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Early volume expansion versus inotrope for prevention of morbidity and mortality in very preterm infants (Review)

Osborn DA, Evans NJ

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[Intervention Review]

Early volume expansion versus inotrope for prevention of morbidity and mortality in very preterm infants

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ABSTRACT

Background

Reduced perfusion of organs such as the brain, heart, kidneys and the gastrointestinal tract may lead to acute dysfunction and be associated with permanent injury. Various strategies have been used to provide cardiovascular support to preterm infants including inotropes, corticosteroids and volume expansion.

Objectives

To determine the effect of early volume expansion compared to inotrope in reducing morbidity and mortality in very preterm infants. Subgroup analysis was planned according to method of diagnosis of poor perfusion, postnatal age of treatment and type of volume expansion and inotrope used.

Search methods

Updated searches were performed of the Cochrane Central Register of Controlled Trials (Issue 3, 2008), MEDLINE (1996 - July 2008), EMBASE (1980 - July 2008), previous reviews including cross references, abstracts and conferences.

Selection criteria

All randomised trials that compared volume expansion to an inotrope in preterm infants born ≦ 32 weeks gestation or ≦ 1500 g in the first days after birth were included.

Data collection and analysis

Data were extracted independently by each author and analysed using the standard methods of the Cochrane Collaboration and its Neonatal Review Group using relative risk (RR), risk difference (RD) and weighted mean difference (WMD).

Main results

Two small studies comparing volume expansion (using albumin) with dopamine were included. Both studies were adequately randomised, unblinded studies of albumin vs. dopamine with no losses to follow-up and analysed by intention to treat. Data for clinical outcomes were available from one study in hypotensive preterm infants in the first day after birth. In this study, albumin had a higher failure rate for correcting hypotension dopamine (RR 5.23; 95% CI 1.33 to 20.55). As 49% of these infants had already been given volume, the question of which treatment should be given first was not answered. A second study compared albumin with dopamine in preterm infants with a normal mean blood pressure (BP) at a mean age of 32 hours. Dopamine produced a significant increase in mean BP when compared to infants who received albumin or no treatment, although the difference between the dopamine and albumin groups did not reach

significance. Albumin and dopamine produced similar increases in left ventricular output but no significant change in cerebral blood flow. No difference was found in mortality (RR 1.45; 95% CI 0.53 to 3.95) or morbidity including any P/IVH, chronic lung disease or retinopathy. There was a higher rate of grade 2 - 4 P/IVH of borderline statistical significance in infants who received albumin in one study (RR 1.47; 95% CI 0.96 to 2.25: RD 0.27, 95% CI 0.00 to 0.54). No data were available for neurodevelopmental outcomes.

Authors' conclusions

Dopamine was more successful than albumin at correcting low BP in hypotensive preterm infants, many of whom had already received volume. Neither intervention has been shown to be superior at improving blood flow or in improving mortality and morbidity in preterm infants. The trials do not allow any firm conclusions to be made as to whether or when volume or dopamine should be used in preterm infants.

PLAIN LANGUAGE SUMMARY

Early volume expansion versus inotrope for prevention of morbidity and mortality in very preterm infants

Not enough evidence to show the effect of early volume expansion in very preterm babies. Low blood pressure and blood flow are common in preterm babies and can cause brain injury, organ damage and developmental problems. Increasing the amount of fluid in the blood stream (volume expansion) using albumin or salt solutions may increase the blood pressure and flow of blood. Inotrope drugs such as dopamine are used to increase the heart rate and blood pressure. The review of trials compared early volume expansion with inotropes. The review found dopamine is more effective than albumin at correcting low blood pressure in preterm babies but neither improves outcomes for babies. More research is needed.

BACKGROUND

Reduced perfusion of organs such as the brain, heart, kidneys and the gastrointestinal tract may lead to acute dysfunction and be associated with permanent injury. Twenty percent of surviving babies born very premature have some degree of neurodevelopmental disability (Lorenz 1998). Peri/intraventricular haemorrhage (P/IVH) is a major risk factor for neurodevelopmental disability (Vohr 2000). Low systemic blood pressure (BP) and blood flow have both been linked to cerebral injury (Miall-Allen 1987; Goldstein 1995; Low 1993). Low upper body blood flow (Kluckow 2000; Osborn 2003; Miletin 2008) and low cerebral blood flow (Meek 1999) in the first day after birth are also associated with late P/IVH. In addition, low upper body blood flow on the first day of life (as measured by flow in the superior vena cava) is associated with a significant increase in mortality (Osborn 2003; Kluckow 2000), necrotising enterocolitis (Osborn 2007) and subsequent neurodevelopmental impairment (Hunt 2004; Osborn 2007) in infants born < 30 weeks' gestation.

Clinical features suggesting reduced perfusion include low BP, reduced cutaneous perfusion and metabolic acidosis. However, systemic arterial pressure has been shown to be poorly correlated with systemic blood flow (SBF) in preterm infants (Kluckow 1996; Kluckow 2000; Osborn 2004). In addition, clinical measures of hypovolaemia including systemic hypotension have been found to be poorly correlated to blood volume (Barr 1977; Bauer 1993).

Various therapeutic strategies have been used to provide cardiovascular support to preterm infants including inotropes, corticosteroids and volume expansion. Most strategies have targeted low BP using inotropes such as dopamine vs. dobutamine (Greenough 1993; Hentschel 1995; Klarr 1994; Roze 1993), dopamine vs. adrenaline (Pellicer 2005; Valverde 2006), corticosteroids (Gaissmaier 1999), and corticosteroids vs. dopamine (Bourchier 1997). Trials of dopamine vs. dobutamine in very preterm infants with systemic hypotension have not found a difference between these inotropes at preventing mortality and P/IVH. Dopamine was more effective than dobutamine at treating systemic hypotension in very preterm infants (Subhedar 2003). Despite an increase in systemic BP, dopamine was shown to reduce aortic blood flow in one study (Roze 1993). In another study in very preterm infants with low SBF, dobutamine produced little change in BP but a significantly greater increase in SBF than dopamine, despite dopamine resulting in a significantly greater increase in BP (Osborn 2002). However, there was no significant difference in long-term outcomes (Osborn 2007; Osborn 2007a). Strategies to correct systemic hypotension and hypovolaemia have also included volume expansion. Observational studies have found increases in cardiac output after albumin infusion in sick preterm infants (Pladys 1997) and a small increase in systemic BP in hypotensive preterm infants (Barr 1977; Bignall 1989). Short-term increases in SBF have also been reported after saline infusion in preterm infants with low SBF (Osborn 2002). Observational studies have also reported an increase in P/IVH (Goldberg 1980) and chronic lung disease (Van Marter 1990) in preterm infants receiving volume expansion. A systematic review of randomised controlled trials of albumin infusions in critically ill patients including those with hypovolaemia, burns and hypoalbuminaemia found a significantly increased mortality for those patients receiving albumin compared to control (Alderson 2004).

This review evaluates the evidence from randomised controlled trials regarding the use of early volume expansion compared to inotrope to prevent mortality and morbidity in very preterm infants. In view of the difficulties of identifying infants with poor perfusion and hypovolaemia, subgroup analyses were planned according to method of diagnosis of poor perfusion [unselected preterm infants, preterm infants with clinical indicators of poor perfusion (low BP, reduced cutaneous perfusion and metabolic acidosis) and infants with ultrasound Doppler detected low blood flow]. As there is evidence to suggest that late P/IVH is associated with systemic hypotension and low SBF on the first day of life (Miall-Allen 1987; Goldstein 1995; Kluckow 2000; Miletin 2008; Osborn 2003), subgroup analyses were planned with the hypothesis that trials that treated infants early (before 12 to 24 hours) were more likely to prevent P/IVH. As different volume expanders and inotropes have different effects, subgroup analyses were planned according to type of volume expansion (normal saline, fresh frozen plasma, albumin, plasma substitute or blood) and inotrope used.

OBJECTIVES

To determine the effect of early volume expansion compared to early inotrope use in reducing morbidity and mortality in very preterm infants. Subgroup analyses were planned according to method of diagnosis of poor perfusion [unselected preterm infants, preterm infants with clinical indicators of poor perfusion (eg. low BP, reduced cutaneous perfusion and metabolic acidosis) and infants with ultrasound Doppler detected low blood flow], postnatal age at treatment and type of volume expansion and inotrope used.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials that compare volume expansion with an inotrope.

Types of participants

Very preterm infants born ≦ 32 weeks' gestation or ≦ 1500g and enrolled and treated in the first 72 hours after birth. The mean or median age was taken as the criterion for inclusion. Eligible trials enrolled either unselected preterm infants (not selected on the basis of cardiovascular compromise), preterm infants with low BP or preterm infants with low blood flow. Trials enrolling only infants with suspected hypovolaemia due to acute blood loss (eg infants born with history of documented peripartum blood loss, tachycardia and pallor) were excluded.

Types of interventions

Volume expansion (including normal saline, fresh frozen plasma, plasma substitute or albumin) compared to inotrope infusion (including dopamine, dobutamine, epinephrine or isoprenaline).

Types of outcome measures

Primary outcome measures included any of the following:

1. Neonatal mortality and mortality to discharge
2. Peri/intraventricular haemorrhage (any or severe grades)
3. Periventricular leucomalacia

4. Neurodevelopmental disability (neurological abnormality including cerebral palsy, developmental delay or sensory impairment)

Secondary outcome measures included any of the following;

1. Backup use of volume or inotropes (in first 72 hours)
2. Failure to correct low SBF (eg Doppler ultrasound after volume expansion)
3. Failure to correct systemic hypotension (enrolment criteria used in trial)
4. Patent ductus arteriosus (PDA)
5. Renal impairment (creatinine ≧ 120 micromol/l, oliguria ≦ 0.5ml/kg/hour)
6. Airleak (any and gross including pneumothorax or pneumomediastinum)
7. Chronic lung disease (at 28 postnatal days or near term postmenstrual age)
8. Proven necrotising enterocolitis
9. Retinopathy of prematurity (any stage and severe stage 3 or greater)

Subgroup analyses were planned for the following identified subcategories:

1. Including only trials where volume expansion was given a) in the first day after birth, and b) in the first 12 hours after birth,
2. According to type of volume expansion used (normal saline, fresh frozen plasma, albumin or blood), and type of inotrope (dopamine, dobutamine. isoprenaline, adrenaline),
3. According to whether trials enrolled:

- Unselected preterm infants,
- Preterm infants with clinical indicators of poor perfusion (low BP, poor cutaneous perfusion or metabolic acidosis),
- Preterm infants with ultrasound Doppler diagnosed low blood flow,

All primary and secondary outcomes were to be included in subgroup analysis where available.

Search methods for identification of studies

An updated search was performed of Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library Issue 3, 2008), MEDLINE (1996 - July 2008), EMBASE (1980 - July 2008), previous reviews including cross references (all articles referenced), abstracts and conferences (Perinatal Society of Australia and New Zealand, and Pediatric Academic Societies and American Academy of Pediatrics meetings 2004 - 2008). The previously documented search strategy was expanded to include MeSH terms "[polygeline or albumins]" and text terms "[starch or albumin or albumen or gelofusine or plasma]"

This review updates a previous version (Osborn 2001). The previous update reported no new eligible reviews found up to January 2004. All updates used the standard search strategy of the Neonatal Review Group. The original review (Osborn 2001) included searches of the Oxford Database of Perinatal Trials. The January 2004 update included searches of CENTRAL (The Cochrane Library, Issue 1, 2004), MEDLINE (January 2004), previous reviews including cross references, abstracts and conferences (Perinatal Society of Australia and New Zealand, and Pediatric Academic Societies and American Academy of Pediatrics Meetings 1998 - 2003). The search of MEDLINE 1966 - January 2004 included MeSH searches using the following terms ("[colloids or plasma substitutes or sodium chloride or serum albumin or hypotension] and [dopamine or dobutamine or epinephrine or isoproterenol] and [infant-premature or newborn]") and text words were searched using the following terms ("[colloid or crystalloid or saline or volume or hypotension] and [dopamine or dobutamine or epinephrine or isoproterenol or inotrope or adrenaline or dopexamine or isoprenaline] and [infant-premature]"). No language restriction was used.

Data collection and analysis

Criteria and methods used to assess the methodological quality of the included trials: Standard methods of the Cochrane Collaboration and its Neonatal Review Group were used. The methodological quality of each trial was reviewed independently by the second author. Particular emphasis was placed on allocation concealment, blinding, completeness of follow-up and blinding of outcome assessment. Allocation concealment was ranked: Grade A: adequate; Grade B: uncertain; Grade C: clearly inadequate.

Methods used to collect data from the included trials: Each author extracted data separately, then compared and resolved differences. Additional data will be requested from authors of each trial for the next update.

Methods used to synthesise the data: Standard method of Neonatal Review Group with use of relative risk, risk difference and weighted mean difference where appropriate. The fixed effects model using RevMan 5.0 was used for meta-analysis.

Sensitivity analysis was planned on the basis of methodological quality.

RESULTS

Description of studies

See table 'Characteristics of included studies'. No new studies comparing use of volume expansion vs. an inotrope in very preterm infants were found.

Two studies met criteria for inclusion in this review (Gill 1993; Lundstrom 2000). One non-randomised study comparing an inotrope to volume was excluded (Kawczynski 1996). No additional eligible studies were found. One additional study found was excluded (Rennie 1989) as it was a non-randomised comparison of infants receiving dopamine and plasma.

Participants: Both eligible studies enrolled very preterm infants either < 1501 g (Gill 1993) or < 33 weeks (Lundstrom 2000). Infants in the study by Gill 1993 were hypotensive (mean BP < 10th percentile) infants < 24 hours age with an indwelling arterial line. They were given 20 ml/kg plasma protein fraction prior to enrolment if thought to be in shock (49% of infants). Infants in the study by Lundstrom 2000 were enrolled if the mean BP was in the normal range (29 - 40 mmHg) and they had not received volume or inotrope in the preceding three hours. The authors state that this group were considered to be above the presumed normal upper limit for hypotension but from previous work may still be at risk of low left ventricular output and cerebral blood flow. The mean age of

enrolment was 31.8 hours (range 5 - 224). The sample sizes were small with 39 infants in the study by Gill 1993 and 24 infants in the Lundstrom 2000 study. Lundstrom 2000 had a control group of 12 infants who received no treatment. The data for this group are not presented in this review but the statistical significance using ANOVA as reported in the paper is documented. The standard deviations for mean BP, left ventricular output and cerebral blood flow are calculated from the reported 95% confidence intervals.

Interventions: Gill 1993 compared albumin 4.5% 20 ml/kg over 20 minutes (repeated if the mean BP remained < 10th percentile) to dopamine 5 mcg/kg/min (increased every 30 minutes by 2.5 mcg/kg/min to maximum 10 mcg/kg/min if mean BP remained < 10th percentile). Lundstrom 2000 compared albumin 20% 15 ml/kg to dopamine 5 mcg/kg/min.

Outcomes: Gill 1993's primary outcome was correction of hypotension (mean BP > 10th percentile). Clinical data were available for P/IVH, duration of ventilation, chronic lung disease (abnormal x-ray and oxygen at 28 days) and retinopathy. Lundstrom 2000's primary outcome was change in cerebral blood flow measured using xenon clearance. Invasive arterial mean BP and ultrasound determined left ventricular outputs were also measured. No periventricular leucomalacia was observed. No other clinical data were available according to randomised groups.

Risk of bias in included studies

Both Gill 1993 and Lundstrom 2000 are adequately randomised, unblinded studies of volume vs. dopamine with no losses to follow-up and analysed by intention to treat (see table 'Characteristics of included studies').

Effects of interventions

ALBUMIN VS. DOPAMINE IN PRETERM INFANTS (Comparison 1):

Mortality: Two trials reported mortality (Gill 1993; Lundstrom 2000). Neither found evidence of effect. The meta-analysis showed no significant difference in mortality between infants receiving albumin and dopamine (RR 1.45; 95% CI 0.53 to 3.95: RD 0.08, 95% CI -0.12 to 0.27).

Peri/intraventricular haemorrhage: One study reported P/IVH (Gill 1993). All infants were reported to have a P/IVH, any grade. There was an increase in rate of grade 2 - 4 P/IVH with albumin that was of borderline statistical significance (RR 1.47; 95% CI 0.96 to 2.25: RD 0.27, 95% CI 0.00 to 0.54). Periventricular leucomalacia was reported by Lundstrom 2000 with no infants having this outcome.

Failed treatment: One study (Gill 1993) enrolled hypotensive very preterm infants and reported rates of treatment failure (hypotension). Infants receiving albumin had a higher failure rate (persistent hypotension) compared to infants receiving dopamine (RR 5.23; 95% CI 1.33 to 20.55; RD 0.44, 95% CI 0.19 to 0.70).

Chronic lung disease and retinopathy of prematurity were reported by one study (Gill 1993). No difference in the incidence of chronic lung disease (RR 0.7, 95% CI 0.4 to 1.3: RD -0.18, 95% CI -0.49 to 0.13) or retinopathy of prematurity (RR 0.83, 95% CI 0.37 to 1.84: RD -0.07, 95% CI -0.38 to 0.23) was found.

Neurodevelopmental outcome was not reported by either study.

Blood pressure and cardiovascular response: Lundstrom 2000 reported albumin produced a trend to a lower percent increase in mean BP compared to dopamine (Mean Difference -13.9%, 95% CI -43.6 to 15.8%). When compared to volume and no treatment, dopamine produced a significantly greater percent increase in mean BP (reported ANOVA in paper) . Infants receiving albumin and dopamine had similar increases in left ventricular output (MD 3.4%, 95% CI -47.2 to 54.0%). These changes were significant compared to the untreated control group (reported ANOVA in paper). Changes in cerebral blood flow were not significantly different from each other (MD 5.9%, 95% CI -25.0 to 36.8%) or from the untreated control group.

SUBGROUP ANALYSIS:

Subgroup analysis by timing of intervention (< 24 hours): Gill 1993 enrolled infants < 24 hours of age and demonstrated no difference in mortality. There was an increased rate of grade 2 - 4 P/IVH of borderline significance in infants receiving albumin. This observation is consistent with the original hypothesis that early treatment is more likely to prevent P/IVH. The rate of failed treatment was higher in the albumin group (see above).

Subgroup analysis by types of infants enrolled: Lundstrom 2000 enrolled 'unselected' infants (without clinical evidence of cardiovascular compromise). No difference in rates of mortality or periventricular leucomalacia were found. Dopamine was better than albumin and control (but not albumin alone) at increasing mean BP and had similar effects to albumin on blood flow. Gill 1993 enrolled hypotensive preterm infants. No difference in mortality was found. Rates of grade 2 - 4 P/IVH were of borderline significance (see above). The rate of failed treatment was higher in the albumin group (see above).

Subgroup analysis by type of intervention: Both studies compared albumin and dopamine. No other analysis was possible.

HETEROGENEITY

There was no heterogeneity between the two studies for mortality, the only outcome where both studies contributed to the meta-analysis.

DISCUSSION

In a single small study enrolling hypotensive very preterm infants on the first day after birth, dopamine was better than albumin at increasing BP. As 49% of these infants had already been given volume, the question of which treatment should be given first was not answered. In normotensive preterm infants with a mean age of 32 hours, albumin and dopamine produced similar increases in left ventricular output and did not affect cerebral blood flow. No difference was found in mortality or any morbidity including P/IVH, chronic lung disease and retinopathy. Infants who received dopamine had a lower rate of grade 2 - 4 P/IVH of borderline statistical significance compared to those receiving albumin in one study. No data were available for neurodevelopmental outcomes.

Limitations to the studies in this review include their small size limiting the power to detect clinically important outcomes, the enrolment of infants who may not have cardiovascular compromise, the unblinded treatment of infants and measurement of outcomes, and the failure to measure important outcomes including neurodevelopment. Whereas low BP has been linked

to cerebral injury (Low 1993, Miall-Allen 1987), low BP is poorly correlated with cardiac output in very preterm infants in the first days after birth (Kluckow 1996; Osborn 2004). Low blood flow in the first day of life is strongly predictive of cerebral injury (Hunt 2004; Kluckow 2000; Meek 1999; Osborn 2003; Osborn 2007). It is uncertain whether selecting infants on the basis of a low mean BP and using BP as the primary outcome accurately identifies those infants in need of cardiovascular intervention and appropriately evaluates response to treatment. The study which examined the effect of volume and dopamine on blood flow enrolled normotensive preterm infants.

AUTHORS' CONCLUSIONS

Implications for practice

Dopamine was more successful than albumin at correcting low BP in hypotensive preterm infants. Neither intervention has been shown to be superior at improving blood flow, or in improving mortality and morbidity in preterm infants. The trials do not allow any firm conclusions to be made as to whether or when volume or dopamine should be used in preterm infants.

Implications for research

Studies are needed that identify infants with cardiovascular compromise and have the power to detect clinically important outcomes including mortality, peri/intraventricular haemorrhage and neurodevelopmental disability. In measuring short-term effects, measures of cerebral and organ blood flow or cardiac output should be included.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Gill 1993

Methods	Adequate randomisation: yes, random number generator, blocks of 10, using sealed envelopes Allocation concealment: yes Blinding of intervention: no Blinding of measurement: no Losses to follow up: none
Participants	Preterm infants < 1501 g and < 24 hours age, indwelling arterial line, hypotensive (mean BP < 10th percentile), given 20 mls/kg plasma protein fraction prior to insertion of line if clinician felt infant to be 'shocked' Mean gestation: Group 1: 26.5 weeks (range 604-1452); Group 2: 27 (23-31) Mean birthweight: Group 1: 980g (range 640-1300); Group 2: 990g (660-1450)
Interventions	Group 1 (n = 20): albumin 4.5% 20 mls/kg over 30 mins, repeated if mean BP not increased to > 10th percentile Group 2 (n = 19): dopamine 5 mcg/kg/min, increased by 2.5 mcg/kg/min every 30 mins up to maximum 10 mcg/kg/min or mean BP > 10th percentile
Outcomes	Stated primary outcome: correction of hypotension (mean BP < 10th percentile) Other outcomes: peri/intraventricular haemorrhage, duration of ventilation, chronic lung disease (oxygen at 28 days with abnormal chest x-ray), retinopathy of prematurity, mortality
Notes	49% of infants received volume expansion prior to study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Lundstrom 2000

Methods	Adequate randomisation: yes, sealed envelopes Allocation concealment: yes Blinding of intervention: no Blinding of measurement: not stated Losses to follow up: none
Participants	Preterm infants < 33 weeks (median 28, range 25-32), arterial line, mean arterial BP 29 to 40 mmHg, normal blood glucose, no volume or inotrope support within preceding 3 hours Mean postnatal age = 31.8 hrs (range 5-224) Mean gestation: Group 1: 27.9 weeks; Group 2: 28.6 Mean birthweight: Group 1: 1134g; Group 2: 1238g
Interventions	Intervention: Group 1 (n = 13): albumin 20% 15 mls/kg Group 2 (n = 11): dopamine 5 mcg/kg/min
Outcomes	Stated primary outcome: mean arterial BP, left ventricular output, global cerebral blood flow Other outcomes: mortality, peri/intraventricular haemorrhage, periventricular leucomalacia
Notes	Clinical data for mortality obtained from author.

Lundstrom 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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

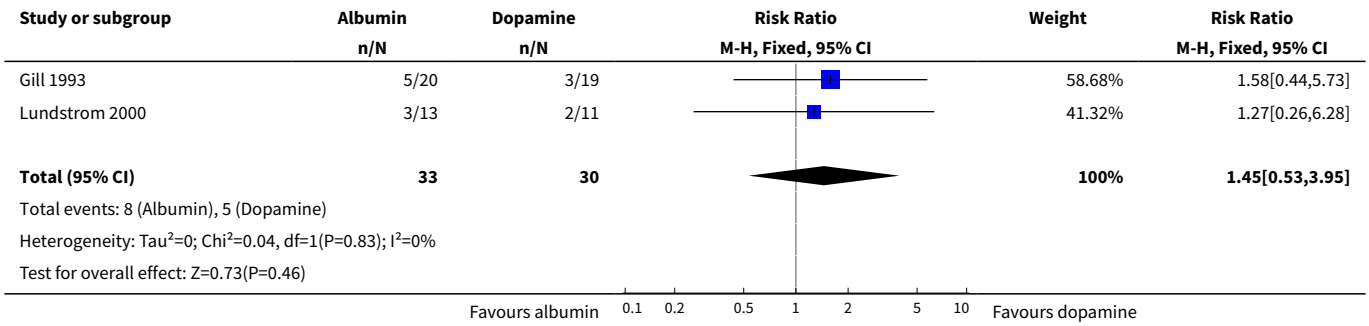
Study	Reason for exclusion
Kawczynski 1996	Not randomized.
Rennie 1989	Non randomised comparison of dopamine and plasma.

DATA AND ANALYSES

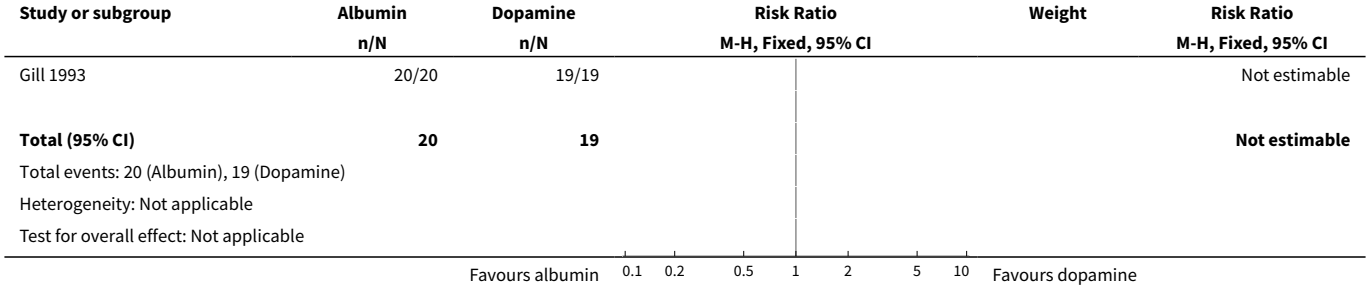
Comparison 1. Albumin versus dopamine in preterm infants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2	63	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.53, 3.95]
2 Peri/intraventricular haemorrhage, any grade	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Peri/intraventricular haemorrhage, grade 2-4	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.96, 2.25]
4 Periventricular leucomalacia	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Failed treatment (persistent hypotension)	1	39	Risk Ratio (M-H, Fixed, 95% CI)	5.23 [1.33, 20.55]
6 CLD (oxygen at 28 days)	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.39, 1.29]
7 Retinopathy of prematurity	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.37, 1.84]
8 Change in cerebral blood flow (%)	1	24	Mean Difference (IV, Fixed, 95% CI)	5.9 [-24.98, 36.78]
9 Change in left ventricular output (%)	1	24	Mean Difference (IV, Fixed, 95% CI)	3.40 [-47.24, 54.04]
10 Change in mean BP (%)	1	24	Mean Difference (IV, Fixed, 95% CI)	-13.9 [-43.56, 15.76]

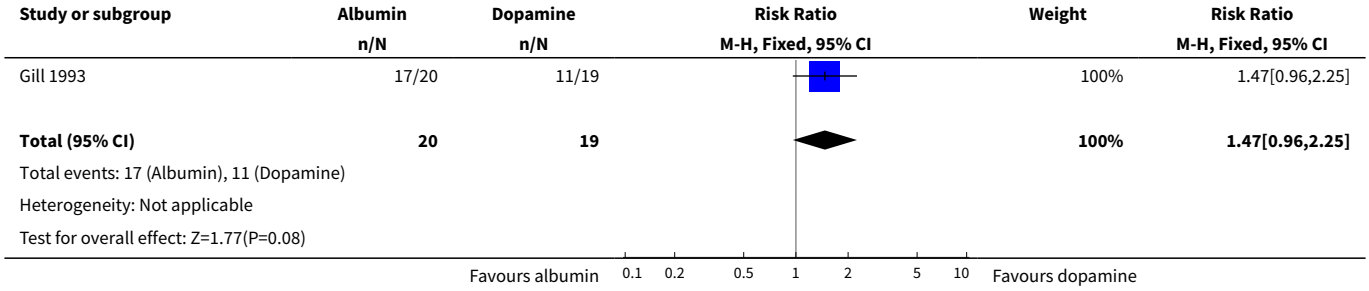
Analysis 1.1. Comparison 1 Albumin versus dopamine in preterm infants, Outcome 1 Death.



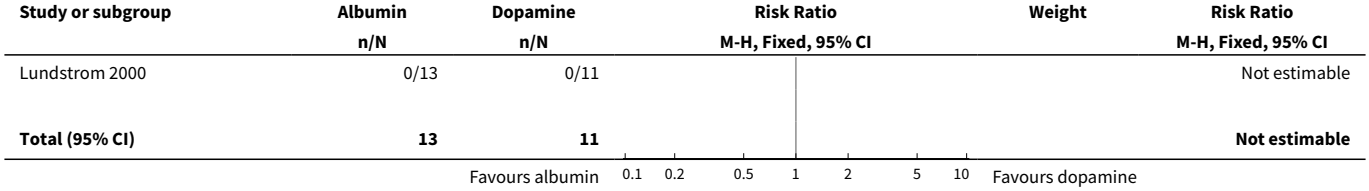
Analysis 1.2. Comparison 1 Albumin versus dopamine in preterm infants, Outcome 2 Peri/intraventricular haemorrhage, any grade.

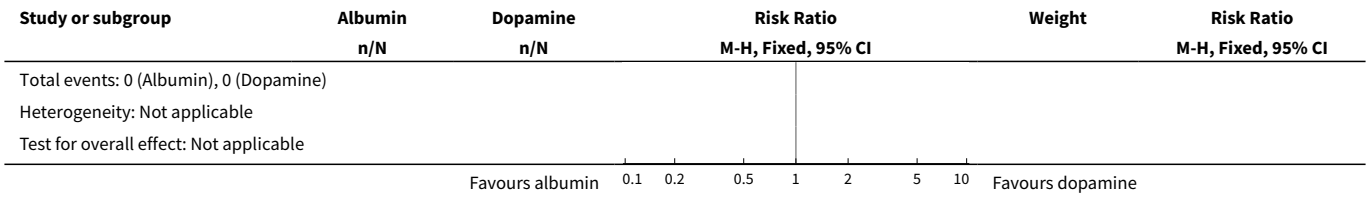


Analysis 1.3. Comparison 1 Albumin versus dopamine in preterm infants, Outcome 3 Peri/intraventricular haemorrhage, grade 2-4.

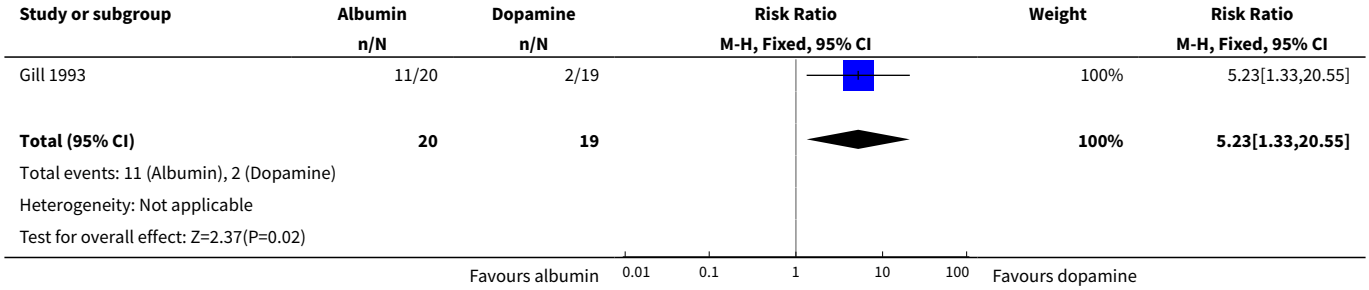


Analysis 1.4. Comparison 1 Albumin versus dopamine in preterm infants, Outcome 4 Periventricular leucomalacia.

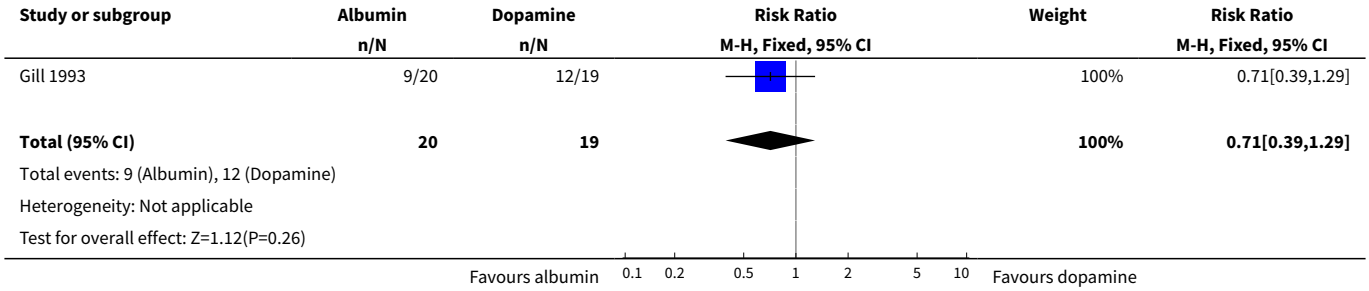




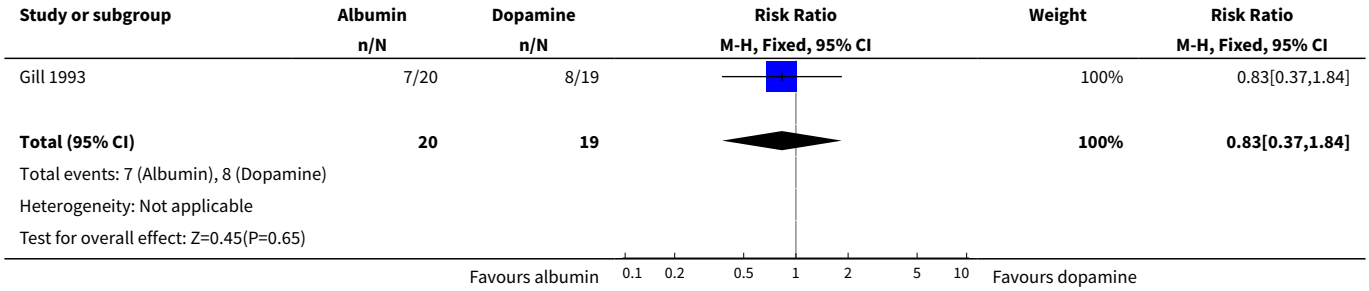
Analysis 1.5. Comparison 1 Albumin versus dopamine in preterm infants, Outcome 5 Failed treatment (persistent hypotension).



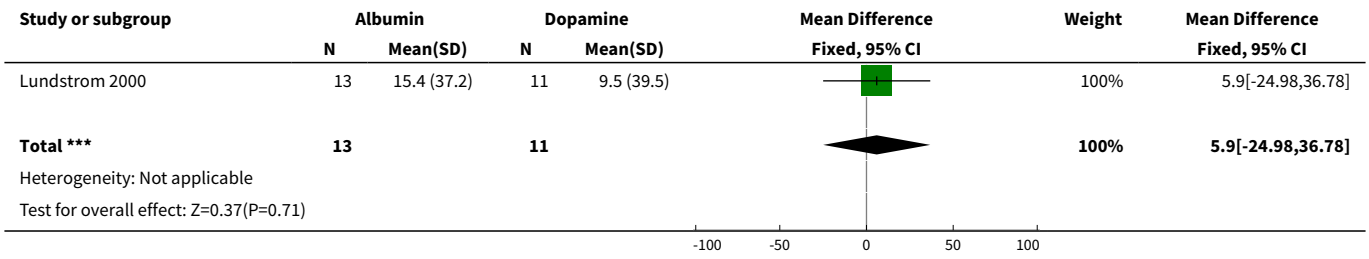
Analysis 1.6. Comparison 1 Albumin versus dopamine in preterm infants, Outcome 6 CLD (oxygen at 28 days).



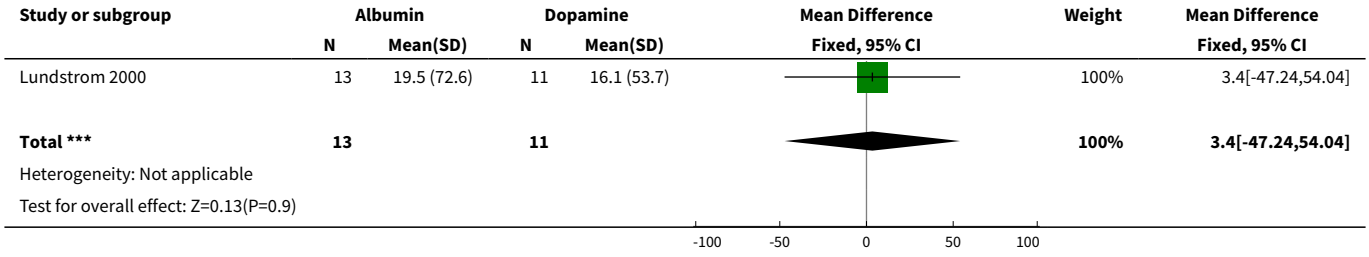
Analysis 1.7. Comparison 1 Albumin versus dopamine in preterm infants, Outcome 7 Retinopathy of prematurity.



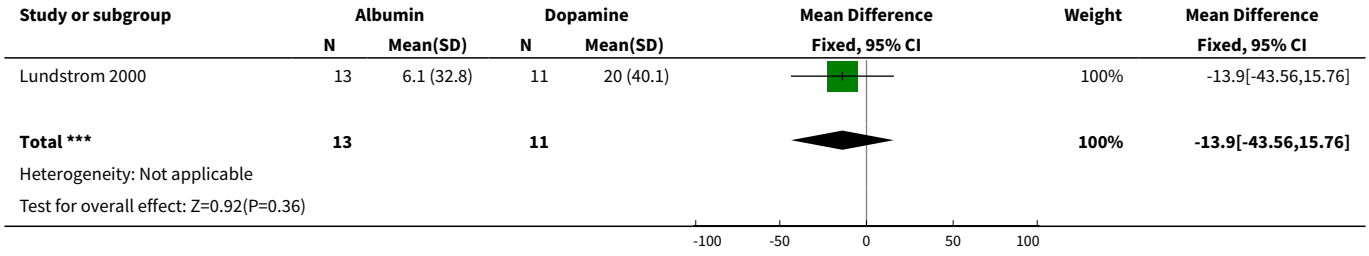
Analysis 1.8. Comparison 1 Albumin versus dopamine in preterm infants, Outcome 8 Change in cerebral blood flow (%).



Analysis 1.9. Comparison 1 Albumin versus dopamine in preterm infants, Outcome 9 Change in left ventricular output (%).



Analysis 1.10. Comparison 1 Albumin versus dopamine in preterm infants, Outcome 10 Change in mean BP (%).



WHAT'S NEW

Date	Event	Description
31 July 2008	New search has been performed	This review updates the existing review of "Early volume expansion versus inotrope for prevention of morbidity and mortality in very preterm infants" published in the Cochrane Database of Systematic Reviews, Issue 2, 2004 (Osborn 2004). Updated literature search found no new studies. Background updated. No changes in conclusions.

Date	Event	Description
20 April 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 2, 2001

Date	Event	Description
9 February 2004	New search has been performed	This review updates the existing review of "Early volume expansion versus inotrope for prevention of morbidity and mortality in very preterm infants" published in The Cochrane Library, Issue 3, 2001 (Osborn 2001). Searches of data bases were updated to January 2004. One additional study found was ineligible for inclusion. No change made to included studies, results or conclusions.
15 February 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

DO wrote the review update. Both authors performed the literature search.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- RPA Newborn Care, Royal Prince Alfred Hospital, Sydney, Australia.

External sources

- Centre for Perinatal Health Services Research, University of Sydney, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

*Blood Volume; Albumins [administration & dosage]; Cardiotonic Agents [*administration & dosage]; Dopamine [administration & dosage]; Infant Mortality; Infant, Low Birth Weight [physiology]; Infant, Premature [*physiology]; Plasma Substitutes [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn