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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	6
METHODS	6
RESULTS	9
Figure 1.	10
Figure 2.	12
Figure 3.	13
DISCUSSION	14
AUTHORS' CONCLUSIONS	15
ACKNOWLEDGEMENTS	15
REFERENCES	16
CHARACTERISTICS OF STUDIES	17
DATA AND ANALYSES	18
Analysis 1.1. Comparison 1 Pair-wise comparison of exchange blood transfusion (EBT) plus 10% calcium gluconate intravenously versus EBT alone (change from baseline), Outcome 1 All-cause death.	18
Analysis 1.2. Comparison 1 Pair-wise comparison of exchange blood transfusion (EBT) plus 10% calcium gluconate intravenously versus EBT alone (change from baseline), Outcome 2 Mean total serum calcium levels.	18
Analysis 1.3. Comparison 1 Pair-wise comparison of exchange blood transfusion (EBT) plus 10% calcium gluconate intravenously versus EBT alone (change from baseline), Outcome 3 Mean ionised serum calcium levels.	19
Analysis 1.4. Comparison 1 Pair-wise comparison of exchange blood transfusion (EBT) plus 10% calcium gluconate intravenously versus EBT alone (change from baseline), Outcome 4 Adverse reactions.	19
APPENDICES	19
CONTRIBUTIONS OF AUTHORS	20
DECLARATIONS OF INTEREST	20
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	20
INDEX TERMS	20

[Intervention Review]

Prophylactic intravenous calcium therapy for exchange blood transfusion in the newborn

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ABSTRACT

Background

Exchange blood transfusion (EBT) is a form of whole blood transfusion in which the total blood volume is replaced within a few hours. In perinatal and neonatal medicine, EBT is most often used in the management of severe anaemia or severe hyperbilirubinaemia in the first week of life. Hypocalcaemia, one of the common morbidities associated with EBT, is thought to arise from the chelating effects of the citrate commonly used as an anticoagulant in the donor's blood. This disorder manifests with muscular and nervous irritability and cardiac arrhythmias.

Objectives

To determine whether the use of prophylactic calcium reduces the risk of hypocalcaemia-related morbidities and death among newborn infants receiving EBT.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review group to search the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 5), MEDLINE via PubMed (1966 to 29 June 2016), Embase (1980 to 29 June 2016), and CINAHL (1982 to 29 June 2016). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

All randomised and quasi-randomised trials of prophylactic intravenous calcium in EBT for newborns.

Data collection and analysis

Two review authors independently assessed and extracted data on methods, participants, interventions, and outcomes (mean total and ionised serum calcium before and after EBT and the presence of adverse events such as hypoglycaemia, apnoea, cardiac arrest, and death immediately after EBT). We reported results as means difference (MD) with 95% confidence intervals (CI) for continuous outcomes and risk ratio (RR) and risk differences (RD) and 95% CIs for dichotomous outcomes. We assessed quality using the Cochrane 'Risk of bias' assessment tool and the GRADE system.

Main results

We found only one quasi-randomised trial with 30 participants that met our inclusion criteria. In the small trial, total and ionised serum calcium levels were measured immediately before and immediately after EBT. All the participants were included in the final analysis and all the important outcomes were reported.

Primary outcomes

There was one death in each group (RR 1.00, 95% CI 0.07 to 14.55; RD 0.00, 95% CI -0.18 to 0.18; participants = 30; studies = 1). The study did not report the presence of cardiac arrhythmias within one week of EBT and the number of infants with serum calcium levels (total less than 8 mg/dL (2 mmol/L) or ionised less than 4.4 mg/dL (1.1 mmol/L)).

Pair-wise comparison of EBT with intravenous 10% calcium gluconate versus EBT without intravenous calcium (change from baseline) showed mean total serum calcium was raised in the intervention group compared to the control group (MD -0.46, 95% CI -0.81 to -0.11; participants = 30; studies = 1). Very low-quality evidence also indicated an increase in the levels of mean ionised serum calcium in the intervention group compared to the control group (MD -0.22, 95% CI -0.33 to -0.11; participants = 30; studies = 1).

Secondary outcomes

Adverse reactions to intravenous calcium therapy included cardiac arrest in one neonate in the intervention arm (RR 3.00, 95% CI 0.13 to 68.26; RD 0.07, 95% CI -0.10 to 0.23; participants = 30; studies = 1). There was apnoea and hypoglycaemia (RR 1.00, 95% CI 0.07 to 14.55; RD 0.00, 95% CI -0.18 to 0.18; participants = 30; studies = 1) in the two neonates who died. Data were not available for other major secondary outcomes such as the number of infants with reduced serum magnesium, reduced parathormone, increased calcitonin, presence of seizures, carpopedal spasm, jitteriness and prolonged QTc interval on electrocardiography within one week of EBT.

Authors' conclusions

Very low-quality data from one quasi-randomised controlled trial suggested that the mean serum total and ionised calcium increased in the study group but decreased in the control group immediately after EBT. However, the mean values of total and ionised calcium in both arms of studies remained within international reference ranges. Unfortunately, data were not available to assess the trend of total and ionised serum calcium to the end of the first week after EBT. Therefore, due to the very low quality of evidence available, it is difficult to support or reject the continual use of prophylactic intravenous calcium in newborn infants receiving EBT. Researchers are encouraged to conduct more robustly designed trials with larger numbers of participants, and particularly, addressing the pattern of differences based on gestational age of participants, type of anticoagulant used, and the volume of blood used.

PLAIN LANGUAGE SUMMARY

Use of calcium during exchange blood transfusion for newborn infants

Review question: does the administration of calcium during exchange blood transfusion (EBT) reduce the risk of low blood calcium and risk of death from low blood calcium levels among neonates receiving exchange blood transfusion?

Background: EBT is a type of massive blood transfusion (where blood is taken from a healthy person and infused into the bloodstream of an ill person) which predisposes to low blood calcium as a result of the bonding (chelating) effect of anticlotting chemicals used to preserve donor's blood. Low blood calcium can cause abnormal functions of muscles (including the heart) and nerves. In this review, we investigated the benefits of administered calcium on blood calcium levels and the safety of calcium administration to newborn infants receiving EBT.

We searched medical databases for clinical trials that administered calcium or no calcium to newborns aged from birth to 28 days receiving EBT and monitored a range of symptoms including death and heart problems.

Study characteristics: we identified only one poorly designed study for inclusion.

Results: we found that giving calcium to newborn infants raised blood calcium levels immediately after EBT while blood calcium was reduced among newborn infants who did not receive calcium during EBT. However, despite the observed trends in the values of blood calcium in both groups of the study, the average values of blood calcium in both groups remained within normal limits. In addition, the information available for this review was limited as the effects of giving or not giving calcium during EBT was not studied beyond the time of EBT.

Conclusion: based on the findings in this review, there is no good-quality evidence to support or reject continual use of calcium during EBT. We are unable to make conclusions, as the evidence that we found is limited and of very low quality and could change if more results from larger and better-designed studies become available.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Pair-wise comparison of exchange blood transfusion (EBT) plus 10% calcium gluconate intravenously versus EBT alone (change from baseline) for exchange blood transfusion in the newborn

Pair-wise comparison of EBT plus 10% calcium gluconate intravenously versus EBT alone (change from baseline) for EBT in the newborn

Patient or population: neonates receiving EBT

Settings:

Intervention: EBT + 10% calcium gluconate IV versus EBT alone (change from baseline)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	EBT	EBT + 10% calcium gluconate IV				
All-cause death Number of events	Study population		See comment	30 (1 study)	⊕⊕⊕⊕ Low ^a	Risks were calculated from pooled risk differences.
	67 per 1000	67 per 1000 (-113 to 247)				
	Moderate					
	67 per 1000	67 per 1000 (-114 to 248)				
Mean total serum calcium levels Mean difference	-	The mean total serum calcium levels in the intervention group was 0.46 lower (0.81 to 0.11 lower)	-	30 (1 study)	⊕⊕⊕⊕ Very low ^{b,c,d}	-
Mean ionised serum calcium levels Mean ionised serum calcium	-	The mean ionised serum calcium levels in the intervention group was 0.22 lower (0.33 to 0.11 lower)	-	30 (1 study)	⊕⊕⊕⊕ Very low ^{b,c,d}	-
Adverse reaction: cardiac arrest Number of events	Study population		See comment	30 (1 study)	⊕⊕⊕⊕ Very low ^{b,c,d}	Risks were calculated from pooled risk differences.
	0 per 1000	0 per 1000 (0 to 0)				

	Moderate					
	0 per 1000	0 per 1000 (0 to 0)				
Adverse reaction: ap- noea and hypoglycaemia	Study population		See comment	30 (1 study)	⊕⊕⊕⊕ Very low ^{b,c,d}	Risks were cal- culated from pooled risk differ- ences.
Number of events	67 per 1000	67 per 1000 (-113 to 247)				
	Moderate					
	67 per 1000	67 per 1000 (-114 to 248)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **EBT:** exchange blood transfusion; **IV:** intravenous; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aQuasi-randomised controlled study with no blinding; we are very uncertain if death was due to the effect of intervention or EBT.

^bQuasi-randomised controlled study with no blinding; we are very uncertain about the estimate of effect.

^cOne small study with very few participants.

^dQuasi-randomised control trial, baseline characteristics not reported and no information on the length of follow-up.

BACKGROUND

Exchange blood transfusions (EBT) have been reported as accounting for close to two-thirds of blood transfusions among newborns in low- and middle-income countries (Pam 2004; Ogunlesi 2011). On the contrary, centres in high-income countries rarely employ EBT in the care of newborn infants (MacLennan 2001; Flaherman 2012). This difference is due to the varying pattern of indications for EBT (such as haemolytic diseases and other causes of hyperbilirubinaemia (increased levels of bilirubin in the blood) in the newborn infants) in low- and middle-income countries compared to high-income countries.

Description of the condition

EBT is a form of whole blood transfusion in which the total blood volume is replaced within a period of 24 hours. In perinatal and neonatal medicine, EBT is most often used for rapid removal of toxins (such as bilirubin and sensitised red cells), or to replace red blood cells. Two types of EBT are commonly used in newborns; single-volume or double-volume exchange transfusion. Single-volume EBT implies transfusion with 80 mL/kg to 85 mL/kg of blood, which is the estimated total blood volume of the infant, whereas double-volume EBT implies transfusion with double the estimated total blood volume of an infant (160 mL/kg to 170 mL/kg) (Maisels 2001). Traditionally, double-volume EBT is used in the management of severe hyperbilirubinaemia, while single-volume EBT is commonly used in the management of severe neonatal anaemia, especially within the first week of life. Double-volume EBT is used in infants with severe hyperbilirubinaemia arising from haemolytic (blood) diseases such as blood group incompatibilities (particularly ABO and Rhesus), enzymopathies (such as glucose-6-phosphate dehydrogenase deficiency), and membranopathies (causing red blood cell anomalies such as erythrocytosis and elliptocytosis). Other indications include septicaemia, prematurity, cephalohematoma or subgaleal haematoma (collections of blood in the scalp), disseminated intravascular coagulation (clotting anomaly), and metabolic derangements such as intractable hypoglycaemia (low blood sugar levels).

Description of the intervention

Fresh whole blood, usually preserved with acid citrate dextrose or citrate phosphate dextrose, is used for EBT. The calculated volume of blood is administered in small aliquots of 5 mL to 10 mL, depending on the weight of the infant, using a three-way valve. The valve is connected to an umbilical venous catheter through which the transfusion is performed over about two hours. When done effectively, the double-volume procedure replaces between 85% and 90% of the red cells in circulation, and reduces the serum bilirubin level to about 60% of the pre-EBT level, while the single-volume procedure raises the haematocrit (level of red blood cells) of the infant close to that of the blood used for the procedure (Maisels 2001). Complications during EBT may arise from the process of umbilical catheterisation, the biochemical properties of the anticoagulant used, and the presence of microbes in the blood.

EBT-related morbidities include hypocalcaemia (low blood calcium), hypothermia (low body temperature), hypoglycaemia, metabolic acidosis (overproduction of acid), hyperkalaemia (high blood potassium), thrombocytopenia (low platelet concentration), cardiac arrhythmias (irregularities in heart beats), air embolism, apnoea (cessation of breathing), septicaemia (infection of the

blood), omphalitis (infections of the umbilical stump), necrotising enterocolitis (tissue death in the bowel), and intestinal perforation (Patra 2004; Sanpavat 2005; Gharehbaghi 2010; Hosseinpour Sakha 2010).

Hypocalcaemia (defined as serum total calcium less than 8 mg/dL (2 mmol/L) or serum ionised calcium less than 4.4 mg/dL (1.1 mmol/L)) is routinely prevented with calcium administration during or immediately after EBT (Nelson 1989; Maisels 2001). However, studies have shown that not all newborn infants with EBT-related hypocalcaemia get calcium treatment (Steiner 2007). Hypocalcaemia may be asymptomatic, but some of the common manifestations include jitteriness, abnormal cry, lethargy, irritability, apnoea, hypotonia (low muscle tone), carpopedal spasm (affecting hands and feet), or seizures (Maisels 2001). These clinical features do not reflect the severity of calcium deficiency, and may occur in any combination. Evidence of a prolonged QTc interval on electrocardiography is suggestive of severe hypocalcaemia requiring treatment. The use of clinical assessment for hypocalcaemia may be justifiable in low- and middle-income countries where laboratory facilities required for the detection of hypocalcaemia may not be available.

This intervention may be administered in pulses during the procedure, or as a slow bolus (dose) immediately after the procedure.

As a result of the risk of significant morbidity and mortality associated with hypocalcaemia, some practitioners - and even standard textbooks of neonatal medicine - suggest routine prophylactic administration of calcium to infants undergoing EBT as described above. Although, some practitioners still advocate routine prophylactic calcium administration for EBT, most current guidelines on transfusion practices are silent on the need for routine calcium administration to infants requiring EBT or stipulate that routine administration of calcium is not recommended (NICE 2010). It has yet to be confirmed that this practice is necessary, safe, and effective.

How the intervention might work

Hypocalcaemia that occurs during EBT is thought to arise from the chelating (metal binding) effects of citrate commonly used as an anticoagulant in transfused blood. Serum calcium levels have been shown to fall significantly during EBT without accompanying clinical manifestations, and to rise transiently to hypercalcaemic (high calcium level) ranges following calcium administration (Nelson 1989; Lo 1990). The two extremes of this fluctuation pose great risk of cardiac arrhythmias to the infant undergoing EBT. However, there have been suggestions that changes in ionised serum calcium level during EBT are not remarkable (Kreuger 1975; Jasso-Gutierrez 1982). Furthermore, serum calcium levels have been reported to normalise within 24 hours of EBT, even without calcium therapy (Nelson 1989).

The interaction between the chelating agent and serum calcium is complex. When blood containing citrate is administered, the citrate binds calcium and forms unionised calcium complexes. Citrate causes a fall in ionised serum calcium levels resulting in a compensatory stimulation of parathormone secretion and mobilisation of calcium and phosphorus in order to normalise the serum calcium level. However, use of heparin as an anticoagulant for blood preserves the serum ionised calcium levels, in addition

to those of albumin and parathyroid hormone, during EBT (Milner 1975). As citrate is more commonly used as an anticoagulant than heparin, newborn infants receiving EBT are expected to develop hypocalcaemia. Therefore, newborn infants receiving EBT with citrated blood should benefit from routinely given prophylactic intravenous calcium to prevent EBT-related hypocalcaemia.

Potential adverse effects

The adverse effects of intravenous calcium include vomiting, constipation, rapid vasodilation with hypotension (widening of blood vessels causing low blood pressure), bradycardia (slow heart rate), cardiac dysrhythmias (irregular heartbeat), and possibly cardiac arrest in severe cases. It also causes intense irritation at the site of administration and ultimately, tissue necrosis if extravasation (leakage from the vein) occurs.

Why it is important to do this review

Infants undergoing EBT may develop extremely low serum levels of total and ionised calcium. Some infants undergoing EBT may develop hypocalcaemia and require treatment during EBT, while others may not require treatment with calcium (Steiner 2007). Fluctuations in serum calcium levels may cause dangerously high serum calcium levels with the risk of cardiac toxicity.

It is important to know the extent to which hypocalcaemia, which requires treatment, occurs during EBT, and if it is necessary and safe to administer prophylactic intravenous calcium routinely to infants requiring EBT.

OBJECTIVES

To determine whether the use of prophylactic calcium reduces the risk of hypocalcaemia-related morbidities and death among newborn infants receiving EBT.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials and quasi-randomised controlled trials (individually or cluster-randomised) that compared the outcome of newborn infants undergoing EBT who received or did not receive prophylactic calcium.

Types of participants

Newborn infants aged from birth to 28 days who required EBT (single- or double-volume) for any reason and irrespective of postmenstrual age (whether or not the infant was premature).

Types of interventions

We considered for inclusion infants who received prophylactic intravenous calcium irrespective of the dose and type of calcium salt administered and the time of calcium administration (during or within one hour of EBT). The control arm included infants who did not receive intravenous calcium or received placebo.

Types of outcome measures

Primary outcomes

1. All-cause death until discharge.

2. Presence of cardiac dysrhythmias within one week of EBT.
3. Number of infants with total serum calcium levels less than 8 mg/dL (2 mmol/L) or ionised calcium levels less than 4.4 mg/dL (1.1 mmol/L) within one week of EBT.

Secondary outcomes

1. Number of infants with serum magnesium under 1.5 mg/dL within one week of EBT.
2. Number of infants with serum parathormone under 10 pg/mL within one week of EBT.
3. Number of infants with serum calcitonin over 10 pg/mL within one week of EBT.
4. Duration of hospitalisation (in days).
5. Incidence of partial or generalised seizures within one week of EBT (clinically diagnosed as tonic extension of limbs or clonic, jerky movements of the limbs, or diagnosed by electroencephalography).
6. Incidence of carpopedal spasms within one week of EBT (clinically diagnosed as sustained contraction of the muscles of the extremities).
7. Incidence of jitteriness within one week of EBT (clinically diagnosed as brief myoclonic twitching of the muscles of the extremities occurring in clusters).
8. Incidence of prolonged QTc interval on electrocardiography within one week of EBT.
9. Adverse reactions to calcium therapy within one week of EBT (skin necrosis, vomiting, constipation, hypotension, apnoea, cardiac arrest) occurring singly or in combination.
 - a. Skin necrosis defined as an obvious discontinuity in the skin layer at the site of calcium administration.
 - b. Vomiting defined as a reflex act of expelling the gastric contents.
 - c. Constipation defined as a frequency of bowel opening that was less than three times per week.
 - d. Hypotension defined as mean arterial pressure less than 30 mmHg.
 - e. Apnoea defined as cessation of breathing for more than 20 seconds associated with cyanosis (blue tinge to skin) and bradycardia.
 - f. Cardiac arrest defined as a sudden cessation of cardiac output and effective circulation.

Outcomes included post hoc:

1. Mean total serum calcium levels
2. Mean ionised serum calcium levels

Search methods for identification of studies

Electronic searches

We used the criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group (see [the Cochrane Neonatal Group search strategy for specialized register](#)).

We conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 5) in the Cochrane Library; MEDLINE via PubMed (1966 to 29 June 2016); Embase(1980 to 29 June 2016); and CINAHL (1982 to 29 June 2016) using the following search terms: (transfusion OR exchange

transfusion OR exchange blood transfusion OR blood transfusion) AND (calcium)), plus database-specific limiters for RCTs and neonates (see [Appendix 1](#) for the full search strategies for each database). We applied no language restrictions.

We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization International Trials Registry and Platform www.who.int/ictrp/search/en/, and the [ISRCTN Registry](#)).

Searching other resources

We handsearched journals; published abstracts; and proceedings of major conferences such as the International Neonatology Conference, conferences of the Royal College of Paediatrics and Child Health, and the American Academy of Pediatrics. We searched the reference lists of articles obtained. We searched the Web of Science for relevant citations in journal databases and in the conference proceedings citation index.

Data collection and analysis

Selection of studies

Two review authors (TAO and FEAL) independently assessed the eligibility of trials identified through searching for inclusion in the review. We retrieved full reports of the potentially relevant trials, and independently determined if they met the inclusion criteria using a pretested eligibility form. We listed all excluded studies, along with the reasons for excluding them (see Characteristics of excluded studies table). We would have ensured that trials with multiple publications were included only once, and where the multiple publications included different but relevant outcomes, we would have included all the publications in the review. We would have grouped multiple publications so that each study, rather than each publication, was the unit of analysis. We resolved any disagreements through discussion.

Data extraction and management

Two review authors (TAO and OO) independently extracted data from the eligible study using the pretested data extraction form. One review author (OO) entered the data into Review Manager 5 ([RevMan 2014](#)), while the second review author (TAO) cross-checked the data for completeness and accuracy. We extracted the number of participants randomised and the number analysed in each group for each reported outcome.

For continuous outcomes, we extracted the number of participants for each treatment arm, arithmetic means and standard deviations (SDs). We extracted data on reported adverse events as dichotomous outcomes.

We attempted to contact the trial authors where the relevant details were not recorded or were unclear.

Assessment of risk of bias in included studies

Two review authors (TAO and OO) independently assessed the risk of bias for the included study using the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We assessed the risk of bias in relation to random sequence generation, allocation concealment, blinding, handling of incomplete outcome data, selective outcome reporting, and

other bias, giving ratings of 'low risk of bias', 'high risk of bias,' and 'unclear risk of bias' for each domain.

Randomisation sequence generation

If the included study was an RCT, we would have described the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups.

The assessment would have been graded as follows:

1. low risk of bias (truly random processes such as the use of a table of random numbers or computer-generated random numbers);
2. high risk of bias (non-random processes such as use of hospital record numbers or dates of birth);
3. unclear risk of bias.

Allocation concealment

If the included study was an RCT, we would have described the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been predicted before or changed after recruitment. The methods would have been graded as follows:

1. low risk of bias (use of central allocation which may be web-based or pharmacy-controlled; sequentially numbered, opaque, sealed envelopes);
2. high risk of bias (unsealed, non-opaque assignment envelopes or not sequentially numbered, allocation by alternation or rotation);
3. unclear risk of bias (method of concealment not described in significant detail to allow a definite judgement).

Blinding of participants and researchers

For an RCT, we would have described the methods used to blind study participants and researchers from knowledge of which intervention a participant received. Blinded studies, or studies in which non-blinding was not likely to have affected the results significantly, would have been classified as having a low risk of bias. Non-blinded studies would have been classified as having a high risk of bias.

Incomplete outcome data

If the included study was an RCT, we would have described the methods used to account for incomplete outcome data, with regards to the amount, nature, and handling of incomplete outcome data. In instances where outcome data were not completely reported, we would have attempted to obtain missing data from the study authors. We would have extracted and reported on data on attrition and exclusions as well as the numbers involved (compared with total randomised), reasons for attrition/exclusion where reported or obtained from investigators, and any re-inclusions in analyses performed by review authors if such data were available. Unbiased follow-up would have been considered to have happened when at least 80% of the participants were followed up. Based upon this, we would have judged whether the researchers dealt with incomplete data.

Selective outcome reporting

We attempted to assess the possibility of selective outcome reporting by the investigators in the included trial. We could not

examine the study protocols as the authors of the study could not be reached; based upon this, we would have judged whether reports of the study were free from suggestion of selective outcome reporting.

Other bias

We explored other sources of bias, particularly the sources of funding of the included study and other study peculiarities.

Measures of treatment effect

The type of treatment effect used in describing each of the listed outcomes depended on the type of data extracted for the specific outcome.

Continuous data

We reported the mean difference (MD) for continuous outcomes. We presented all measures of effect with their corresponding 95% confidence intervals (CI). We extracted postintervention values and utilised the mean and SD for the analysis.

Binary data

We analysed binary outcomes by calculating the risk ratio (RR), with 95% CIs.

Unit of analysis issues

Not applicable.

Dealing with missing data

We attempted to contact the original authors of included study to request unreported data (e.g. baseline characteristics and number of loss to follow-up) but received no response. Therefore, we performed the analysis using the available data.

Assessment of heterogeneity

It was not feasible to assess for heterogeneity because we included only one quasi-randomised study. However, we would have identified statistical heterogeneity in each of the included study using the χ^2 test and I^2 statistic. We would also have used visual assessment of forest plots to identify obvious overlaps and outliers. We would have agreed on how to handle heterogeneity depending on the degree indicated by the I^2 statistic. As an approximate guide, I^2 values of less than 25% would have been treated as indicating no heterogeneity, values of 25% to 49% as indicative of low heterogeneity, values of 50% to 74% as indicative of moderate heterogeneity and values of 75% or above as indicative of high heterogeneity (Higgins 2003). When heterogeneity was significant, outliers would have been investigated and we would have attempted to explain the heterogeneity. When heterogeneity was significant and could not be explained, we would have used subgroup analyses and sensitivity analysis to resolve the discrepancy.

Assessment of reporting biases

We examined the included study for within-study selective outcome reporting. We did not have access to the study protocol, therefore, we could not detect or investigate selective reporting.

Data synthesis

We did not perform a meta-analysis because only one study was included in this review.

Quality of evidence

We used the GRADE approach, as outlined in the *GRADE handbook for grading quality of evidence and strength of recommendations* (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: all-cause mortality, mean total serum calcium levels (total less than 8 mg/dL (2 mmol/L); ionised calcium less than 4.4 mg/dL (1.1 mmol/L)) within one week of EBT and adverse reactions to intervention (apnoea, hypoglycaemia, and cardiac arrest).

Two review authors (TAO and OO) independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from randomised controlled trials as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used the GRADEpro Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades.

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: 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.
3. Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analysis.

1. Preterm (less than 37 weeks' gestation) versus term (37 weeks' gestation or greater).
2. Type of anticoagulant in the blood transfused (citrate versus heparin).
3. Volume of blood used (single-volume EBT versus double-volume EBT).
4. Timing of administration of calcium (administration during EBT versus administration immediately after EBT).

Sensitivity analysis

We planned to agree on eligibility criteria (age range of participants, comparator group, range of doses of intervention, and the range of time points to be evaluated in the analysis), type of data to be analysed (dichotomous or continuous), and the method of data analysis to be adopted. We planned to conduct sensitivity analyses if we encountered disparities with respect to any of the eligibility criteria earlier agreed upon. We planned to input missing data with replacement values and assume all the participants with missing

data had a poor outcome. We would have contacted the Cochrane Neonatal Group's statistician when this decision was taken. We planned to perform sensitivity analysis to assess how sensitive the findings were if we assumed that all those participants with missing data had a poor outcome. We planned to use a 'Summary of Findings' table to report the findings of sensitivity analyses.

RESULTS

Description of studies

Results of the search

Our search yielded 383 studies after removing duplicates ([Figure 1](#)), and 382 of these were clearly irrelevant. The one potentially relevant study involved 30 neonates and met our inclusion criteria ([Locham 2002](#)).

Figure 1. Study flow diagram.

Included studies

One study with high risk of bias conducted on 30 healthy appropriate for gestational age babies with neonatal jaundice, requiring EBT. Participants were allocated alternatively to two groups; study group and control group. There was no specific randomisation or blinding. Fifteen participants in study group received 1 mL of 10% calcium gluconate intravenously for every 100 mL of citrate phosphate dextrose blood exchanged. The control group received only EBT.

Excluded studies

We excluded no studies.

Risk of bias in included studies

We included one small study with an overall high risk of bias as there was no specific randomisation or blinding done ([Locham 2002](#)). Participants were allocated alternatively to two groups; study group and control group ([Figure 2](#); [Figure 3](#)).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

The study was at high risk of selection bias as allocation was not concealed.

Blinding

The study was at high risk of performance bias and detection bias as there was no blinding.

Incomplete outcome data

The study was at low risk of attrition bias as all participants were included in the final analysis.

Selective reporting

The study was at unclear risk of reporting bias as, since we could not access the study protocol, it was unclear if there was selective reporting. However, all important outcomes were reported.

Other potential sources of bias

The study was at unclear risk of other bias as the study did not report baseline characteristics of participants and length of follow-up.

Effects of interventions

See: [Summary of findings for the main comparison](#) Pair-wise comparison of exchange blood transfusion (EBT) plus 10% calcium gluconate intravenously versus EBT alone (change from baseline) for exchange blood transfusion in the newborn

We found one study comparing EBT plus calcium with EBT alone in 30 healthy neonates ([Locham 2002](#)).

Primary outcomes

All-cause death

There was no difference in risk of death until discharge as there was one death in each group (RR 1.00, 95% CI 0.07 to 14.55; RD 0.00, 95% CI -0.18 to 0.18; participants = 30; studies = 1) ([Locham 2002](#)).

Presence of cardiac dysrhythmias

The study did not report presence of cardiac dysrhythmias within one week of EBT.

Number of infants with abnormally low serum calcium level

The study did not report the number of infants with abnormally low serum calcium level (total less than 8 mg/dL (2 mmol/L) or ionised less than 4.4 mg/dL (1.1 mmol/L)) within one week of EBT.

However, pair-wise comparison of EBT plus 10% calcium gluconate intravenously versus EBT alone (change from baseline) showed that mean total serum calcium was raised in the study group compared to the control group (MD -0.46, 95% CI -0.81 to -0.11; participants = 30; studies = 1).

There was a similar effect on mean ionised serum calcium levels (MD -0.22, 95% CI -0.33 to -0.11; participants = 30; studies = 1).

Secondary outcomes

Number of infants with serum magnesium under 1.5 mg/dL

The study did not report the number of infants with low serum magnesium level (under 1.5 mg/dL) within one week of EBT.

Number of infants with serum parathormone under 10 pg/mL

The study did not report the number of infants with low serum parathormone level (under 10 pg/mL) within one week of EBT.

Number of infants with serum calcitonin over 10 pg/mL

The study did not report the number of infants with high calcitonin level (over 10 pg/mL) within one week of EBT.

Duration of hospitalisation

The study did not report duration of hospitalisation.

Incidence of partial or generalised seizures

The study did not report the incidence of partial or generalised seizures within one week of EBT.

Incidence of carpopedal spasms

The study did not report the incidence of carpopedal spasms within one week of EBT.

Incidence of jitteriness

The study did not report the incidence of jitteriness within one week of EBT.

Incidence of prolonged QTc interval

The study did not report the incidence of prolonged QTc interval on electrocardiography within one week of EBT.

Adverse reactions

The two neonates that died experienced adverse reactions (apnoea and hypoglycaemia) (one in each group) (RR 1.00, 95% CI 0.07 to 14.55; RD 0.00, 95% CI -0.18 to 0.18; participants = 30; studies = 1) and one neonate in the study group had a cardiac arrest (RR 3.00, 95% CI 0.13 to 68.26; RD 0.07, 95% CI -0.10 to 0.23; participants = 30; studies = 1).

Subgroup analysis

Data were available for one small study, therefore investigation of heterogeneity was not feasible.

Sensitivity analysis

We did not perform sensitivity analysis because we only included one small quasi-randomised study.

DISCUSSION

Summary of main results

The main objective of this review was to determine the role of prophylactic intravenous calcium therapy in the amelioration of hypocalcaemia-related morbidities and mortality among neonates who received EBT. Basic science suggests that massive blood transfusions are associated with the risk of hypocalcaemia following the chelating properties of commonly used anticoagulants. This fact informed the age-long practice of prophylactic administration of intravenous calcium to neonates during EBT. However, the few studies reporting rarity of hypocalcaemia-related morbidities among neonates who had EBT raised doubts about the usefulness of the practice of prophylactic administration of intravenous calcium. This review was designed to generate evidence-based conclusions on the occurrence of hypocalcaemia and the need for prophylactic intravenous calcium therapy during EBT.

Our search identified only one small study of high risk of bias conducted in a low-income country that met the inclusion criteria. The study measured total and ionised serum calcium levels in the neonates immediately before and immediately after EBT. The post-EBT total and ionised calcium levels in the control group increased while the corresponding levels in the intervention group decreased. The increase in the post-exchange blood transfusion mean serum calcium levels in the intervention group suggests a protective role

of the intervention against exchange blood transfusion-related hypocalcaemia. On the other hand, the decrease in the post-exchange blood transfusion mean serum calcium levels in the control group plausibly suggests the likelihood of a decrease in total and ionised serum calcium levels in the absence of the intervention. However, the reported mean total and ionised serum calcium in both arms of study, prior to and after the procedure, were within the internationally known reference values for neonates. Although this queries the usefulness of the intervention since the mean values did not reflect hypocalcaemia (but it is important to add that the total and ionised serum calcium values for individual participants were not reported hence) it is uncertain if none of the participants was truly hypocalcaemic. Unfortunately, the only trial available for this review did not reveal longitudinally collected data on the trends of total and ionised serum calcium up to the end of the first week as stipulated in the objectives of the index review. Therefore, it is impossible to infer with emphasis, whether the mean total and ionised serum calcium levels changed or clinical manifestations of hypocalcaemia evolved over time or not.

One participant in each of the two arms of the study had apnoea, hypoglycaemia, and eventually died whereas an additional participant in the study group had a cardiac arrest. Although, the details of the events leading to the observed complications were not available, hypoglycaemia and apnoea are known complications of both severe hyperbilirubinaemia, which is an indication for EBT, and the transfusion procedure itself. Within the limits of information available for this review, it is difficult to clearly attribute the observed hypoglycaemia and apnoea to either the disease or the procedure. Cardiac arrest may also arise during EBT from hypothermia, catheter-related cardiac arrhythmias, or from transient hypercalcaemia following intravenous calcium administration. Unfortunately, details were sparse in the text reporting the trial and the authors of the trial could not be reached to provide additional information on the likely cause and outcome of the infant in the study group who had a cardiac arrest.

Overall completeness and applicability of evidence

The lack of follow-up data made it impossible to ascertain long-term needs or effects of the prophylactic administration of intravenous calcium among participants. The only included trial was a small study with high risk of bias that evaluated total and ionised serum calcium without reporting clinical manifestations of possible derangement either immediately after EBT or to the end of the first week as stated in the objectives. Therefore, it is difficult to make an evidence-based pronouncement on the need for, and the effects of, prophylactic intravenous calcium administration for EBT in the newborn. In addition, due to the shallow scope of the available trial, we are unable to provide answers to any of the questions raised under planned subgroup analyses.

Quality of the evidence

This review analysed data from a quasi-randomised trial with high risk of bias accrued from non-concealment of allocation and non-blinding although all the participants were available for analysis at the defined exit point of the trial. In addition, only immediate post-EBT total and ionised serum calcium levels and occurrence of adverse events were the outcome variables available for analysis. These shortcomings limit the scope of conclusions which can be drawn on the need for, and possible effects of, the intervention, which are key issues that needed to be

addressed among clinicians. This review has highlighted the dearth of evidence-based information on this critical clinical issue. In the assessment of the quality of evidence using the GRADE system, the mean total and ionised calcium levels, and the occurrence of adverse events (apnoea, hypoglycaemia, and cardiac arrest, as well as death) were rated very low-quality (Guyatt 2011).

Potential biases in the review process

The assessment of this review for bias is limited by the fact that it is based on only one quasi-randomised trial. In addition, we were unable to search the Science Citation Index and Latin American Caribbean Health Sciences Literature (LILACS) databases.

Agreements and disagreements with other studies or reviews

We are not aware of any previous systematic review focused on this important clinical issue. Therefore, we are unable to make pronouncements on the likelihood of agreement or disagreement between the findings in this review and any other similar studies.

AUTHORS' CONCLUSIONS

Implications for practice

Prophylactic administration of intravenous calcium prevents the reduction in the total and ionised serum calcium in neonates receiving exchange blood transfusion (EBT) immediately after the procedure. This has the potential of preventing clinically significant EBT-related hypocalcaemia but it is uncertain if this likely benefit is of any clinical significance or if the perceived benefit would be retained and justifiable hours and days after the procedure. Therefore, with the high risk of bias in the available trial and the accrued very low quality of evidence in the index review, there is, at present, not enough evidence to support or reject prophylactic administration of intravenous calcium to neonates receiving EBT.

Implications for research

This review shows the very low-quality evidence on potential benefits/harms of prophylactic administration of intravenous calcium to neonates receiving EBT. This observation shows a significant gap in evidence-based knowledge and lack of reliable data to inform clinical practice for a common clinical intervention in perinatal and neonatal medicine, particularly in the parts of the world where the procedure is still frequently carried out. Well-designed and appropriately powered randomised controlled trials are required to investigate the clinical utility or otherwise of prophylactic administration of intravenous calcium to neonates receiving EBT to prevent hypocalcaemia-related morbidities and mortality. These studies should address the trend of total and ionised serum calcium during and after EBT, the hormonal changes which accompany the procedure, as well as the pattern of cardiac response when calcium is administered to neonates during the procedure. In addition, it is important to build into the studies the likely effects of other morbidities associated with EBT and how these effects may vary with or without calcium administration. Specific attention should be paid to the maturity of the neonates as determined by the estimated gestational age, the type of anticoagulant used to preserve donor blood, and the volume of blood transfused. While double-volume EBT is no longer frequently performed in the technologically advanced parts of the world due to more efficient management of neonatal hyperbilirubinaemia, single-volume EBT is still widely performed in the management of severe neonatal anaemia the world over. Therefore, these studies should aim at findings from multicentre research across low- to high-income countries as the application of the findings would, most likely, be global.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Locham 2002

Methods	Quasi-randomised controlled trial.
Participants	30 healthy appropriate for gestational age babies with neonatal jaundice requiring EBT.
Interventions	Intervention: 1 mL of 10% calcium gluconate IV for every 100 mL of citrate phosphate dextrose blood exchanged + EBT (n = 15). Control: EBT alone (n = 15).
Outcomes	Total and ionised serum calcium, total and differential serum bilirubin after the completion of EBT.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were allocated alternatively to 2 groups; intervention and control.
Allocation concealment (selection bias)	High risk	Allocation not concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.
Selective reporting (reporting bias)	Unclear risk	Study protocol not available, unclear if there was selective reporting.
Other bias	Unclear risk	Baseline characteristics of participants not reported so unclear if report was skewed.

EBT: exchange blood transfusion; IV: intravenous; n: number of participants.

DATA AND ANALYSES

Comparison 1. Pair-wise comparison of exchange blood transfusion (EBT) plus 10% calcium gluconate intravenously versus EBT alone (change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause death	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
2 Mean total serum calcium levels	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.46 [-0.81, -0.11]
3 Mean ionised serum calcium levels	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.33, -0.11]
4 Adverse reactions	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Cardiac arrest	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
4.2 Apnoea, hypoglycaemia	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]

Analysis 1.1. Comparison 1 Pair-wise comparison of exchange blood transfusion (EBT) plus 10% calcium gluconate intravenously versus EBT alone (change from baseline), Outcome 1 All-cause death.

Analysis 1.2. Comparison 1 Pair-wise comparison of exchange blood transfusion (EBT) plus 10% calcium gluconate intravenously versus EBT alone (change from baseline), Outcome 2 Mean total serum calcium levels.

Analysis 1.3. Comparison 1 Pair-wise comparison of exchange blood transfusion (EBT) plus 10% calcium gluconate intravenously versus EBT alone (change from baseline), Outcome 3 Mean ionised serum calcium levels.

Analysis 1.4. Comparison 1 Pair-wise comparison of exchange blood transfusion (EBT) plus 10% calcium gluconate intravenously versus EBT alone (change from baseline), Outcome 4 Adverse reactions.

APPENDICES

Appendix 1. Standard search methodology

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomised [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

CONTRIBUTIONS OF AUTHORS

TAO: made substantial intellectual contributions to the protocol; initiated and designed the review.

FEAL: made substantial intellectual contributions to the protocol; contributed to the design of the review.

OO: performed data analysis.

All the authors contributed to data interpretation and drafting of the review.

DECLARATIONS OF INTEREST

TAO: nothing to declare.

FEAL: nothing to declare.

OO: nothing to declare.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We were unable to search the Science Citation Index and Latin American Caribbean Health Sciences Literature (LILACS) databases.

We added 'Other bias' to the 'Risk of bias' table, which encompasses difference between groups such as baseline characteristics, funding, etc.

Outcomes included post hoc: Mean total serum calcium levels; Mean ionised serum calcium levels.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Intravenous; Apnea [etiology]; Calcium [*administration & dosage] [adverse effects] [blood]; Exchange Transfusion, Whole Blood [*adverse effects]; Heart Arrest [etiology]; Hypocalcemia [etiology] [*prevention & control]; Hypoglycemia [etiology]

MeSH check words

Humans; Infant, Newborn