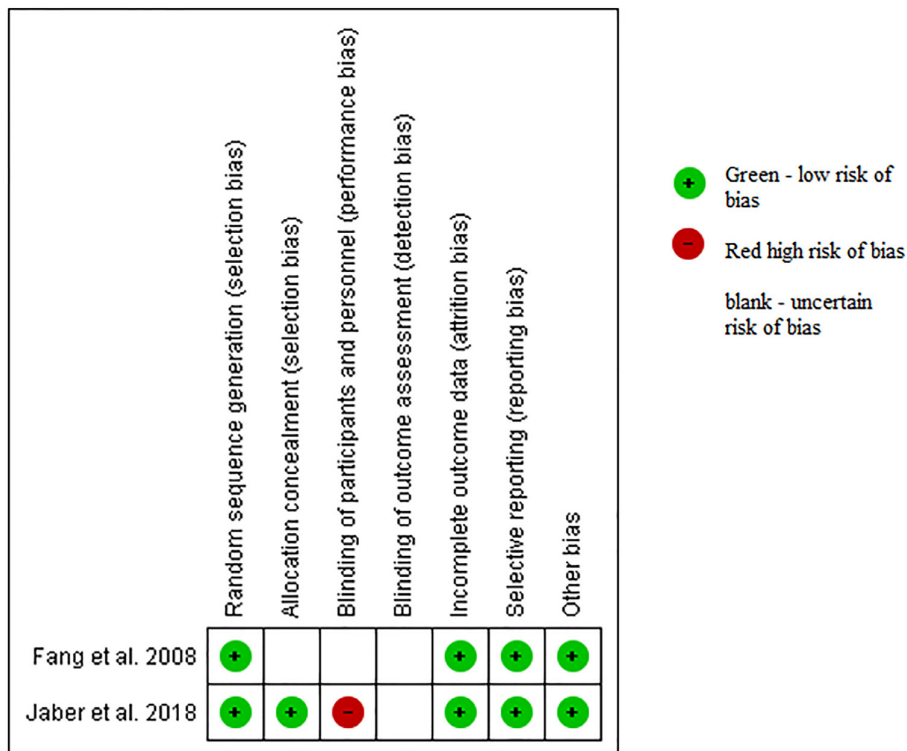
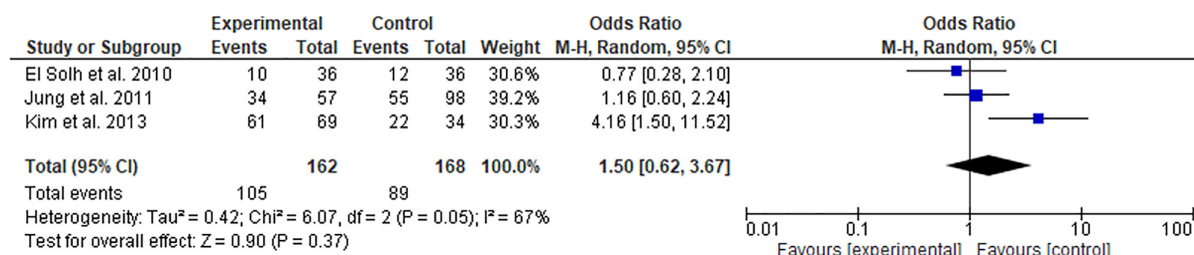


Fig. 2. Risk of bias summary among included randomized controlled trials.

Analysis of nonrandomized studies with mortality as outcome



Analysis of randomized controlled trials with mortality as outcome

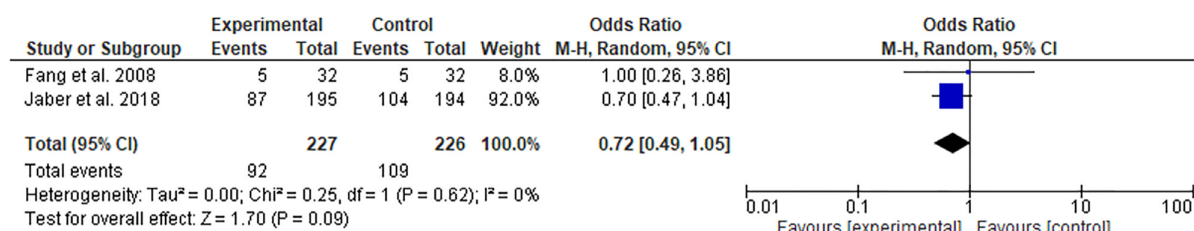


Fig. 3. Forest plot showing pooled odds ratios for mortality in both observational and randomized controlled trials separately.

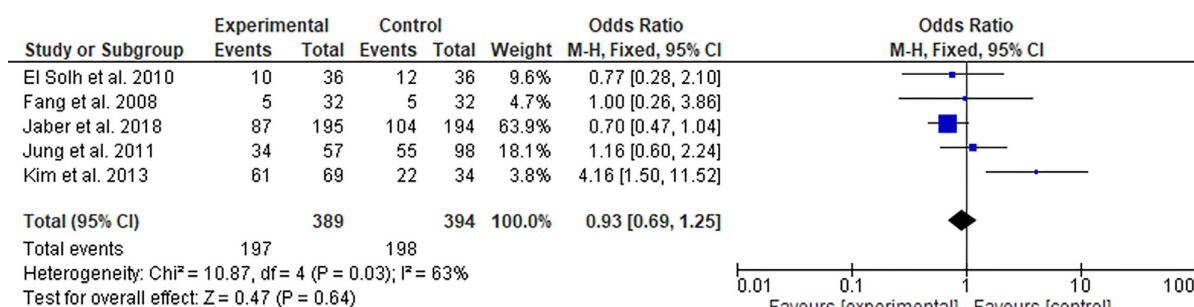


Fig. 4. Forest plot showing pooled odds ratios for mortality in both observational and randomized controlled trials combined.

renal outcomes in the subset of patients with acute kidney injury. Since the current available information is limited, further studies are necessary to provide stronger evidence to guide the clinician in the treatment of these patients.

Funding

There was no monetary or material support for this research investigation.

Declaration of Competing Interest

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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