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[Intervention Review]

Sodium bicarbonate supplements for treating acute kidney injury

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ABSTRACT

Background

Acute kidney injury (AKI) is a common, serious, but potentially treatable condition. Because AKI is often associated with acidosis, it has become common practice to recommend administration of sodium bicarbonate to correct acid imbalance.

Objectives

To assess the benefits and harms of the use of sodium bicarbonate for people with AKI. The primary outcome measure was all-cause mortality, and secondary outcome measures were patients' need for renal replacement therapy; return to baseline kidney function; and overall survival.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register up to 12 May 2017 through contact with the Information Specialist using search terms relevant to this review.

Selection criteria

All randomised controlled trials (RCTs) that investigated the use of sodium bicarbonate supplements, administered by any route, for the treatment of adults with AKI were to be included. The search strategy did not restrict inclusion based on an upper age limit or publication language. We did not consider inclusion of studies that investigated use of sodium bicarbonate for AKI prevention.

Data collection and analysis

All authors planned to independently assess and extract information. Information was to be collected on methods, participants, interventions and outcomes. Results were to be expressed as risk ratios (RR) for dichotomous outcomes or as mean differences (MD) for continuous data with 95% confidence intervals (CI).

Main results

Although our literature search identified four studies, none of these met our predetermined selection criteria. Hence, no suitable studies were identified for inclusion in this review.

Authors' conclusions

We found no RCT evidence - supportive or otherwise - for the use of sodium bicarbonate for people with AKI. We concluded that there is an urgent need for well conducted RCTs in this area.

PLAIN LANGUAGE SUMMARY

Is sodium bicarbonate therapy helpful for people with acute kidney problems?

Acute kidney damage is a common problem that is often found in people who need treatment for problems not related to kidney health. Failing kidney health often causes more acid than normal in the blood (acidosis), which in itself is thought to cause harm.

It has been suggested that a treatment strategy for patients with acidosis is to give alkaline solutions to counteract or neutralise effects of the acid. Sodium bicarbonate is the alkaline solution normally used.

We searched the medical literature for evidence about the benefits or harms of giving sodium bicarbonate to people whose kidneys are failing. We did not find any randomised controlled trials (RCTs) that assessed the benefits or harms of giving sodium bicarbonate to people with acute kidney problems.

Therefore, we cannot recommend or dismiss the use of sodium bicarbonate for people with kidney problems. We recommend that RCTs are conducted to answer this question.

BACKGROUND

Acute kidney injury (AKI) is a common, serious, but potentially treatable condition that occurs as a result of a range of clinical conditions that can be either intrinsic or extrinsic to the kidney. AKI is often associated with acidosis, and consequently, it has become common practice to recommend administration of alkaline, usually sodium bicarbonate, to correct any acidosis. We conducted this review to assess the evidence for the use of sodium bicarbonate for people with AKI.

Description of the condition

AKI, (also known as acute renal failure/acute kidney failure), is the rapid loss of kidney (renal) function secondary to a pathological process causing structural or functional damage to the kidney (Mehta 2007). It is a medical emergency characterised by an accumulation of nitrogenous (urea and creatinine) and non-nitrogenous waste products that would otherwise be excreted. People with AKI can experience metabolic disturbances that increase in duration and severity, including acidosis (an excess of acid in the blood); hyperkalaemia (too much potassium); and alterations in fluid balance (usually excess fluid). AKI has been estimated to affect from 2% to 10% of hospitalised patients, depending on the definition of AKI applied (Lafrance 2010; Waikar 2006). The literature suggests that AKI incidence is increasing (Nash 2002; Waikar 2006). AKI is independently associated with increased hospital and long-term mortality, hospital length of stay, and costs (Chertow 2005; Coca 2009).

AKI is a heterogeneous condition with many causes. AKI causes are classically characterised into processes affecting the blood supply to the kidney (pre-renal), intrinsic damage to the kidney (renal), and those obstructing urine flow from the kidney (post-renal). Pre-renal AKI is the most common form of the condition (Nash 2002).

As yet, there is no uniformly accepted definition of AKI. In a systematic review of 48 publications on AKI, Coca 2009 identified 15 different definitions. Clinically, AKI is diagnosed by identifying increased creatinine or urea levels in patients' blood, or reduction in urine output (oliguria). In recent years, efforts to standardise the definition of AKI have been made to facilitate work in the area. The RIFLE criteria were introduced in 2004, and in 2007 the AKI Network introduced the AKIN definition (Bellomo 2004; Mehta 2007). The AKIN definition is staged and accounts for small rises in serum creatinine levels beginning with an acute rise of more than or equal to 0.3 mg/dL (26.4 µmol/L) or a 50% increase in creatinine above the baseline level, or a reduction in urine output characterised by documented oliguria of less than 0.5 mL/kg/hour for more than six hours.

The mainstay of AKI management is to identify and correct causative factors while providing supportive care and treating acute complications. An acute complication of AKI is symptomatic uraemia and results from an accumulation of toxic substances in the blood. Clinical manifestations include encephalopathy and pericardial effusion. Other potentially dangerous complications include metabolic abnormalities of hyperkalaemia and acidosis, and fluid overload.

Owing to its heterogeneous nature, AKI can manifest across a range of severities. In the most severe instances, the definitive treatment is to provide dialysis. Dialysis involves blood filtration to

remove excess fluid and toxic substances and stabilise metabolic imbalances such as hyperkalaemia and acidosis. Despite dialysis treatment, AKI-associated mortality remains high. In intensive care settings, in-hospital mortality rates of severe AKI involving multiple organ failure has been reported to be over 70% (Yegenaga 2004).

In people whose AKI is less severe, where rapid resolution is anticipated; or in situations where dialysis therapy may not be readily available, medical means may be used to treat the complications of hyperkalaemia and acidosis. Medical treatment of acidosis involves administration of sodium bicarbonate either orally, or more commonly in this setting, intravenously (Kraut 2010; Lameire 2005).

How the intervention might work

The primary goal of acidosis therapy is restoration of normal tissue perfusion and oxygen delivery. It has been suggested that in people with severe acidaemia (arterial pH < 7.15), acidaemia itself may cause myocardial depression and systemic vasodilatation, further reducing oxygen delivery (Kraut 2010). As a result, raising extracellular pH by the administration of sodium bicarbonate may directly improve cardiovascular function and tissue perfusion.

Furthermore, acute acidosis impairs cellular function, causes insulin resistance, cognitive impairment and promotes interleukin production. Potentially, all of these outcomes could be improved by raising extracellular pH (Kraut 2010).

Why it is important to do this review

The use of sodium bicarbonate for the treatment of acidosis is not without controversy. Metabolic acidosis can occur in conditions other than AKI, such as in shock, where it is associated with reduced tissue perfusion causing lactic acidosis. Sodium bicarbonate use in these areas has been studied extensively, and its association with potentially detrimental side effects reported (Forsythe 2000). Apart from rebound metabolic alkalosis, sodium bicarbonate can cause reduced ionised calcium levels, which may be responsible for cardiac suppression (Cooper 1990). In concentrated intravenous boluses, sodium bicarbonate has been shown to cause transient fall in arterial pressure and transient rise in intracranial pressure (Huesby 1981). Sodium bicarbonate has also been shown to reduce oxygen delivery through its effects on the oxyhaemoglobin dissociation curve which may have detrimental effects in acute settings (Bellingham 1971). There were no haemodynamic benefits demonstrated in studies conducted in acutely ill patients with lactic acidosis who were administered sodium bicarbonate solutions (Cooper 1990; Mathieu 1991). Although the clinical relevance of many of these effects is unclear, some authors have advocated avoiding use of sodium bicarbonate (Forsythe 2000).

However, despite the lack of evidence to support the use of sodium bicarbonate in many clinical settings, it remains in common use for the treatment of AKI-associated acidosis, and is recommended as a supportive therapy for people with AKI in major nephrology textbooks (Clarkson 2007).

OBJECTIVES

The purpose of this review was to assess the evidence for the benefits and harms for use of sodium bicarbonate in the management of people with AKI.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) that investigated the use of sodium bicarbonate supplements for treating AKI were selected. Sodium bicarbonate is also used for preventing AKI, such as in the context of preventing contrast-induced nephropathy (Brown 2009).

It was noted that sodium bicarbonate has been used in other specific conditions, such as lactic acidosis or rhabdomyolysis, which may be associated with AKI, but for the purpose of this review, we considered its use as a generic treatment in AKI only.

Types of participants

Our inclusion criteria addressed:

- Studies that enrolled adult hospitalised patients (aged 18 years and over) with AKI. We included all patients regardless of baseline kidney function.
- AKI defined according to the first stage of the AKIN definition: an increase in serum creatinine of 26.4 µmol/L over the baseline value; an increase of more than 50% over the baseline value; or a reduction in urine output characterised by documented oliguria of less than 0.5 mL/kg/h for more than six hours. These criteria were taken together with any cases defined as requiring dialysis (renal replacement therapy; RRT).
- Both male and female participants were included. There was no upper age limit for exclusion.

Types of interventions

We sought studies that investigated and reported:

- Any dose of sodium bicarbonate given by any route immediately after development of AKI in hospitalised patients
 - * Sodium bicarbonate and standard care versus standard care alone. Standard care refers to treatment received by study participants who were not randomised to receive sodium bicarbonate
 - * Different doses and/or durations of sodium bicarbonate
- Studies reporting sodium bicarbonate in combination with other pharmacological therapies were considered for inclusion where sodium bicarbonate was the intervention randomised.

Types of outcome measures

Primary outcomes

- All-cause mortality during the same hospitalisation stay.

Secondary outcomes

- Need for RRT (filtration, haemodialysis) in the short- or long-term
- Return to baseline kidney function: serum creatinine, urea, estimated glomerular filtration rate (eGFR)
- Overall survival

Search methods for identification of studies

Electronic searches

We searched the [Cochrane Kidney and Transplant Specialised Register](#) up to 12 May 2017 through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about [Cochrane Kidney and Transplant](#).

See [Appendix 1](#) for search terms used in strategies for this review.

Searching other resources

1. Reference lists of nephrology textbooks, review articles and relevant studies.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that were relevant to the review. The titles and abstracts were screened independently by three authors who discarded studies that were not applicable. However, studies and reviews that might include relevant data or information on studies were retained initially. The authors independently assessed and retrieved abstracts, and where necessary, the full text.

Data extraction and management

Data extraction was carried out independently by the same authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was used in the analyses. Any discrepancy between published versions was to be highlighted. Disagreements were resolved in consultation with a fourth author.

Assessment of risk of bias in included studies

The following items were to be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
 - * Participants and personnel
 - * Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes, such as death during the current admission; five-year mortality; RRT; and adverse effects, results were to be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were to be used to assess the effects of treatment, such as serum creatinine, the mean difference (MD) was to be used, or the standardised mean difference (SMD) if different scales were used.

Unit of analysis issues

It was not envisaged that studies with nonstandard designs would be included. If cluster, cross-over or multiple intervention RCTs were found, specialist advice would have been sought.

Dealing with missing data

Any further information required from the original author was to be requested by written correspondence, and any relevant information obtained in this manner was included in the review. All analyses were to be conducted using intention-to-treat principles.

Assessment of heterogeneity

Heterogeneity was to be analysed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test (Higgins 2003). I² values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

A comprehensive search strategy, unlimited by language of publication, was designed and applied to minimise publication

bias. If possible, funnel plots were used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data were to be pooled using the random-effects model, but the fixed-effect model was also to be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Sodium bicarbonate may be given in the context of AKI to correct acidosis. We did not consider interventions that used sodium bicarbonate to prevent acidosis. Sodium bicarbonate can be given in various dose strengths and durations. All doses and durations were to be considered, but differences noted. Any differences were likely to influence the results obtained. Similarly, sodium bicarbonate can be administered either orally or intravenously, and these differences were to be highlighted.

Subgroup analysis was to be used to explore possible sources of heterogeneity (such as participants, interventions, and study quality). Heterogeneity among participants could be related to underlying renal pathology, and AKI definition used, and study inclusion. Heterogeneity in treatments could be related to the agent, dose, and duration of therapy used. A further source of heterogeneity could be related to the different types of standard care received by patients in different studies. Adverse effects were to be tabulated and assessed using descriptive techniques, because they were likely to be different for various agents used. Where possible, the risk difference with 95% confidence intervals was to be calculated for each adverse effect, either compared with no treatment or another agent.

Sensitivity analysis

If appropriate, we planned to performed sensitivity analyses to explore the influence of a number of factors on effect size. Sensitivity analyses to be included were:

- repeating the analysis excluding unpublished studies;
- repeating the analysis taking account of risk of bias, as specified;
- repeating the analysis excluding any large studies to establish if they dominated results and by how much; and
- repeating the analysis excluding studies using filters for: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

RESULTS

Description of studies

Results of the search

We identified 25 potential reports. (see Figure 1).

Figure 1. Study flow diagram

Included studies

After screening and full-text assessment, no studies met our inclusion criteria.

Excluded studies

We have provided here a description of the four excluded studies which were identified from our initial search. Two were not RCTs (Mark 1990; Ngugi 1997); one study included the wrong population/setting (Brito-Ashurst 2009); and one used the wrong intervention (Sitzwohl 2009)

Brito-Ashurst 2009 published an abstract and subsequent paper on the use of oral bicarbonate supplements in people with chronic renal impairment over a two-year period. This was a well conducted, high quality, RCT whose outcomes included the rate of decline of eGFR and nutritional status. Their results suggested that oral bicarbonate supplements were beneficial. People assigned to bicarbonate had a slower rate of progression of kidney disease and

improved nutritional parameters. It did not however, assess the use of bicarbonate in the acute setting and therefore was not included in our review.

Mark 1990, which has only been published in abstract form, was a study of patients who developed metabolic acidosis during cardiac surgery. They studied a total of 20 patients in two groups who received either sodium bicarbonate or sodium chloride. They do not state whether they randomised treatment and only included people who developed biochemical abnormalities during surgery. This was not a RCT and involved a highly selected group of patients. This study did not meet our inclusion criteria and was excluded from this review.

The study considered oxygen consumption and blood lactate levels. Their results suggested that the people who received bicarbonate had decreased oxygen consumption and increased blood lactate levels. This suggested an increased amount of

anaerobic metabolism in the bicarbonate group and thus a detrimental effect of acute bicarbonate.

Ngugi 1997 did not satisfy the inclusion criteria for this review. It was not a RCT. It considered patients with both acute and chronic kidney failure patients who had hyperkalaemia. They assessed seven different treatment options. They concluded that combination therapies for hyperkalaemia were advantageous when compared to single therapies.

Sitzwohl 2009 assigned patients who had sustained major trauma and muscle damage with associated muscle breakdown to receive a forced diuresis with fluid infusion, mannitol and frusemide. They randomly assigned 30 patients to receive active alkalisation of their urine with intravenous bicarbonate and 30 to receive only the forced diuresis. This was a preventative study in order to assess the common therapeutic option of a forced alkaline diuresis in people at high risk of rhabdomyolysis. They demonstrated no advantage from the additional alkalisation of patients' urine.

This study came closest to inclusion in our review. However, we predetermined that included studies should only be those that treated AKI, not those that attempted to prevent it, such as this one. Therefore it was excluded.

Risk of bias in included studies

We did not include any studies.

Effects of interventions

There were no interventions.

DISCUSSION

We did not identify any RCTs that assessed use of sodium bicarbonate for the treatment of people with AKI. The lack of data highlighted by our review identifies a clear need for well conducted studies in this area.

Although our review found no evidence to support or refute the use of this intervention, sodium bicarbonate is nevertheless widely used as a treatment option in the management of people with AKI. Clinical equipoise can therefore be said to exist. If costly and time consuming RCTs are to succeed, these need to be driven by observational data. Hence, we strongly recommend that large, well-conducted and generalizable observational data are collected. These data would help to guide appropriate planning and successful recruitment into any such RCT.

Of the four studies we analysed in detail, only two investigated sodium bicarbonate in acute care settings; however, neither met our review inclusion criteria. Of these, one study suggested that sodium bicarbonate was not beneficial in patients who underwent forced diuresis following trauma with associated muscle damage (Sitzwohl 2009). The other, undertaken in people who became acidotic during cardiac surgery, suggested that sodium bicarbonate was potentially detrimental (Mark 1990).

In the UK and elsewhere, sodium bicarbonate is regularly prescribed for people with AKI, and is commonly recommended as

an appropriate treatment option in the current literature. However, until proven otherwise, it is as likely as not that sodium bicarbonate for people is harmful to patients with AKI. This review cannot recommend or discourage its use on the evidence identified.

Summary of main results

Our results did not identify any studies for analysis.

Overall completeness and applicability of evidence

The evidence generated, or perhaps of greater relevance, the lack of evidence, is applicable to routine clinical care and future research in this topic.

Quality of the evidence

Our results did not identify any studies for analysis.

Agreements and disagreements with other studies or reviews

Our results did not identify any studies for analysis. Neither could we identify any high quality observational studies which addressed this issue.

AUTHORS' CONCLUSIONS

Implications for practice

An absence of relevant studies meant that results from this review could not recommend or refute the use of sodium bicarbonate for the treatment of patients with AKI. As a matter of course, treatment regimens; doses; or routes of administration could not be identified, supported, or refuted.

Implications for research

Large scale, well-conducted RCTs are required to inform assessment of benefits, treatment regimens, or potential harms associated with use of sodium bicarbonate for people with AKI.

Sodium bicarbonate is currently used in the management of AKI, and therefore, equipoise exists. To facilitate future investigation, we recommend that consideration be given to conducting large scale, well-conducted observational studies to inform planning before undertaking RCTs.

In the authors opinion there is clinical equipoise regarding the benefit or harms of administration of sodium bicarbonate therapy, as such adequately powered and well-designed studies are needed to address this issue. Such a study should include adults of all ages with AKI, to reflect our aging society. The intervention should be sodium bicarbonate compared to placebo and outcomes should include mortality, the long term use of dialysis, and length of hospital stay.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brito-Ashurst 2009	Oral bicarbonate use over a two year period in people with established renal disease.
Sitzwohl 2009	This study investigated the prophylactic use of sodium bicarbonate in people with muscle damage after trauma. Sodium bicarbonate was administered to alkalisate urine in people undergoing forced diuresis.

RCT - randomised controlled trial

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	<ol style="list-style-type: none"> 1. MeSH descriptor Sodium Bicarbonate, this term only 2. (sodium bicarbonat*):ti,ab,kw in Clinical Trials 3. (1 OR 2) 4. MeSH descriptor Acute Kidney Injury/ explode all trees 5. (acute renal insufficien* or acute kidney insufficien*):ti,ab,kw in Clinical Trials 6. (acute kidney failur* or acute renal failur*):ti,ab,kw in Clinical Trials 7. (ARF or AKF or ATN):ti,ab,kw in Clinical Trials 8. (acute kidney injur* or acute renal injur*):ti,ab,kw in Clinical Trials 9. acute tubular necrosis.tw 10.(4 OR 5 OR 6 OR 7 OR 8 or 9) 11.(3 AND 10)
MEDLINE	<ol style="list-style-type: none"> 1. Sodium Bicarbonate/ 2. sodium bicarbonat\$.tw 3. or/1-2 4. exp Acute Kidney Injury/ 5. (acute kidney failure or acute renal failure).tw.

(Continued)

6. (acute kidney injur\$ or acute renal injur\$).tw.
7. (acute kidney insufficie\$ or acute renal insufficie\$).tw.
8. acute tubular necrosis.tw.
9. (ARF or AKF or ATN).tw.
- 10.or/4-9
- 11.and/3,10

EMBASE

1. Bicarbonate/
2. sodium bicarbonate\$.tw.
3. or/1-2
4. acute kidney failure/ or acute kidney tubule necrosis/
5. (acute renal insufficien\$ or acute kidney insufficien\$).tw.
6. (acute kidney failur\$ or acute renal failure\$).tw.
7. (acute kidney injur\$ or acute renal injur\$).tw.
8. (ARF or AKF or ATN).tw.
9. acute tubular necrosis.tw
- 10.or/4-9
- 11.and/3,10

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	<i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random). <i>High risk of bias:</i> Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention. <i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	<i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes). <i>High risk of bias:</i> Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure. <i>Unclear:</i> Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants	<i>Low risk of bias:</i> No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

(Continued)

and personnel during the study

High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Unclear: Insufficient information to permit judgement

Blinding of outcome assessment

Detection bias due to knowledge of the allocated interventions by outcome assessors.

Low risk of bias: No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Unclear: Insufficient information to permit judgement

Incomplete outcome data

Attrition bias due to amount, nature or handling of incomplete outcome data.

Low risk of bias: No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.

High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Unclear: Insufficient information to permit judgement

Selective reporting

Reporting bias due to selective outcome reporting

Low risk of bias: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear: Insufficient information to permit judgement

Other bias

Bias due to problems not covered elsewhere in the table

Low risk of bias: The study appears to be free of other sources of bias.

High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

(Continued)

Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
1 June 2017	Review declared as stable	New search undertaken in May 2017 - no studies identified

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: JH, MU, NH, GVR, KM
2. Study selection: NH, JH, KM
3. Extract data from studies: JH, NH, KM
4. Enter data into RevMan: NH, JH, KM
5. Carry out the analysis: JH, KM
6. Interpret the analysis: JH, KM
7. Draft the final review: JH, MU, NH, GVR, KM
8. Disagreement resolution: JH, GVR
9. Update the review: JH, MU, NH, GVR, KM

DECLARATIONS OF INTEREST

The authors declare no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Portsmouth Hospitals Trust, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A secondary outcome, "adverse effects attributable to the intervention", was omitted from the review after considering a referee's comment that this criterion lacked specificity around the definition of "any" adverse effects and "potential" adverse effects and how such impacts were measured as being attributable to health outcomes. In addition, we did not identify any robust data related to reporting adverse effects.

NOTES

New search undertaken in May 2017 - no studies identified.

INDEX TERMS

Medical Subject Headings (MeSH)

Acidosis [*drug therapy] [etiology]; Acute Kidney Injury [complications] [*drug therapy]; Sodium Bicarbonate [*therapeutic use]

MeSH check words

Adult; Humans