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Bicarbonate for acute acidosis

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ABSTRACT

Objectives
This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of adding bicarbonate to usual care in people with acute metabolic acidosis or respiratory acidosis.
BACKGROUND

Description of the condition

Acidosis is defined as a process that increases the hydrogen ion ($H^+$) concentration in the extracellular fluid (all body fluid outside the cells). In most medical literature, acidosis refers to acidaemia (increased acidity in the blood), defined as a low arterial pH ($<7.35$; (Ali 2012; Emmett 2020a)). Acidosis is traditionally divided into metabolic acidosis and respiratory acidosis (Schoolwerth 2006; Kraut 2010; Ali 2012; Emmett 2020). The most detrimental adverse effect of acidosis seen in animal studies is depression of both myocardial contractility and cardiac output (Opie 1965; Wildenthal 1968; Orchard 1990), and a decreased responsiveness to inotropes (Beierholm 1975; Tajimi 1983; Kosugi 1985; Kaplan 1988). Laboratory studies of isolated human myocardium exposed to an external pH $<7.2$ have also shown acidosis decrease in the contractility of the muscle and a dull response to inotrope stimulation (Schotola 2012). Table 1 displays adverse events associated with severe acidosis. On the other hand, acidosis has been thought to have potential protective capabilities in hypoxic and ischaemic events, as a lower pH conserves intracellular energy stores (Bing 1973; Tombaugh 1990; Unno 1997; Levraut 2003). Furthermore, acidosis theoretically results in a rightward shift of the oxyhaemoglobin dissociation curve, promoting the release of oxygen (the Bohr effect; Ijland 2010).

Animal studies suggest that hypercapnia and acidosis might have a protective effect independent of the low tidal volume ventilation (Laffey 1999; Laffey 2000a; Laffey 2000b; Kavanagh 2006; Pesenti 2007). More recent studies have suggested that hypercapnia and acidosis have protective effects independent of the low tidal volume ventilation. (Laffey 1999; Laffey 2000a; Laffey 2000b; Kavanagh 2006; Pesenti 2007). As these potentially harmful or protective effects of acidosis are mostly based on animal or in-vitro studies, one should be cautious when interpreting them (Handy 2008).

Metabolic acidosis

Metabolic acidosis is a pathological condition where the increase in $H^+$ concentration in the extracellular fluid is due to either the accumulation of acids or a loss of bicarbonate ($HCO_3^-$); (Levraut 2003; Emmett 2020a)). Metabolic acidosis is a common problem in the intensive care unit (Gauthier 2002; Gunnerson 2006; Schoolwerth 2006). It is especially prevalent in people with sepsis, hepatic failure, trauma, or cardiac failure (Gunnerson 2006; Khosravani 2009; Noritomi 2009). Some studies have shown that acidosis, compared with no acidosis, was associated with higher mortality, although the causative relationship between acidosis and mortality is still unclear (Husain 2003; Gunnerson 2006; Lim 2007). Metabolic acidosis may be classified based on either the assumed aetiology, anion gap, or means of metabolism (Lim 2007); definitions of the different classifications follow.

Classification based on the assumed aetiology

The underlying presumed aetiology of metabolic acidosis may be either:

- metabolic acidosis caused by increased acid generation, due to an increased concentration of organic anions (e.g. lactate or ketones), or intake of exogenous non-organic anions (e.g. poisoning or iatrogenic acidosis; (Emmett 2020a));
- metabolic acidosis caused by decreased renal acid excretion in conjunction with a reduction in glomerular filtration rate or primary tubular dysfunction (e.g. kidney failure or distal renal tubular acidosis; (Stewart 1983; Levraut 2003; Al-Jaghbeer 2015; Emmett 2020a));
- metabolic acidosis caused by loss of bicarbonate, e.g. due to diarrhoea or proximal renal tubular acidosis (Stewart 1983; Levraut 2003; Al-Jaghbeer 2015; Emmett 2020a).

Classification based on anion gap

Anion gap is defined as the difference between serum concentrations of the major extracellular cations (primarily sodium) and the two major extracellular anions (chloride and bicarbonate; (Ishihara 1998; Lim 2007)).

Under normal circumstances, this gap is $12 \pm 4$ mEq/L if $K^+$ is included as a cation, and $8 \pm 4$ mEq/L if $K^+$ is not included as a cation (Ishihara 1998; Kellum 2005). The anion gap can be used to categorise the metabolic acidoses into three groups.

- Normal anion gap metabolic acidosis (hyperchloraemic (high plasma chloride) metabolic acidosis). Metabolic acidosis with a normal anion gap is accompanied by hyperchloraemia relative to the sodium concentration, in which case there is a loss of bicarbonate from the gastrointestinal tract or the kidneys (Lim 2007; Emmett 2020a). The most common causes of hyperchloraemic metabolic acidosis are gastrointestinal bicarbonate loss (e.g. diarrhoea), renal tubular acidosis, drug-induced hyperkalaemia (high plasma potassium), and administration of acids (Ishihara 1998; Fall 2000; Lim 2007; Kraut 2015).
- High anion gap metabolic acidosis. Metabolic acidosis with a high anion gap is the result of the accumulation of endogenous acids that consume bicarbonate and lead to a fall in serum bicarbonate (Lim 2007). The causes of high anion gap metabolic acidosis include lactic acidosis, ketoacidosis, renal failure, intoxication with methanol, salicylate, ethylene glycol, pyrogulutamic acid (5-oxoproline), propylene glycol, or djenkol beans (‘djenkolism’; (Ishihara 1998; Lim 2007; Kraut 2015)). Conditions associated with high anion gap metabolic acidosis and normal anion gap metabolic acidoses are summarised in Table 2.
- Low anion gap metabolic acidosis. The clinical significance of metabolic acidosis with a low anion gap is uncertain. Causes of low anion gap are conditions such as hypalbuminaemia (low plasma albumin), hypercalcemia (high plasma calcium), and hyperkalaemia (Oster 1990; Vasuyattakul 1995; Ishihara 1998; Lim 2007).

Classification according to means of metabolism

Metabolic acidosis may further be classified by blood excess of non-metabolisable anions (mineral acidosis) or metabolisable anions (organic acidosis; (Fall 2000; Levraut 2003)).

Respiratory acidosis

Respiratory acidosis is an acid-base balance disturbance where the increase in $H^+$ concentration in the extracellular fluid is due to an elevation of arterial CO$_2$ due to insufficient pulmonary clearance of CO$_2$ (Fall 2000; Corey 2005; Schoolwerth 2006; Ali 2012; Emmett 2020; Feller-Kopman 2020). This may be caused by underlying conditions that either reduce minute ventilation (e.g. sedative-induced hypoventilation, global hypoventilation), increase dead space (e.g. pulmonary embolism, pulmonary vascular disease, obstructive pulmonary disease, end-stage interstitial lung disease),
Bicarbonate is an intermediate form in the deprotonation of carbonic acid in the body. Bicarbonate is a polyatomic anion with the chemical formula $\text{HCO}_3^-$. It serves a crucial biochemical role in the physiological pH buffering system. Intravenous bicarbonate is an aqueous solution that may be used for people with acidosis, or when insufficient bicarbonate ions are in the blood (Adrogue 1998).

An American survey showed that the vast majority of clinicians (89% of intensive care physicians and 98% of nephrologists) would give bicarbonate for acidosis under some circumstances, i.e. not otherwise specified (Kraut 2006). Clinicians often consider the use of bicarbonate for metabolic acidosis when the serum bicarbonate is very low, and the pH is below 7.1 (Emmett 2020a).

The recommended treatment of metabolic acidosis depends on the underlying disorder (Adrogue 1998; Levraut 2003; Al-Jagheer 2015; Emmett 2020a). After addressing the underlying pathophysiological process, the general approach for how to add bicarbonate to usual care in adults with metabolic acidosis depends on the severity of the acidosis. Large discrepancies exist between guidelines in regards to pH cutoffs (e.g. $\text{pH} < 7.15$, $< 7.1$, $< 7.0$, or $< 6.9$; (Kraut 2010; Dellinger 2013; Dhatriya 2013; Rhodes 2017; Hirsch 2020)).

It is also recommended that treatment of respiratory acidosis be based on the management of the underlying condition, such as removing the airway obstruction, removing respiratory depressant drugs, performing thoracocentesis, treating pneumonia, asthma, or pulmonary edema (Adrogue 1998; Johnson 2017; Feller-Kopman 2020). Bicarbonate is not currently recommended for the treatment of isolated respiratory acidosis (Adrogue 1998; Feller-Kopman 2020).

How the intervention might work

Bicarbonate is one of the major physiological buffers for changes in the extracellular pH and the most important extracellular buffer (McMurtry 2010). It reacts with a proton $\text{H}^+$ to yield carbonic acid, $\text{H}_2\text{CO}_3$, which in turn decomposes rapidly into $\text{CO}_2$ and $\text{H}_2\text{O}$ (McMurtry 2010). The rationale behind bicarbonate intervention is that the state of acidosis is harmful, hence correction of the low arterial pH seen in acidosis might reduce the risk of harms (Hopper 2017).

Bicarbonate is thought to alleviate the detrimental effects of severe acidosis, especially the harmful cardiovascular effects, as acidosis has been associated with depression of myocardial contractility, decreased cardiac output, and decreased responsiveness to inotropes (Narins 1987; Adrogue 1998).

Why it is important to do this review

A preliminary search identified three randomised clinical trials that assessed the effects of bicarbonate administration for people with metabolic acidosis (Cooper 1990; Mathieu 1991; Vukmir 2006). Two of these trials did not show any beneficial or harmful effects on either mortality or haemodynamic status, which may be due to very small sample sizes (randomising only 10 and 14 participants with lactic acidosis; (Cooper 1990; Mathieu 1991)). The results of the third trial (randomising 874 participants with cardiopulmonary arrest) suggested that bicarbonate for metabolic acidosis might be beneficial in certain circumstances, as increased survival was seen in people with prolonged cardiac arrest (32.8% in the bicarbonate group survived compared with 15.4% in the placebo group; $P = 0.007$; (Vukmir 2006)). Another trial, randomising only 20 participants, reported that oral bicarbonate might decrease blood pressure in people with hypertension (Luft 1990).

In observational studies, the use of bicarbonate for different conditions (e.g. sepsis shock, lactate acidosis, or diabetic ketoacidosis) was shown to be associated with adverse effects, such as metabolic alkalosis, hyperkalaemia (El-Solh 2010), hypocaplaemia, hypercapnia, and prolongation of the QTc interval on electrocardiogram (Cooper 1990; Walley 1990; Boyd 2008; El-Solh 2010; Di Iorio 2012). A retrospective observational study also suggested that bicarbonate might facilitate tissue hypoxia and cerebrospinal fluid acidosis (Lever 1983). Such observational studies are at high risk of being confounded, so this type of evidence is very weak (Jakobsen 2013; Garattini 2016; Collins 2020).

Bicarbonate is neither routinely recommended in guidelines for respiratory acidosis, nor for non-severe metabolic acidosis (Feihl 1994; Adrogue 1998; Curley 2010; Feller-Kopman 2020). However, some guidelines recommend that bicarbonate be considered for severe mineral metabolic acidosis, and for acidosis when it is caused by a chronic disorder (Levraut 2003; Dhatriya 2013; Tiruvoipati 2013; Al-Jagheer 2015; Misra 2015; Hirsch 2020). These recommendations are not based on systematic reviews that include all relevant trials (Garattini 2016). Two recent reviews assessed the use of bicarbonate for critically ill patients with metabolic acidosis; but neither of them published a peer reviewed protocol (one of the reviews was registered on PROSPERO), they searched a limited number of databases, did not assess the methodological quality of included trials, and one of the reviews did not conduct meta-analysis (Fujii 2019; Ghauri 2019).

It remains unknown whether correcting the acid-base status in people with any acute acidosis improves clinical outcomes (Al-Jagheer 2015; Emmett 2020a; Feller-Kopman 2020). There is still considerable use of bicarbonate among clinicians, despite the lack of evidence (Kraut 2006; Velissaris 2016). To our knowledge, no former systematic review has examined the harms and benefits of bicarbonate for people with acute metabolic acidosis or respiratory acidosis.

OBJECTIVES

To assess the benefits and harms of adding bicarbonate to usual care in people with acute metabolic acidosis or respiratory acidosis.

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METHODS

Criteria for considering studies for this review

Types of studies
We will include randomised clinical trials, irrespective of type of design, publication type, publication status, publication date, outcomes reported, or language.

We will include parallel, cluster-, and cross-over randomised controlled trials (RCTs) that have compared bicarbonate versus placebo, or no intervention. We will not include studies considered to be quasi-randomised, as the allocation method used in these studies is not truly random.

If, during the selection of randomised clinical trials that fulfil the inclusion criteria of our review, we come across quasi-randomised and other observational studies (i.e. cohort studies, or patient reports), retrieved with our searches for randomised clinical trials, which report on adverse events caused by bicarbonate, we will extract the relevant data on harm, and present these data narratively. By not doing a separate systematic search for observational studies only, we are aware that our data on harms in the finalised systematic review will be limited. If we find benefits of bicarbonate administration, then we will need a systematic review of harms, based on observational studies (Storebo 2018).

Types of participants
Trial participants, irrespective of sex, age, location, and setting, diagnosed with acute metabolic acidosis or respiratory acidosis (as defined by trialists).

Types of interventions
Experimental intervention
- bicarbonate in addition to usual care, regardless of route of administration, duration, and dosage

Control intervention
- placebo, or no intervention, in addition to usual care

Co-interventions
- we will accept any co-intervention (e.g. usual care (or similar terms) or medical co-interventions) if trial participants in the experimental and control groups are treated equally with these co-interventions

Types of outcome measures
Primary outcomes
- All-cause mortality
- Health-related quality of life, measured on any valid scale (e.g. SF-36; Ware 2000))
- Proportion of participants with one or more serious adverse events. We will define a serious adverse event as any untoward medical occurrence that resulted in death, congenital anomaly or birth defect, was life threatening, led to persistent or significant disability, hospitalisation, or prolonged hospitalisation (ICH-GCP 2018).

As we expect the reporting of serious adverse events to be very heterogeneous, and not defined according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines (ICH-GCP) in many trials, we will include the event as a serious adverse event if the trialists either: 1) use the term ‘serious adverse event’ but not refer to ICH-GCP, or 2) report the proportion of participants with an event that we consider fulfils the ICH-GCP definition. If several such events are reported, we will choose the highest proportion reported in each trial, to avoid double-counting.

Secondary outcomes
- Proportion of participants with an adverse event considered to be non-serious (ICH-GCP 2016)
- Proportion of participants experiencing shock during follow-up (as defined by trialists)
- Proportion of participants in need of respiratory support (any type of mechanical ventilation)
- Proportion of participants in need of circulatory support (e.g. fluid expansion or vasoactive drugs)
- Change in pH from baseline

We will assess all dichotomous and continuous outcomes at maximum follow-up (primary time point), and at the time closest to one month (secondary time point).

Search methods for identification of studies

Electronic searches
We will search the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, LILACS (Latin American and Caribbean Health Science Information database; Bireme), BIOSIS (Web of Science), Science Citation Index Expanded (Web of Science), and Conference Proceedings Citation Index-Science (Web of Science) in order to identify relevant trials (Royle 2003). Appendix 1 gives the preliminary search strategies with the expected time spans of the searches.

In addition, we will search the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp); clinicaltrials.gov; Turning Research Into Practice (TRIP); and Google Scholar.

Searching other resources
We will scan bibliographic references of the identified trials for additional trial publications. We will search Elsevier’s Scopus for scientific journals, books, and conference proceedings.

We will search the web sites of the European Medicines Agency (EMA; www.ema.europa.eu), the US Food and Drug Administration (FDA; www.fda.gov), and pharmaceutical company sources (e.g. www.astrazeneca-us.com; lifepharmaceuticalcompany.com; pharma.bayer.com; www.abbott.com; www.bostonscientific.com/en-US/Home.html; www.medtronic.com/us-en/index.html; www.njnj.com/about-njnj; and pl.gsk.com/) for ongoing or unpublished trials.

We will search for errata or retractions of included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed), and we will record this information with the date. We will also
contact experts in the field to enquire whether they are aware of additional trials.

Data collection and analysis

Selection of studies

Two review authors will independently screen titles and abstracts, and retrieve the full-text report of those that appear to be potentially relevant. The same two review authors will independently screen the full text of the publications, identify trials for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion, or if required, we will consult a third person (JCJ). We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009).

Data extraction and management

We will use a data extraction form, piloted on at least one trial in the review. Two review authors will independently extract the following trials characteristics.

1. Methods: trial design, number of trial centres and location, trial registration; protocol published or not; risk of bias domains, trial setting, and date of trial start and completion.
2. Participants: number of participants in each intervention group, mean age, sex, primary diagnosis, withdrawals, inclusion criteria, and exclusion criteria.
3. Interventions: intervention and comparison, including co-interventions; details regarding administration of the interventions.
4. Outcomes: primary, secondary, and exploratory outcomes, specified in the trial protocol and in the trial publication, and time points reported.
5. Notes: funding for trial, declared or suspected conflicts of interest of trial authors.

One review author will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way, and another author will recheck the information. We will resolve disagreements by consensus, or by involving a third person (JCJ).

In case data are missing, we will attempt to contact trial authors.

We will present the data on harm that we come across in the retrieved observational studies of interest to our review narratively.

Assessment of risk of bias in included studies

We will use the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions in our evaluation of the trial methodology as reported in the publications, and hence the risk of bias of the included trials (Sterne 2019; Higgins 2021a). Two review authors (SKK and SS) will independently assess the risk of bias in the included trials. In case of disagreements, a third review author (JCJ) will arbitrate.

We will assess the effect of assignment to the intervention, using RoB 2 (Higgins 2021a). Therefore, we will conduct analysis based on the intention-to-treat (ITT) principle, which includes all randomised participants, irrespective of the interventions that participants actually received.

We will use the following domains to assess the trial methodology for individually randomised trials, including cross-over trials (Higgins 2021a; Higgins 2021b; Appendix 2):

- bias arising from the randomisation process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

For cross-over trials, we will only use data from the first period of the cross-over, and we will use the RoB 2 guidance for cross-over trials when we prepare our review (Higgins 2020; Higgins 2021b). For trials that allocated clusters of individuals, in addition to the above bias domains, as a second domain, we will include a domain specific to the trial design (Eldridge 2016), i.e. bias arising from the timing of identification or recruitment of individual participants within clusters.

When we are preparing our review, we will use the latest RoB 2 document that contains guidance on preliminary considerations for assessing risk of bias, the signalling questions to be used, and the response options for the signalling questions (Yes, Probably yes, No, Probably no, and No information; (Sterne 2019; Higgins 2021a)). We will use the most recent RoB 2 Excel tool (Sterne 2019). An algorithm, in Excel, maps the responses to the signalling questions per outcome, and proposes a 'Risk of bias' judgement for each domain.

Overall risk of bias

The overall rating assigns one of the three levels of judgement:

- low risk of bias: the trial is judged to be at low risk of bias for all domains for this result;
- some concerns: the trial is judged to raise some concerns in at least one domain for this result, but is not at high risk of bias for any of the remaining domains;
- high risk of bias: the trial is judged to be at high risk of bias in at least one domain for this result, or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

The overall 'Risk of bias' judgements across different trials for each of the domains listed will be the same as for the individual domains such as low risk of bias, some concerns, or high risk of bias. Judging a result to be at a particular level of risk of bias for an individual domain implies that the result has an overall risk of bias at least this severe. We will follow the guidance on preliminary consideration for assessing risk of bias on how to record risk of bias in trial data obtained through different resources, e.g. unpublished data, correspondence with a trialist, etc. We will store our RoB 2 evaluation data on local secure computers, and we will provide links to our evaluation data in the publication of the review.

The 'Risk of bias' assessments will feed into one domain of the GRADE approach for assessing certainty of a body of evidence (Schünemann 2021a).

We will focus on consumer-related outcomes: therefore, we will assess the risk of bias of all-cause mortality; quality of life; proportion of participants with one or more serious adverse events; proportion of participants with an adverse
event considered to be non-serious; proportion of participants experiencing shock during follow-up; proportion of participants in need of respiratory support; and proportion of participants in need of circulatory support. We will present the outcomes in ‘Summary of findings’ (SoF) tables (described below). We will assess risk of bias at our primary time point of interest (maximum follow-up).

**Measures of treatment effect**

**Dichotomous outcomes**

We will calculate and report risk ratios (RRs) with 95% confidence interval (CI).

**Continuous outcomes**

We will calculate and report the mean differences (MDs) with 95% CI. We will use the standardised mean difference (SMD) and its 95% CI to report outcomes when different scales are used to measure the same outcome. We will interpret SMD as follows: SMD of 0.2 for small intervention effects; SMD of 0.5 for moderate intervention effects; and SMD of 0.8 for large intervention effects (Faraone 2008). We will describe skewed data reported as medians and interquartile ranges narratively.

**Unit of analysis issues**

The unit of analysis will be the randomised individual participant, in the individually randomised trials.

In trials with a cross-over design, we will include the data from the first trial period to avoid residual effects from the treatment (Higgins 2021b). In order to avoid repeated observations on trial participants, we will use participant trial data at the longest follow-up (Higgins 2021b).

We will analyse cluster-randomised trials using the procedures referenced in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2021b). When results did not control for clustering, we will contact trial authors to request an estimate of the intracluster correlation coefficient (ICC). If the trial authors are unable to provide an ICC, we will calculate the ICC using design effects (Killip 2004).

When multiple trial intervention groups are reported in a single trial, we will only include the intervention groups that meet our inclusion criteria. If there are two experimental groups of interest to our review and a common control group in the same meta-analysis, we will split the control group in half to avoid double-counting.

**Dealing with missing data**

We will contact investigators and trial sponsors to verify key trial characteristics and obtain missing numerical outcome data where possible, no matter the publication format.

**Dichotomous outcomes**

We will not impute missing values for any outcomes. In two of our sensitivity analyses, we will impute missing data (see Sensitivity analysis).

**Continuous outcomes**

If standard deviations (SDs) are not reported, we will calculate the SDs using data from the trial, if possible. We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes. We will impute data in our sensitivity analysis for continuous outcomes, see Sensitivity analysis.

**Assessment of heterogeneity**

We will visually inspect forest plots to assess signs of heterogeneity, and explore possible heterogeneity in our prespecified subgroup analyses. We will also inspect trial characteristics across trials to identify clinical heterogeneity. We will assess the presence of statistical heterogeneity by the Chi² test (threshold P < 0.10), and measure the quantity of heterogeneity with the I² statistic. We will interpret heterogeneity as in Deeks 2021:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

If we identify substantial heterogeneity (I² > 50%), we will report it, and explore the possible causes by prespecified subgroup analyses.

**Assessment of reporting biases**

We will develop a funnel plot to assess reporting bias if ten or more trials are included. We will visually inspect funnel plots to assess the risk of bias. For dichotomous outcomes, we will test asymmetry with the Harbord test (Harbord 2006). For continuous outcomes, we will use the regression asymmetry test (Egger 1997) and the adjusted rank correlation (Begg 1994).

**Data synthesis**

**Meta-analysis**

We will undertake meta-analyses according to the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2021; Higgins 2021c). We will use the statistical software Review Manager Web (RevMan Web), provided by Cochrane, to analyse data (RevMan Web 2020). We will include participants with both metabolic and respiratory acidosis in all analyses, but based on our planned subgroup analysis and our assessments of heterogeneity, we will ultimately decide if pooling both types of participants is warranted.

We will apply the intention-to-treat principle to analyse outcome data whenever possible, reporting both random-effects meta-analyses (DerSimonian 1986) and fixed-effect meta-analyses results (DeMets 1987). We will primarily use the most conservative point estimate (closest to zero effect) of the two (Jakobsen 2014). If the two estimates are similar, we will use the estimate with the widest CI. When trial data for intention-to-treat are not complete, we will use the data available to us.

If there are data from one trial only, we will calculate an effect estimate with confidence intervals to illustrate the size of the effect in RevMan Web. We will present such estimates in forest plots.

**Subgroup analysis and investigation of heterogeneity**

We plan to carry out the following subgroup analyses for our primary outcomes.
**Sensitivity analysis**

We will perform a sensitivity analysis only including trial results at low risk of bias for all primary and secondary outcomes (Boutron 2021). We will base our primary analysis on the trials at overall low risk of bias.

We will also use Trial Sequential Analysis to assess imprecision, and then compare this assessment with our GRADE assessment of imprecision for all outcomes.

**Trial Sequential Analysis**

Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data (Pogue 1997; Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Higgins 2011; Wetterslev 2017). Trial Sequential Analysis (TSA) can be applied to assess and control these risks (Thorlund 2017; TSA 2017; Wetterslev 2017). Similar to a sample size calculation in a randomised clinical trial, TSA calculates the required information size for the meta-analysis (that is, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) in order to minimise random errors (Wetterslev 2009). The required information size takes into account the event proportion in the control group, the assumption of a plausible relative risk reduction, and the heterogeneity of the meta-analysis (Wetterslev 2009; Turner 2013). TSA enables one to test for evidence of a difference each time a new trial is included in the meta-analysis. On the basis of the required information size, one can construct trial sequential monitoring boundaries. This enables one to determine the statistical inference concerning cumulative meta-analysis that has not yet reached the required information size (Wetterslev 2008; Wetterslev 2017).

Firm evidence for benefit or harms may be established if the trial sequential monitoring boundary is crossed before reaching the required information size, in which case, further trials may turn out to be superfluous. In contrast, if the boundary is not surpassed, one may conclude that it is necessary to continue with further trials before a certain intervention effect can be detected or rejected. Firm evidence for lack of the postulated intervention effect can also be assessed with TSA. This occurs when the cumulative Z-score crosses the trial sequential monitoring boundaries for futility (Wetterslev 2008; Wetterslev 2017).

As a supplementary analysis for dichotomous outcomes, we will estimate the required information size based on the proportion of participants with an outcome in the control group, a relative risk reduction of 20%, a beta of 10%, and a variance suggested by the trials in a random-effects meta-analysis (diversity-adjusted required information size; (Wetterslev 2009; Jakobsen 2014)). We will use three primary outcomes, therefore, we will consider a P value of 0.025 or less as the threshold for evidence of a difference for the primary outcomes (Jakobsen 2014). We will use four secondary outcomes, and therefore, we will consider a P value of 0.02 or less as the threshold for evidence of a difference for the secondary outcomes (Jakobsen 2016). We will consider a P value of 0.05 or less as the threshold for evidence of a difference for the remaining outcomes, as we only consider these for hypothesis generating (Jakobsen 2014). If there are only data from one trial, we will calculate an effect estimate with confidence intervals to illustrate the size of the effect. If there is evidence of effect of the intervention, a supplementary TSA will use the limit of the confidence interval closest to 1.00 as the anticipated intervention effect (Jakobsen 2014). For dichotomous and continuous data, we will calculate TSA-adjusted CI if the cumulative Z-curve has not broken monitoring boundaries for benefit, futility, or harm (Wetterslev 2017).

As a supplementary analysis for continuous outcomes, we will estimate the required information size based on the standard deviation observed in the control group of trials at low risk of bias, and a minimal relevant difference of SD/2 for continuous outcomes, an alpha of 2.5%, a beta of 10%, and a diversity suggested by the trials in the meta-analysis (Wetterslev 2009; Jakobsen 2014). If there is evidence of effect of the intervention, we will conduct a supplementary TSA with a limit of the CI closest to 0.00 as the anticipated intervention effect (Jakobsen 2014). For dichotomous and continuous data, we will calculate TSA-adjusted CI (Wetterslev 2017).

When downgrading the evidence for imprecision with TSA, we will downgrade by two levels if the cumulative Z-score is below 50% of the diversity-adjusted required information size; one level if between 50% and 100% of the diversity-adjusted required information size; and not downgrade if the Z-curve crosses monitoring boundaries for benefit, futility, or harm (Jakobsen 2014).
Missing data

For the primary outcomes, we will perform the following two sensitivity analyses to assess the potential impact of the missing data.

- 'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group survived and had no serious adverse events. We will also assume that they experienced improved quality of life, defined as both the group mean plus one and two SDs of the group mean (Jakobsen 2014). We will also assume that they experienced reduced quality of life, defined as both the group mean minus one and two SDs of the group mean (Jakobsen 2014).

- 'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group survived and had no serious adverse events. We will also assume that they experienced an improved quality of life, defined as both the group mean plus one and two SDs of the group mean (Jakobsen 2014). We will also assume that they experienced reduced quality of life, defined as both the group mean minus one and two SDs of the group mean (Jakobsen 2014).

We will present the results of both scenarios in our review.

We will assess the potential impact of missing SDs for quality of life as follows: when SDs are missing and it is not possible to calculate them, we will impute SDs from similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials. We will present results of this scenario in our review.

Post-hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results (Jakobsen 2014).

Summary of findings and assessment of the certainty of the evidence

We will construct a ‘Summary of findings’ table for our primary outcomes (all-cause mortality, health-related quality of life, and serious adverse events) and for four of our five secondary outcomes (non-serious adverse events, shock, respiratory support, and circulatory support) at our primary time point of interest (maximum follow-up), using GRADEpro software (GRADEpro GD T). We will use methods and recommendations described in Chapter 8 (Schünemann 2021a), Chapter 14 (Higgins 2021a), and Chapter 15 (Schünemann 2021b) of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2021c), and the GRADE Handbook (Schünemann 2013). We will justify all decisions to downgrade the certainty of evidence using footnotes, and we will make comments to aid the reader’s understanding of the review when necessary.

The levels of evidence are classified as high, moderate, low, or very low certainty.

- **High certainty.** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty.** We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty.** Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- **Very low certainty.** We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Two review authors will independently rate the level of certainty for each outcome, using GRADEpro GD T (GRADEpro GD T). We will resolve any discrepancies through consensus, or by arbitration from a third review author if needed.

Acknowledgements

The review author team would like to acknowledge the editorial team (Cochrane Hepato-Biliary Group and Cochrane Editorial Unit) and peer-reviewers for their professional and highly qualified comments and contributions throughout the process of writing this review.

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**Collins 2020**

**Cooper 1990**

**Corey 2005**

**Curley 2010**

**Deeks 2021**

**Dellinger 2013**

**DeMets 1987**

**DerSimonian 1986**

**Dhatariya 2013**

**Di Iorio 2012**
Egger 1997

Eldridge 2016

El-Solh 2010

Emmett 2020

Emmett 2020a

Fall 2000

Faraone 2008

Feihl 1994

Feller-Kopman 2020

Fujii 2019

Garattini 2016

Gauthier 2002

Ghauri 2019

Gluud 2006

GRADEpro GDT [Computer program]

Gunnerson 2006

Handy 2008

Harbord 2006

Higgins 2011

Higgins 2020
Higgins JPT, Li T, Sterne J. Revised Cochrane 'Risk of bias' tool for randomized trials (RoB 2). Additional considerations for cross-over trials. drive.google.com/file/d/18Ek-uW8HvQcUJa8Lakp1yOhoFk0EMPO/view 2020 (accessed 17 March 2021).

Higgins 2021a

Higgins 2021b
Jakobsen 2016

Johnson 2017

Kaplan 1988

Kavanagh 2006

Kellum 2005

Khosravani 2009

Killip 2004

Kjaergard 2001

Kosugi 1985

Kraut 2006

Kraut 2010

Kraut 2015

Laffey 1999
Laffey 2000a

Laffey 2000b

Lever 1983

Levrault 2003

Lim 2007

Luft 1990

Lundh 2017

Marhong 2014

Mathieu 1991

McMurry 2010

Misra 2015

Moher 1998

Moher 2009

Narins 1987

Noritomi 2009

Opie 1965

Orchard 1990

Oster 1990

Pesenti 2010

Pogue 1997

RevMan Web 2020 [Computer program]

Rhodes 2017

Royle 2003
Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane Reviews: rapid versus exhaustive
Acidic conditions ameliorate both adenosine triphosphate depletion and the development of hyperpermeability in cultured Caco-2BBBe enterocytic monolayers subjected to metabolic inhibition. *Surgery* 1997;121(6):668-80.

Vasuyattakul 1995

Velissaris 2016

Vukmir 2006

Walley 1990

### ADDITIONAL TABLES

**Table 1. Adverse effects of severe acidosis**

<table>
<thead>
<tr>
<th>System</th>
<th>Adverse effects (Adrogué 1998)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Impairment of cardiac contractility</td>
</tr>
<tr>
<td></td>
<td>Arteriolar dilatation, venoconstriction, and centralisation of blood volume</td>
</tr>
<tr>
<td></td>
<td>Increased pulmonary vascular resistance</td>
</tr>
<tr>
<td></td>
<td>Reductions in cardiac output, arterial blood pressure, and hepatic and renal blood flow</td>
</tr>
<tr>
<td></td>
<td>Sensitization to re-entrant arrhythmias and reduction in threshold of ventricular fibrillation</td>
</tr>
<tr>
<td></td>
<td>Attenuation of cardiovascular responsiveness to catecholamines</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Hyperventilation</td>
</tr>
<tr>
<td></td>
<td>Decreased strength of respiratory muscles and promotion of muscle fatigue</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Increased metabolic demands</td>
</tr>
<tr>
<td></td>
<td>Insulin resistance</td>
</tr>
<tr>
<td></td>
<td>Inhibition of anaerobic glycolysis</td>
</tr>
<tr>
<td></td>
<td>Reduction in ATP synthesis</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>Increased protein degradation</td>
</tr>
<tr>
<td>Cerebral</td>
<td>Inhibition of metabolism and cell-volume regulation</td>
</tr>
<tr>
<td></td>
<td>Obtundation and coma</td>
</tr>
</tbody>
</table>

$[^1]$ Bicarbonate for acute acidosis (Protocol)

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Table 2. Types of metabolic acidosis based on anion gap and aetiology

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Increased anion gap</th>
<th>Normal anion gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased acid production</td>
<td>Lactic acidosis</td>
<td>Toluene ingestion (if late and if renal function is preserved – due to excretion of sodium and potassium hippurate in the urine)</td>
</tr>
<tr>
<td></td>
<td>Ketoacidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Starvation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alcohol-associated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methanol</td>
<td></td>
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<tr>
<td></td>
<td>Ethylene glycol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toluene (if early or if kidney function is impaired)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diethylene glycol</td>
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</tr>
<tr>
<td></td>
<td>Propylene glycol</td>
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<tr>
<td></td>
<td>D-lactic acidosis</td>
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<tr>
<td></td>
<td>Pyroglutamic acid (5-oxoproline)</td>
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</tr>
<tr>
<td>Loss of bicarbonate or bicarbonate pre-cursors</td>
<td></td>
<td>Diarrhoea or other intestinal losses (e.g. tube drainage)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type 2 (proximal) renal tubular acidosis</td>
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<tr>
<td></td>
<td></td>
<td>Post-treatment of ketoacidosis</td>
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<tr>
<td></td>
<td></td>
<td>Carbonic anhydrase inhibitors</td>
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<tr>
<td>Decreased renal acid excretion</td>
<td>Chronic kidney disease</td>
<td>Chronic kidney disease and tubular dysfunction (but relatively preserved glomerular filtration rate)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type 1 (distal) renal tubular acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type 4 renal tubular acidosis (hypoaldosteronism)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ureteral diversion (e.g. ileal loop)</td>
</tr>
</tbody>
</table>

APPENDICES

Appendix 1. Search strategies

<table>
<thead>
<tr>
<th>Database</th>
<th>Time span</th>
<th>Search strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bicarbonate for acute acidosis (Protocol)</td>
</tr>
<tr>
<td>Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library</td>
<td>MEDLINE Ovid</td>
<td>Latest issue</td>
</tr>
<tr>
<td>---</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Embase Ovid</th>
<th>1974 to the date of the search</th>
<th>1. exp bicarbonate/</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2. (bicarbonate* or hydrogen<em>carbonate or hydroxidodioxicarbonate</em>).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. 1 or 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. exp acidosis/</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. ((acute or respiratory or metabolic) and acidosis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. 4 or 5</td>
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<tr>
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<td></td>
<td>7. 3 and 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9. 7 and 8</td>
</tr>
</tbody>
</table>
Appendix 2. Descriptions of the bias domains in RoB 2 tool for randomised trials, including cross-over trials, with a summary of the issues addressed

<table>
<thead>
<tr>
<th>Bias domain</th>
<th>Issues addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias arising from the randomisation process</td>
<td>• Was the allocation sequence random?</td>
</tr>
<tr>
<td></td>
<td>• Was the allocation sequence concealed until participants were enrolled and assigned to interventions?</td>
</tr>
<tr>
<td></td>
<td>• Did baseline differences between intervention groups suggest a problem with the randomisation process?</td>
</tr>
<tr>
<td>Risk of bias due to deviation from the intended intervention</td>
<td>Whether:</td>
</tr>
<tr>
<td>(effect of assignment to intervention)</td>
<td>• participants were aware of their assigned intervention during the trial;</td>
</tr>
<tr>
<td></td>
<td>• carers and people delivering the interventions were aware of participants and assigned intervention during the trial.</td>
</tr>
<tr>
<td></td>
<td>When interest is in the effect of assignment to intervention:</td>
</tr>
<tr>
<td></td>
<td>• (if applicable) deviations from the intended intervention arose because of the experimental context, and if so, whether they were unbalanced between groups and likely to have affected the outcome;</td>
</tr>
<tr>
<td></td>
<td>• an appropriate analysis was used to estimate the effect of assignment to intervention.</td>
</tr>
<tr>
<td></td>
<td>For cross-over trials:</td>
</tr>
</tbody>
</table>
Bias due to missing outcome data

Whether:
- data for this outcome were available for all, or nearly all, randomised participants;
- (if applicable) there was evidence that the result was not biased by missing outcome data;
- (if applicable) missingness in the outcome was likely to depend on its true value (e.g. proportion of missing outcome data, or reasons for missing outcome data, differ between intervention groups).

For cross-over trials:

If only data from the first period contribute to the result being assessed for risk of bias, we will examine only the first period of the trial in answering this question.

Bias in measurement of the outcome

Whether:
- the method of measuring the outcome was inappropriate;
- measurement or ascertainment of the outcome could have differed between intervention groups;
- outcome assessors were aware of the intervention received by study participants;
- assessment of the outcome was likely to have been influenced by knowledge of intervention received.

Bias in selection of the reported results

Whether:
- trial was analysed in accordance with a prespecified plan that was finalised before unblinded outcome data were available for analysis;
- the numerical result being assessed is likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain;
- the numerical result being assessed is likely to have been selected, on the basis of the results, from multiple analyses of the data.

HISTORY

Protocol first published: Issue 3, 2021

CONTRIBUTIONS OF AUTHORS

Steven Kwasi Korang (SKK) and Sanam Safi (SS) conceived, designed, and drafted the protocol.

Joshua Feinberg (JF), Emil Eik Nielsen (EEK), Janus C Jakobsen (JCJ), and Christian Gluud (CG) provided general advice and revised the protocol.

All authors approved the protocol for publication.

DECLARATIONS OF INTEREST

The performance of this review is free of any real or perceived bias introduced by receipt of any benefit in cash or kind, on any subsidy derived from any source that may have or be perceived to have an interest in the outcomes of the review.

Steven Kwasi Korang: no known conflict of interest
Sanam Safi: no known conflict of interest
Joshua Feinberg: no known conflict of interest
Emil Eik Nielsen: no known conflict of interest
Christian Gluud: no known conflict of interest
Janus Christian Jakobsen: no known conflict of interest
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- The Copenhagen Trial Unit, Denmark
  The protocol was conducted during work hours

External sources

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