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Loop Diuretics for Patients Receiving Blood Transfusions

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[Intervention Review]

Loop diuretics for patients receiving blood transfusions

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ABSTRACT

Background

Blood transfusions are associated with significant morbidity and mortality. Prophylactic administration of loop diuretics (furosemide, bumetanide, ethacrynic acid, or torsemide) is common practice, especially among people who are at risk for circulatory overload, pulmonary oedema or both.

Objectives

This review aimed to determine if the prophylactic administration of loop diuretics (furosemide, bumetanide, ethacrynic acid, or torsemide) provides a therapeutic advantage (that is, a favourable risk benefit ratio) in adults and children who are recipients of any blood product transfusion versus placebo, no treatment, or general fluid restriction measures.

Search methods

We searched the Cochrane Renal Group's Specialised Register to 13 January 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

All randomised controlled trials (RCTs) and quasi-RCTs assessing a loop diuretic in patients receiving any blood transfusion were considered for inclusion.

Data collection and analysis

Two authors independently assessed study quality and extracted data. Study authors were contacted for additional information. Results were to be expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes, and mean difference (MD) and 95% CI for continuous outcomes. Mean effect sizes were to be calculated using the random-effects models.

Main results

We included four studies that involved 100 participants. Furosemide was the only diuretic investigated in all four studies.

None of the included studies assessed the clinically important outcomes noted in our protocol. The studies focused on various markers of respiratory function. An improvement in fraction of inspired oxygen (in favour of furosemide) was noted in one study. An improvement in pulmonary capillary wedge pressure (in favour of furosemide) was noted in two studies.

Authors' conclusions

There was insufficient evidence to determine whether premedicating people undergoing blood transfusion with loop diuretics prevents clinically important transfusion-related morbidity. Due to the continued use of prophylactic loop diuretics during transfusions, and because this review highlights the absence of evidence to justify this practice, well-conducted RCTs are needed. Given the high mortality, severe morbidity and increasing incidence of transfusion-associated circulatory overload, determining the therapeutic utility of pre-transfusion loop diuresis is an urgent need.

PLAIN LANGUAGE SUMMARY

Loop diuretics for patients receiving blood transfusions

Blood transfusions are often complicated by water retention, which may worsen lung function, heart function and/or kidney function. Loop diuretics, medications that reduce body water by making the kidneys excrete more urine, are thought to prevent water retention. Accordingly, many doctors pre-medicate their blood transfusion recipients with loop diuretics.

The goal of our review was to determine whether pre-medicating blood transfusion recipients with loop diuretics prevents complications of blood transfusion. Our review of four studies and 100 participants determined that there is not enough high-quality evidence about the clinically relevant benefits or harms of using loop diuretics to prevent complications of blood transfusion.

BACKGROUND

Description of the condition

Due to improvements in the quality and effectiveness of blood screening, and the consequent 10,000-fold decrease in transfusion-transmissible infections, non-infectious serious hazards of transfusion have emerged as the leading complications of blood transfusion (Hendrickson 2009). Many of these complications are thought to be preventable. For example, transfusion-associated circulatory overload (TACO) is thought to be prevented by pre-transfusion diuretic therapy (Alam 2013; Fry 2010).

TACO is a common and deadly pulmonary complication of blood transfusion. A typical presentation of TACO includes orthopnoea, cyanosis, tachycardia, hypertension and signs of hypervolaemia during, or within several hours of, transfusion (Popovsky 2004; Skeate 2007). Elevated brain-type natriuretic peptide (BNP) may be present (Zhou 2005). Respiratory distress due to pulmonary oedema is a hallmark (Popovsky 2004; Skeate 2007). While a universal definition is lacking (Skeate 2007), the International Society of Blood Transfusion (ISBT) has proposed one. According to ISBT (Popovsky 2006), the presence of any one of four signs (acute respiratory distress, tachycardia, increased blood pressure, acute or worsening pulmonary oedema, or evidence of positive fluid balance) within six hours of transfusion may indicate TACO. From a pathophysiology perspective, a TACO-related pulmonary complication is comparable to acute congestive heart failure; alveolar fluid accumulates secondary to elevated hydrostatic pressure (Popovsky 2004).

TACO is difficult to distinguish from transfusion-related acute lung injury (TRALI) (Popovsky 2004; Skeate 2007), another common transfusion-related pulmonary complication. Although both conditions cause respiratory distress due to acute pulmonary oedema (Popovsky 2004; Skeate 2007), patients with TRALI present with an immune-mediated permeability pulmonary oedema (Bux 2007). In this type of pulmonary oedema, fluid accumulation is caused by alveolar tissue injury (Bux 2007), and is not related to elevated hydrostatic pressure (Popovsky 2004; Skeate 2007). Patients with TRALI usually do not have elevated BNP (Zhou 2005). Patients are often euvolaemic or hypovolaemic (Skeate 2007). The role of pre-transfusion diuresis to prevent TRALI is therefore problematic; in theory, the hypovolaemic effect of loop diuresis may worsen outcomes in these patients.

Incidence, morbidity and mortality of the condition

TACO is a common complication of blood transfusion. From 2008 to 2012, 248 cases of TACO were reported to Serious Hazards of Transfusion (SHOT), the United Kingdom's haemovigilance system (Bolton-Maggs 2013). Incidence peaked in 2012, when 82 cases were reported, making TACO the fourth most

common transfusion-related complication in the United Kingdom (Bolton-Maggs 2013). Canada's Transfusion Transmitted Injuries Surveillance System (TTISS) reported 110 cases of TACO in 2004 and 147 cases in 2005 (PHAC 2008). For the two-year period, TACO, representing 39.2% of all cases of adverse transfusion events reported to the TTISS, and was the most common adverse transfusion event (PHAC 2008). In a recent prospective cohort study (Li 2011), 6% of critically ill patients developed TACO. Previous retrospective studies have reported an incidence between 1% and 8% (Popovsky 2004).

TACO is an important cause of transfusion-related morbidity and mortality. The 2012 SHOT report linked TACO to 29 cases of major morbidity: 28 patients required ICU care and one required dialysis (Bolton-Maggs 2013). The TTISS graded the severity of adverse transfusion events; 38.5% of TACO cases (99/257 cases) were either "severe" or "life-threatening" (PHAC 2008). The mortality rate of TACO was 7.3% (6 deaths/82 cases) in the SHOT report and 1.2% (3 deaths/257 cases) in the TTISS report (Bolton-Maggs 2013; PHAC 2008). The TTISS reported a total of 13 transfusion-related deaths; TACO was responsible for three of these (PHAC 2008). Similarly, in the US, TACO is responsible for 18% of transfusion-related deaths, making TACO the second most common cause of transfusion-related death (US FDA 2012).

How the intervention might work

The rationale for pre-transfusion loop diuretic therapy is threefold:

1. Loop diuretics block the Na/K/2Cl co-transporter in the thick ascending loop of Henle to increase water excretion and thus reduce extracellular volume, including pulmonary interstitial volume (Eades 1998).
2. Loop diuretics can shift alveolar fluid to the intravascular space (Eades 1998). Purported mechanisms are reduced pulmonary congestion due to increased venous capacitance and pulmonary venodilation (Schuster 1984).
3. Loop diuretics may improve lung compliance (Eades 1998). In a study (O'Donovan 1989) of premature infants with respiratory distress syndrome, furosemide was associated with improved survival, independent of diuresis. A possible mechanism includes relaxation of airway smooth muscle (O'Donovan 1989).

Patients receiving blood transfusions are acutely ill, and adverse drug reactions are a risk in this population. Adverse effects associated with loop diuretics include severe hypovolaemia, hypernatraemia, hypokalaemia, hypochloraemia, hypercalciuria, metabolic alkalosis and hyperuricaemia (Eades 1998). Additionally, transient and permanent ototoxicity, interstitial nephritis, and ductus arteriosus have been linked to loop diuretics (Eades 1998).

Why it is important to do this review

Diuretic pre-medication for patients receiving blood transfusion is common, especially in those who are at increased risk for fluid overload or pulmonary oedema. In a recent retrospective chart review of 50 TACO patients, Lieberman 2013 found that pre-emptive diuretics were used 29% of the time. A retrospective review of paediatric ICU cases found that 43% (17/40) of patients requiring transfusion received furosemide (Agrawal 2012). Piccin 2009 noted a similar usage, while Fry 2010 noted a usage of 0.6% (2/324) in a retrospective chart review. Indeed, the pre-transfusion risk assessment checklist advocated by Alam 2013 provides an option to order furosemide for certain patient populations. Controversially, justification for this practice relies on anecdotal evidence, biological theories and a few small studies. A rigorous and comprehensive summary of benefits and risks is needed to clarify the role of pre-transfusion diuretic therapy for the prevention of transfusion-related pulmonary complications (i.e. TACO).

OBJECTIVES

This review aimed to determine if the prophylactic administration of loop diuretics (furosemide, bumetanide, ethacrynic acid, or torsemide) provides a therapeutic advantage (that is, a favourable risk benefit ratio) in adults and children who are recipients of any blood product transfusion versus placebo, no treatment, or general fluid restriction measures.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) that looked at loop diuretic use in patients receiving any blood transfusion. When full study reports were unavailable, authors were contacted to obtain relevant data.

Types of participants

All adults and children who received, or were to receive, a transfusion of any blood product either as an inpatient or outpatient.

Types of interventions

- Treatment: any loop diuretic at any dose or formulation given within 24 hours for a blood transfusion (before or after the transfusion). The loop diuretic had only been given for the purposes of the blood transfusion.
- Control: placebo, no treatment, or specific fluid restriction measures.

Types of outcome measures

Primary outcomes

1. TACO, characterised by any four of the following outcomes during or within six hours of transfusion (Popovsky 2004).
    - Acute respiratory distress
    - Tachycardia
    - Increased blood pressure
    - Acute or worsening pulmonary oedema evident on frontal chest x-ray
    - Evidence of positive fluid balance
2. TRALI, defined as new onset acute lung injury during or within six hours of transfusion with no evidence of circulatory overload and no temporal relationship to other acute lung injury risk factors (Kleinman 2004; Toy 2005).

Secondary outcomes

1. Mortality
2. Serious adverse events, including:
    - Hospitalisation (prolonged or initial)
    - Disability or permanent damage
    - Intervention required to prevent heart failure (Killip stages I or II) (Cannon 2001)
    - Death or life-threatening event
3. Acute heart failure
    - We graded heart failure severity according to the Killip classification (severity ranked in ascending order) (Cannon 2001):
        - Stage I. Characterised by an absence of rales over the lung fields and an absence of S3
        - Stage II. Characterised by rales over 50% or less of the lung fields or the presence of an S3
        - Stage III. Characterised by rales over more than 50% of the lung fields
        - Stage IV (cardiogenic shock). Characterised by hypotension (SBP < 90 mm Hg for at least 30 minutes or the need for supportive measures), end-organ hypoperfusion (cold extremities and a heart rate of at least 60 beats/min) and haemodynamic changes (cardiac index of no more than 2.2 L/min/m² and a pulmonary-capillary wedge pressure of at least 15 mm Hg)
4. Acute kidney injury (AKI)
    - We used the consensus definition from the KDIGO Clinical Practice Guideline for Acute Kidney Injury (KDIGO 2012):
        - increase in serum creatinine by 26.5 µmol/L within 48 hours; or
        - increase in serum creatinine to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
        - urine volume less than 0.5 mL/kg/h for 6 hours
    - Using KDIGO criteria (KDIGO 2012), we categorised AKI according to the following stages of severity (severity ranked in ascending order):
        - Stage I. Serum creatinine increase from 1.5 to 1.9 times baseline or by at least 26.5 µmol/L; or urine output less than 0.5 mL/kg/h for more than 6 hours
        - Stage II. Serum creatinine increase from 2.0 to 2.9 times baseline; or urine output less than 0.5 mL/kg/h for more than 12 hours
        - Stage III. Serum creatinine increase to 3.0 times baseline, or to at least 353.6 µmol/L, or initiation of renal replacement therapy; or urine output less than 0.3 mL/kg/h for 24 hours, or anuria for 12 hours
5. Diuretic-related electrolyte abnormalities: hyponatraemia, hypokalaemia, hypochloraemia, hypercalciuria, hyperuricaemia or metabolic alkalosis
6. Ototoxicity.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register to 13 January 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's 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 renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal 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 the Cochrane Renal Group. Details of these strategies as well as a list of handsearched journals, conference proceed-

ings and current awareness alerts are available in the Specialised Register section of information about the Cochrane Renal Group. See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of 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 review was undertaken by two authors. 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 both authors, who discarded studies that were not applicable; however, studies and reviews that included relevant data or information on other studies were retained initially. Both authors independently assessed and retrieved abstracts and necessary full texts to determine which studies satisfied the inclusion criteria.

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.

Assessment of risk of bias in included studies

The following items were 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

Dichotomous outcomes were to be analysed by calculating the relative risk (RR) for each study, with the uncertainty in each result expressed with 95% confidence intervals (CI). Continuous outcomes were to be analysed by calculating the mean difference (MD) or the standardised mean difference (SMD) with 95% CI. For outcomes assessed by scales we were to compare and pool the mean score differences from the end of treatment to baseline (post minus pre) in the experimental and control group. However, due to significant methodological differences (and heterogeneity of reported outcomes) in the included studies, no meta-analyses were performed.

Unit of analysis issues

Due to significant methodological differences in the included studies, no meta-analyses were performed

Dealing with missing data

Any further information required from the original author was requested by written correspondence and any relevant information obtained in this manner was included in the review. However, due to significant methodological differences in the included studies, no meta-analyses were performed.

Assessment of heterogeneity

Heterogeneity was to be analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). However, due to significant methodological differences in the included studies, no meta-analyses were performed.

Assessment of reporting biases

Sensitivity analyses were to be performed to assess the impact of missing data. However, reporting bias was not an issue in the included studies.

Data synthesis

We planned to pool data using the random-effects model. However, due to significant methodological differences (and heterogeneity of reported outcomes) in the included studies, no meta-analyses were performed.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was to be used to explore possible sources of heterogeneity (such as participants, interventions, timing of loop diuretic administration). However, due to a lack of adequate studies and data, we were unable to conduct these analyses.

Sensitivity analysis

Sensitivity analysis was planned to test for the robustness of the results. Analysis of the following categories was to be undertaken separately.

- Studies without proper randomisation or concealment of allocation compared to those without these characteristics;
- Studies performed without intention-to-treat analysis compared to those with an intention-to-treat analysis;
- Unblinded versus blinded studies.

However, due to a lack of adequate studies and data, we were unable to conduct these analyses.

RESULTS

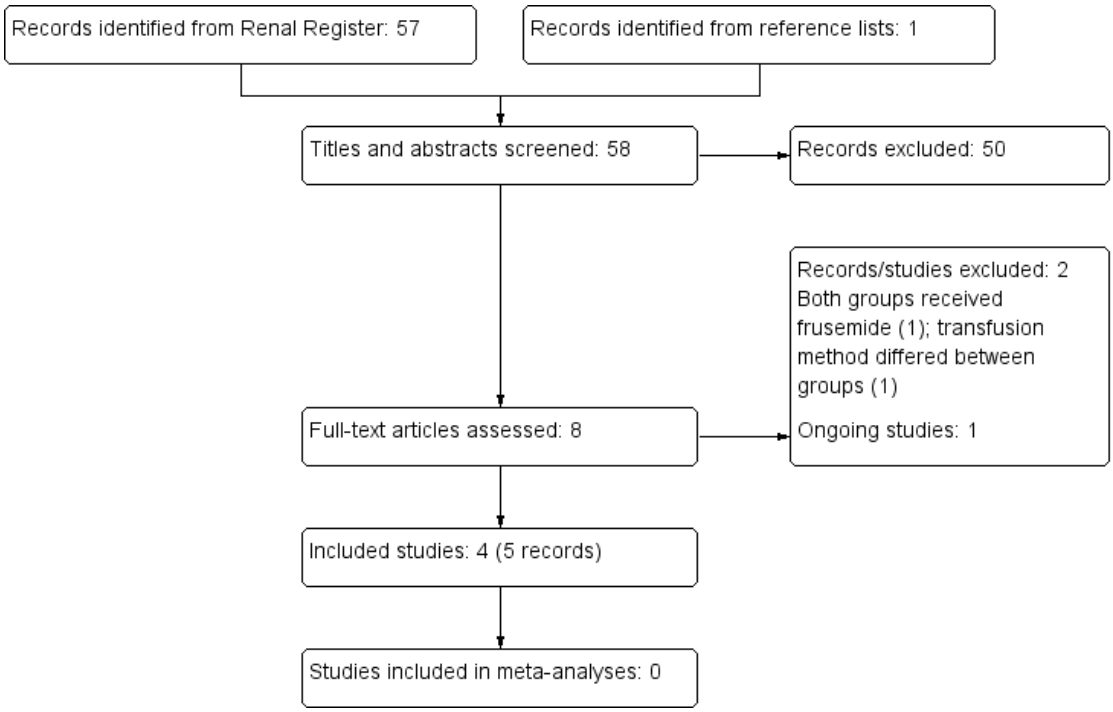
Description of studies

Results of the search

The search identified 57 records. After preliminary screening of abstracts and titles we assessed the full-text of six records. We excluded two records (see Characteristics of excluded studies), and identified another study (Sarkar 2008) for inclusion after a review of the reference list of Balegar 2011. One ongoing study was identified and will be assessed in a future update of this review (NCT00618852).

Our review included four studies (five records) that involved 100 participants (Figure 1).

Figure 1. Study flow diagram



Included studies

Patient demographics, reasons for blood transfusion, types of blood transfusion and dose of furosemide varied among studies. Nand 1985 and Nand 1986 studied adults who required whole blood for chronic anaemia, all of whom were pre-treated with furosemide 40 mg IV. Balegar 2011 and Sarkar 2008 studied preterm infants who required packed red blood cell (PRBC) trans-

fusion. In Sarkar 2008, PRBC transfusion recipients were post-treated with a single dose of furosemide 1 mg/kg IV; in Balegar 2011, study participants were pre-treated with a single dose of furosemide 1 mg/kg IV just before transfusion.
See Characteristics of included studies.

Excluded studies

The two excluded studies lacked an adequate placebo control group. In Reiter 1998, both groups received a loop diuretic; one group received a furosemide 1 mg/kg IV bolus, while the other received a 6-hour furosemide 0.9 mg/kg IV infusion. In Harrison 1971, the control group did not match the treatment group: one group was given 1200 mL of packed cells, and the other group received 500 mL packed cells (to which 50 mg of ethacrynic acid had been added).
See Characteristics of excluded studies.

Risk of bias in included studies

All studies demonstrated high risk of selective reporting bias. Nand 1985 and Nand 1986 demonstrated high risk of bias in at least one additional category, while Sarkar 2008 and Balegar 2011 demonstrated low risk of bias in all other categories.
See Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

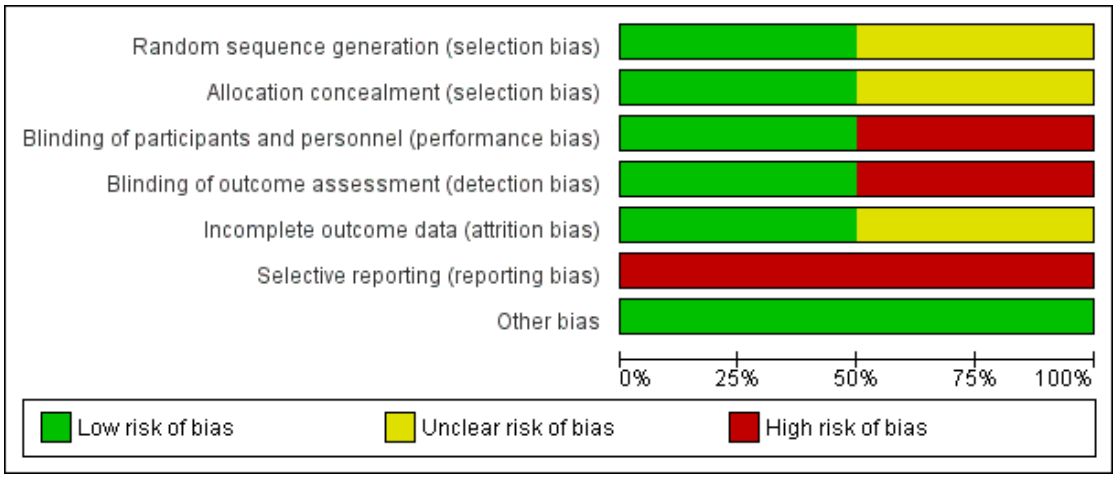
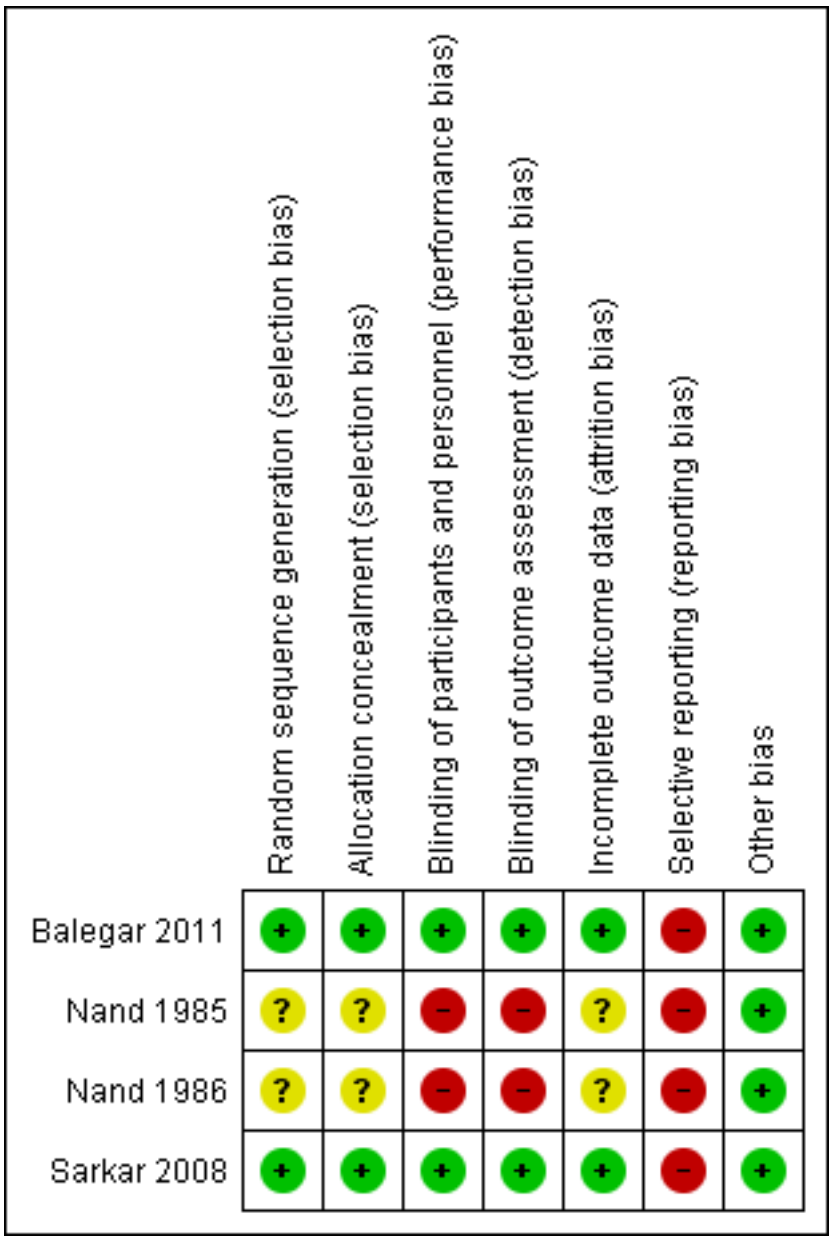


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Two studies (Nand 1985; Nand 1986) did not report on methods of allocation concealment. In Sarkar 2008 and Balegar 2011, the randomisation scheme was available only to third party pharmacy personnel.

Blinding

A matching placebo was not used in Nand 1985 or Nand 1986; clinicians and patients were likely not blinded. Third party pharmacy personnel were responsible for preparing treatment and placebo in Sarkar 2008 and Balegar 2011; clinicians and patients were adequately blinded.

Incomplete outcome data

Sarkar 2008 and Balegar 2011 presented participant flow diagrams and performed intention-to-treat analysis. Nand 1985 and Nand 1986 did not report on attrition.

Selective reporting

Data in Balegar 2011, Nand 1985 and Nand 1986 were not reported in a manner that would allow for inclusion in a meta-analysis.

No study reported our outcomes-of-interest, even though the studies surely recorded at least some of our outcomes-of-interest (i.e. mortality, serious adverse events).

Other potential sources of bias

None

Effects of interventions

The included studies did not report our primary and secondary outcomes. We requested (by email) additional outcomes data from the authors of each study. We received no response. Additionally, there is heterogeneity in the types of outcomes reported by the studies. Therefore, the results of each study are summarised below individually.

Nand 1985

Pulmonary capillary wedge pressure (PCWP) was the primary outcome. Swan-Ganz monitoring catheters were used to measure intracardiac pressures. PWCP increased significantly from baseline in the control group (from 7.75 ± 2.34 to 9.37 ± 2.44; P < 0.001). PWCP in the furosemide group decreased (from 6.80 ± 2.32 to 5.32 ± 1.76; P < 0.001). Between-group statistical comparisons were not reported.

Nand 1986

PCWP was the primary outcome. Swan-Ganz monitoring catheters were used to measure intracardiac pressures. PWCP increased significantly from baseline in the control group (from 8.05 ± 3.58 to 11.27 ± 3.62; P < 0.001). The change in PWCP in the furosemide group (from 7.99 ± 2.89 to 7.69 ± 3.39) was not statistically significant (P > 0.05). Between-group statistical comparisons were not reported.

Sarkar 2008

Pulmonary function was the primary outcome. Multiple indicators of pulmonary function (see Characteristics of included studies) were reported. The difference between the treatment groups was not statistically significant for all reported indicators of pulmonary function. As noted by the authors, the study was underpowered to detect statistically significant changes in pulmonary mechanics data.

Balegar 2011

Increase in fraction of inspired oxygen (FiO_2), a marker for pulmonary distress, was the study's primary outcome. FiO_2 was measured for six hours before transfusion, and for 24 hours after transfusion.

At the end of the study period, the mean percentage change from baseline of FiO_2 was -0.6% ± 2.8 in the furosemide group and 9.1% ± 11.4 in the placebo group (P < 0.05 for between-group comparison).

Changes in most secondary outcomes (various pulmonary, cardiac and electrolyte measures) were not statistically different between the control and treatment groups.

DISCUSSION

Summary of main results

Four small studies enrolling 100 participants were eligible for inclusion. Two studies enrolled preterm infants, and reported on several markers of pulmonary function. Pulmonary function was not clinically different between the treatment and placebo groups in both studies. The other two studies enrolled adults, and reported

PCWP. PCWP increased from baseline in the control groups, and did not change in the treatment groups.
No study reported on adverse events. No study reported on the outcomes we deemed to be clinically meaningful.

Overall completeness and applicability of evidence

The included studies did not address the objectives of our review and did not include results for key outcomes. Outcomes that were expected to be reported include: mortality, serious adverse events, TACO, TRALI and adverse drug reactions (see Types of outcome measures).

Quality of the evidence

All four studies included in our review were conducted at single centres, and had a small sample size. In total, 100 participants were available for analysis. Pooling the studies' data for a meaningful meta-analysis was not attempted for several reasons. The included studies did not assess the important efficacy and safety outcomes defined in our protocol; instead, the studies focused on various pathophysiological parameters. The pathophysiological parameters (e.g. FiO_2, respiratory rate, PCWP) are surrogate markers of health; changes in these markers do not necessarily reflect changes in clinically important outcomes (e.g. serious adverse events, respiratory failure, total adverse events). These various pathophysiological parameters were different in each study (Nand 1985 and Nand 1986 measured intra-cardiac pressures, while Sarkar 2008 and Balegar 2011 collected pulmonary mechanics data). There was also significant heterogeneity in patient population, type of transfusion, duration of transfusion, timing of furosemide administration, and dose of furosemide between studies (see Characteristics of included studies).

Risk of bias implications

Outcomes reporting bias is present in all four included studies. The studies do not report clinically important outcomes, like mortality, serious adverse events, adverse drug reactions, and TACO. Granted, the included studies may not have had sufficient statistical power to detect differences in these outcomes. Given that two of the included studies were published nearly 30 years ago, when reporting standards may have been lower, we do not believe that clinically important outcomes were deliberately withheld. Nevertheless, omission of these important outcomes, leads to an over-representation of the studies' statistically positive results for clinically unimportant outcomes.
It is highly unlikely that information on serious adverse events was not collected during the course of these studies. The issue is that this data has not been made available in the published reports. Regarding outcome measures such as TACO, it seems odd that clinical studies of loop diuretics for blood transfusions would not collect and report this data as these outcomes are important to the patients who received the interventions (loop diuretics or placebo). We encourage investigators of the included studies to contact us with this data if it is still available and we will include it in a subsequent update of this review.
The implications of other biases in the included studies are of minimal importance in this review as none of the studies reported on any pre-specified clinically important outcomes. There are some general statements that can be made. Neither Nand 1985 nor Nand 1986 reported randomisation, allocation concealment, or blinding procedures and we were unable to contact authors to provide details. As such, selection bias and ascertainment bias are possible for both studies; these types of biases are thought to, in general, lead to an overestimation of treatment effects and an underestimation of treatment harms. This could not be tested with sensitivity analyses as data from included studies was not meta-analysed. Second, the likely selection bias in Nand 1985 and Nand 1986 may have led to a carefully selected group of study participants which would limit the generalisability of the findings. Finally, Balegar 2011 and Sarkar 2008 were graded as low risk of bias in 5/6 risk of bias domains therefore the reported results of these studies are likely reliable despite the fact that they do not provide useful information for this review (i.e. they did not report on any of the pre-specified outcomes).

Potential biases in the review process

There were no potential biases noted in the review process.

AUTHORS' CONCLUSIONS

Implications for practice

While the included studies report statistically significant improvements in FiO_2 and PCWP, current evidence does not support the routine use of loop diuretics for the prevention of clinically important (i.e. organ failure, mortality, total serious adverse events) transfusion-related morbidity. Moreover, there is insufficient evidence to assess harm caused by loop diuretics in patients receiving transfusion.

Implications for research

Due to the continued use of prophylactic loop diuretics during transfusions (Alam 2013; Agrawal 2012; Fry 2010; Lieberman 2013; Piccin 2009), and because this review highlights the absence of evidence to justify this practice, well-conducted RCTs are needed. Given the high mortality (Bolton-Maggs 2013), severe

morbidity and increasing incidence of TACO (PHAC 2008), determining the therapeutic utility of pre-transfusion loop diuresis is an urgent need.

Future studies should randomise hospitalised patients who are to receive blood product transfusions to either single dose loop diuretic (given via any formulation) or single dose placebo. Studies should not exclude patients with systemic disease (e.g. kidney dysfunction, heart disease); these patients are most likely to develop transfusion-related pulmonary complications (Murphy 2013). Patients should be followed for at least 30 days, and studies need to be powered to detect differences in clinically important outcomes. Definitions for these outcomes, including TACO, for which a consensus definition is lacking (Skeate 2007), are detailed in the methods section of this review (Types of outcome measures).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Balegar 2011

Methods	• Study design: parallel RCT • Study duration: 1 June 2007 to 31 December 2008
Participants	• Country: Australia • Setting: NICU at Royal North Shore Hospital, Sydney, Australia • Preterm infants (< 37 weeks gestational age at birth) • Health status: haemodynamically stable pre-term infants requiring PRBCT to treat anaemia • Number: treatment group (21); control group (19) • Gestational age ± SD (weeks): treatment group (27.2 ± 1.8); control group (26.6 ± 1.7) • Sex (M/F): treatment group (12/9); control group (9/10) • Exclusion criteria: congenital heart disease; hypotension (e.g. hypovolaemic shock); furosemide/PRBCT in the previous 3 days
Interventions	Treatment group • Furosemide: IV 1 mL/kg • Dosed just prior to PRBCT transfusion (20 mL/kg over 4 hours) Control group • Normal saline • Dosed just prior to PRBCT transfusion (20 mL/kg over 4 hours)
Outcomes	• Study did not report on our outcomes of interest. • The primary outcome was percentage of change in FiO_2** (24 h post-transfusion period compared with 6 h pre-transfusion period) **FiO_2 required to maintain pulse oximeter saturation (SpO_2) in a target range of 85% to 92%
Notes	• Funding provided by the North Shore Heart Research Foundation • The authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated random numbers in blocks of 10"
Allocation concealment (selection bias)	Low risk	"allocation code was concealed in sequentially numbered, opaque, sealed envelopes and were opened by the clinical trials pharmacist only after enrolment by the treating clinician"

Balegar 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"study drug was prepared by the hospital pharmacy as a colourless solution in identical 5 mL transparent syringes containing furosemide 1 mg/mL or placebo labelled with the allocation code. The clinical trials pharmacist was the only person who knew the allocation code and was not involved in patient care. All others were blinded to the treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All others were blinded to the treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participant flow diagram presented; no dropouts
Selective reporting (reporting bias)	High risk	Under-reporting of data: • "secondary" outcomes were published in an online supplement • measures of uncertainty were missing for most reported outcomes Selective choice of data: • Quote: "the mean FiO_2 increase SD in furosemide vs. placebo group was 2.8% 7.1 vs. 4.6% 8.1 during epoch 3 and 0. 6% 2.8 vs. 9.1% 11.4 during epoch 4" • Comment: numerical data were not reported for epoch 1 ($P > 0.05$) and epoch 2 Omission of outcomes: authors did not report on clinically important outcomes (i. e. mortality, serious adverse events), which were likely recorded by authors
Other bias	Low risk	Measures of pulmonary function are subject to observer error; authors minimised observer bias by "having a single operator perform the study, adapting a consistent approach to measurements, and obtaining each variable as the mean value of 5 consecutive measurements"

Nand 1985

Methods	• Study design: parallel RCT • Study duration: not reported
Participants	• Country: India • Setting: setting not clear (likely single, inpatient institution) • Health status: adults with "severe anaemia for more than 6 months and with haemoglobin levels of 6 g% or less" • Number: treatment group (10); control group (10) • Mean age ± SD (years): treatment group (28.7 ± 9.1); control group (26.1 ± 7.9) • Sex (M/F): not reported • Exclusion criteria: "Cases with any associated cardiopulmonary, renal or hepatic disease were excluded"
Interventions	Treatment group • Furosemide: 40 mg IV • Dosed just before the start of 1 unit (300 to 350 mL) whole blood transfusion Control group • Whole blood transfusion: 1 unit (300 to 350 mL) (i.e. no matching placebo)
Outcomes	• Study did not report on our outcomes of interest. • Intracardiac pressures (right atrium, right ventricle, main pulmonary artery, pulmonary capillary wedge) were the primary outcomes. Heart catheterisation was performed using Swan-Ganz monitoring catheters
Notes	• Sources of funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The patients were divided randomly into 2 groups of 10 cases each"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported; participants likely not given matching pre-transfusion placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported; participants likely not given matching pre-transfusion placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study did not address attrition; participant flow diagram not published
Selective reporting (reporting bias)	High risk	Under-reporting of data: data were not reported numerically; instead, authors used narrative descriptions, such as "not signifi-

Nand 1985 (*Continued*)

		cant" or "P < 0.001" Omission of outcomes: authors did not report on clinically important outcomes (i.e. mortality, serious adverse events), which were likely recorded by authors
Other bias	Low risk	Study appears to be free of other sources of bias

Nand 1986

Methods	• Study design: parallel RCT • Study duration: not reported
Participants	• Country: India • Setting: Setting not clear (likely single, inpatient institution) • Health status: adults with "severe anaemia for more than 6 months and with haemoglobin levels of 6 g% or less" • Number: treatment group (10); control group (10) • Mean age ± SD (years): treatment group (30.1 ± 10.4); control group (30.8 ± 13.7) • Sex (M/F): not reported • Exclusion criteria: participants with "any evidence of systemic disease" were excluded
Interventions	Treatment group • Whole blood: 2 units (650 to 700 mL) transfused at a rate of 5 mL/min • Furosemide: 40 mg IV administered before the start of transfusion Control group • Whole blood: 2 units (650 to 700 mL) transfused at a rate of 5 mL/min (i.e. no matching placebo)
Outcomes	• Study did not report on our outcomes of interest • Intracardiac pressures (right atrium, right ventricle, main pulmonary artery, pulmonary capillary wedge) were the primary outcomes. Heart catheterisation was performed using Swan-Ganz monitoring catheters
Notes	• Sources of funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The patients were divided randomly into 2 groups of 10 cases each"
Allocation concealment (selection bias)	Unclear risk	Not reported

Nand 1986 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported; participants likely not given matching pre-transfusion placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported; participants likely not given matching pre-transfusion placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study did not address attrition; a participant flow diagram was not published
Selective reporting (reporting bias)	High risk	Under-reporting of data: between-group statistical comparisons were not made Omission of outcomes: authors did not report on clinically important outcomes (i.e. mortality, serious adverse events), which were likely recorded by authors
Other bias	Low risk	The study appears to be free of other sources of bias

Sarkar 2008

Methods	• Study design: parallel RCT • Duration of study: January 2004 to June 2005
Participants	• Country: USA • Setting: Holden NICU of the University of Michigan Health System • Health status: pre-term very low birth weight infants; diagnosed with RDS; receiving elective top off transfusions (for low haematocrit or blood loss) during the first 2 weeks of life; restricted to mechanically ventilated infants • Number: treatment group (12); control group (8) • Gestational age ± SD (weeks): treatment group (25.8 ± 1.4); control group (26.2 ± 1.3) • Exclusion criteria: contraindications to furosemide (such as hypotension or electrolyte disturbances); major congenital pulmonary, kidney, or cardiac malformations; use of furosemide for other reasons
Interventions	Treatment group • Furosemide IV dose (1 mg/kg), administered after completion of PRBC transfusion Control group • Equivalent volume (1 mL/kg) of normal saline, administered after completion of PRBC transfusion
Outcomes	• Pulmonary parameters (minute ventilation, compliance, and resistance) • Clinical parameters (SpO_2, blood pressure, heart rate, spontaneous respiratory rate)

Sarkar 2008 (*Continued*)

	• Ventilatory parameters (PIP, PEEP, FiO_2, PaO_2, $PaCO_2$) Outcomes were recorded before the start of transfusion (baseline), at the completion of the transfusion (when the study treatment was administered), and 4 hours after completion of the PRBC transfusion Pulmonary mechanic measurements were performed using the VIP GOLD infant/paediatric ventilator
Notes	Study was terminated prematurely because "the chances of any statistically significant clinical benefit afforded by furosemide at the end of the trial were likely to be very small"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"...computer generated randomization scheme."
Allocation concealment (selection bias)	Low risk	"Access to the randomization scheme was restricted to selected pharmacy personnel who were not otherwise involved in the trial"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The treatment dose was dispensed from the pharmacy in identical syringes labelled as 'furosemide study solution' for both furosemide and placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-masked"; probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participant flow diagram presented; no dropouts
Selective reporting (reporting bias)	High risk	Omission of outcomes: authors did not report on clinically important outcomes (i.e. mortality, serious adverse events), which were likely recorded by authors
Other bias	Low risk	The study appears to be free of other sources of bias

FiO_2 - fraction of inspired oxygen; NICU - neonatal intensive care unit; PRBCT - packed red blood cell transfusion; RDS - respiratory distress syndrome; SpO_2 - pulse oximeter saturation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Harrison 1971	Transfusion method differed between treatment and placebo groups
Reiter 1998	Both treatment group and placebo group participants received furosemide

Characteristics of ongoing studies *[ordered by study ID]*

NCT00618852

Trial name or title	A randomized controlled trial of furosemide to prevent fluid overload during red blood cell transfusion in neonates
Methods	Study design: parallel RCT
Participants	Inclusion criteria • Less than 44 weeks corrected gestational age • Receiving a red cell transfusion • Satisfy one of the following criteria:Echocardiographic evidence of a haemodynamically significant ductus arteriosus (HSDA) defined by a transductal diameter > 1.5 mm and unrestrictive systemic-pulmonary trans-ductal flowClinical evidence of significant lung disease defined by a need for respiratory support (assisted ventilation or nasal CPAP) and oxygen supplementation after 28 days of age Exclusion criteria • Infants with multiple congenital anomalies or renal insufficiency • Infants with hypotension, hypertension, or on any cardiac medication • Infants with sepsis causing compromised clinical condition such as disseminated intravascular coagulopathy • Infants with contra-indications to diuretic therapy, such as significant electrolyte imbalance, or endocrine disease
Interventions	Treatment group • Furosemide: 1 mg/kg by intravenous bolus injection Control group • Saline: 1 mg/kg by intravenous bolus injection
Outcomes	Primary outcomes • Cardiac chamber volume loading Secondary outcomes • Clinical cardio-respiratory stability • Myocardial performance, cardiac input and output and pulmonary haemodynamics (echocardiograph exam) • Changes in electrolyte balance, body weight and urine output
Starting date	January 2007

NCT00618852 (*Continued*)

Contact information	Patrick McNamara, MD patrick.mcnamara@sickkids.ca
Notes	

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Sodium Potassium Chloride Symporter Inhibitors explode all trees 2. (sodium potassium chloride symporter inhibitor*):ti,ab,kw in Clinical Trials 3. (furosemid* or frusemid* or fursemid* or furantral*):ti,ab,kw in Clinical Trials 4. (ethacrynic acid* or ethacrynic acid*):ti,ab,kw in Clinical Trials 5. (torasemid* or torsemide*):ti,ab,kw in Clinical Trials 6. (bumetanid* or bumethanid*):ti,ab,kw in Clinical Trials 7. (loop diuretic*):ti,ab,kw in Clinical Trials 8. (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7) 9. MeSH descriptor Blood Transfusion explode all trees 10. (blood transfus*):ti,ab,kw in Clinical Trials 11. (blood and (exchange* or replac* or substitut* or infus*).):ti,ab,kw in Clinical Trials 12. (blood exchange*):ti,ab,kw or (blood replacement*):ti,ab,kw or (blood infus*):ti,ab,kw or (blood substitut*):ti,ab,kw in Clinical Trials 13. (9 OR 10 OR 11 OR 12) 14. (8 AND 13)
MEDLINE	1. exp Sodium Potassium Chloride Symporter Inhibitors/ 2. sodium potassium chloride symporter inhibitor$.tw. 3. (furosemid$ or frusemid$ or fursemid$ or furantral).tw. 4. (ethacrynic acid$ or ethacrynic acid).tw. 5. (torasemid$ or torsemide$).tw. 6. (bumetanid$ or bumethanid$).tw. 7. loop diuretic$.tw. 8. or/1-7 9. exp Blood Transfusion/ 10. blood transfus$.tw. 11. (blood and (exchange$ or replac$ or substitut$ or infus$)).tw. 12. or/9-11 13. and/8,12
EMBASE	1. exp loop diuretic agent/ 2. (furosemid$ or frusemid$).tw. 3. (ethacrynic acid$ or ethacrynic acid).tw. 4. (torasemid$ or torsemide$).tw. 5. bumetanid$.tw. 6. loop diuretic$.tw.

(*Continued*)

	7. azosemide.tw. 8. etozolin.tw. 9. frumil.tw. 10. indacrinone.tw. 11. mefruside.tw. 12. muzolimine.tw. 13. ozolinone.tw. 14. piretanide.tw. 15. torasemide.tw. 16. xipamide.tw. 17. or/1-16 18. exp transfusion/ 19. blood transfus$.tw. 20. (blood and (exchange$ or replac$ or substitut$ or infus$)).tw. 21. or/18-20 22. and/17,21

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	*Low risk of bias:* 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)
	High risk of bias: 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
	Unclear: 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	*Low risk of bias:* 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)

(*Continued*)

	High risk of bias: 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
	Unclear: 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 and personnel during the study	*Low risk of bias*: 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
	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

(*Continued*)

	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

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

None to declare.

INDEX TERMS

Medical Subject Headings (MeSH)

*Transfusion Reaction; Body Water; Confidence Intervals; Furosemide [*administration & dosage]; Infant, Premature; Pulmonary Edema [etiology; *prevention & control]; Randomized Controlled Trials as Topic; Sodium Potassium Chloride Symporter Inhibitors [*administration & dosage]

MeSH check words

Adult; Humans; Infant, Newborn