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**Abstract**

**Background**

Intravenous albumin infusion to treat hypoalbuminaemia is used in intensive care nurseries. Hypoalbuminaemia occurs in a number of clinical situations including prematurity, the acutely unwell infant, respiratory distress syndrome (RDS), chronic lung disease (CLD), necrotising enterocolitis (NEC), intracranial haemorrhage, hydrops fetalis and oedema. Fluid overload is a potential side effect of albumin administration. Albumin is a blood product and therefore carries the potential risk of infection and adverse reactions. Albumin is also a scarce and expensive resource.

**Objectives**

The primary objective was to assess whether albumin infusions, in preterm neonates with low serum albumin, reduces mortality and morbidity. A secondary objective was to assess whether albumin infusion is associated with significant side effects.

**Search strategy**

Searches were made of MEDLINE from 1966 to April 2004, CINAHL from 1982 to April 2004 and the current Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library issue 1, 2004). Previous reviews (including cross references) and abstracts were also searched.

**Selection criteria**

All randomised controlled trials in which individual patients were allocated to albumin infusion versus control were included. Cross-over studies were excluded. Quasi randomised trials were excluded. Participants were preterm infants who had hypoalbuminaemia. Types of interventions included albumin infusion versus placebo (e.g. crystalloid) or no treatment.

**Data collection and analysis**

The reviewers worked independently to search for trials for inclusion and to assess methodological quality. Studies were assessed using the following key criteria: blinding of randomisation, blinding of intervention, completeness of follow up and blinding of outcome measurement.

**Main results**

Only two small studies were found for inclusion in this review and only one reported clinically relevant outcomes - it found no significant differences for our primary outcome measure of death (RR 1.5 [95% confidence interval 0.3 - 7.43]) or secondary outcome measures of intraventricular haemorrhage, patent ductus arteriosus, necrotising enterocolitis, bronchopulmonary dysplasia, duration of mechanical ventilation and duration of oxygen therapy.

**Authors’ conclusions**

There is a lack of evidence from randomised trials to determine whether the routine use of albumin infusion, in preterm neonates with low serum albumin, reduces mortality or morbidity, and no evidence to assess whether albumin infusion is associated with significant side effects. There is a need for good quality, double-blind randomised controlled trials to assess the safety and efficacy of albumin infusions in preterm neonates with low serum albumin.
There is a lack of evidence from randomised trials to either support or refute the routine use of albumin infusion for premature babies with a low albumin level.

Albumin is a substance that is normally present in the blood. In premature babies the albumin level in the blood can be low. Albumin is often given to premature babies with a low albumin level. Only two small randomised controlled trials have studied the use of albumin in sick premature babies, and the trials are not big enough or good enough to decide whether giving albumin helps babies in the short or long term. We, therefore, cannot answer the question of whether giving albumin does any good and is safe.

**BACKGROUND**

Serum albumin levels are routinely measured and reported in intensive care nurseries and hypoalbuminaemia is a common finding in preterm (<37 weeks) neonates (<28 days). An older child or adult with a serum albumin level below 30 g/litre is classified as having hypoalbuminaemia (Greenough 1998). Normal albumin levels in preterm infants have been difficult to define. Serum albumin levels in preterm infants are significantly lower than those in term infants (Berghstrand 1972; Carllidge 1986; Zlotkin 1987; Reading 1990). Carllidge and Rutter (Carllidge 1986) showed serum albumin levels in the early neonatal period increased significantly with gestational age from a mean of 19 g/litre (90% confidence interval -12 to -28 g/litre) below 30 weeks to a mean of 31 g/litre (90% confidence interval -22 to 39 g/litre) at term. Hypoalbuminaemia occurs in a number of clinical situations including prematurity, the acutely unwell infant, respiratory distress syndrome (RDS), chronic lung disease (CLD), necrotising enterocolitis (NEC), intracranial haemorrhage, hydrops fetalis and oedema (Brown 1993; Greenough 1999; Atkinson 1989; Bergstrand 1972; Carllidge 1986; Zlotkin 1987; Reading 1990).

There are several clearly defined physiological functions of serum albumin. These include a binding and transport function, an effect on colloid osmotic pressure with serum albumin accounting for approximately 60-80% of the colloid osmotic pressure, a role as a free radical scavenger and anticoagulant effects primarily in inhibiting platelet aggregation and increasing prothrombin and partial prothrombin time (Margaron 1998). Albumin accounts for approximately 50% of the serum proteins and is the major protein produced by the liver (Vanek 1998).

In acute and chronic lung disease of the newborn, alveolar capillary membrane permeability is increased and high albumin levels are present in the alveolar aspirate (Watts 1995). In conjunction with this, pulmonary oedema is often found. Protein leakage into the alveolar space has been shown to occur in adults with respiratory distress syndrome. Leakage of protein into the alveolar space interferes with lung function and inactivates surfactant (Moiison 1998). It has been suggested that albumin infusions should increase the capillary colloid pressure, thereby resulting in a decrease in flow of fluid out of the capillaries. This should then lessen fluid accumulation in the lungs, bowel wall and other interstitial spaces that could cause decreased pulmonary oxygen uptake, decreased absorption across the bowel wall or increased bowel wall secretions (Vanek 1998). However, it could also be argued that the underlying capillary leak will not be altered by albumin infusion and that increasing the amount of intravascular albumin will increase the amount that leaks out of the circulation, into the tissues, increasing oedema.

Low albumin levels have been found in infants who develop necrotising enterocolitis (Atkinson 1989). Albumin contributes to the antioxidant capacity of plasma; therefore, low levels of plasma albumin may lessen the total plasma antioxidant capacity. This may be of importance for preterm infants who are at risk of disease processes where reactive oxygen species are believed to play an important role such as respiratory distress syndrome, chronic neonatal lung disease and intracranial haemorrhage (Moiison 1998).

Hypoalbuminaemia in adult surgical and medical patients has been associated with an increased incidence of pneumonia, sepsicaemia, mortality and longer hospital stay (Vanek 1998). Goldwasser and Feldman (Goldwasser 1997) showed that in adults, serum albumin concentration is inversely related to the risk of death. Conversely a systematic review of albumin administration in critically ill adults found no evidence that albumin administration reduced mortality and suggested that it may increase mortality in selected patients (Cochrane 1998). Studies in adults have looked at the influence of albumin on duration of intensive care stay and rate of recovery. Stockwell et al (Stockwell 1992) showed no difference between duration of stay, complications or outcomes in two groups of patients who had either albumin or gelatin for fluid replacement.

There are documented cases of the complete absence of albumin, analbuminaemia, as a result of a rare genetic condition (Watkins 1994). These patients suffered only mild abnormalities of lipid metabolism and mild oedema; half of the reported patients were entirely asymptomatic. Several studies have shown that oedema in preterm infants is common but poorly correlated with hypoalbuminaemia (Carllidge 1986; Reading 1990; Kenny 1995) and the routine administration of albumin for oedema is not warranted.

Intravenous albumin infusion to treat hypoalbuminaemia is used...
in intensive care nurseries. Green and Morgan (Green 1993) suggested giving 20% albumin whenever the serum albumin falls below 25 g/litre. Intravenous albumin has also been administered to high risk infants who are hypotensive and in respiratory distress (Lay 1980). It has been advocated in the past that ill infants with RDS should be given albumin infusions whenever their serum albumin falls below 20 g/litre (Greenough 1992); however, it is now recommended that care should be taken as albumin infusions may be harmful (Greenough 1999).

Using albumin to treat hypoalbuminaemia is different from using albumin for volume expansion which has been assessed in other Cochrane reviews (Alderson 2002; Bunn 2002; Osborn 2002).

Fluid overload is a potential side effect of albumin administration. Complications of fluid overload include PDA and NEC and possibly CLD (Greenough 1999). Albumin is a blood product and therefore carries the potential risk of infection and adverse reactions; although the risks are low, they should be considered. Albumin (which comes in a number of commercial preparations with concentrations ranging from 4 - 20%) is also a scarce and expensive resource with hospitals frequently experiencing shortages (Golub 1994).

O B J E C T I V E S

The primary objective was to assess whether albumin infusions, in preterm neonates with low serum albumin, reduces mortality and morbidity. A secondary objective was to assess whether albumin infusion is associated with significant side effects.

Data permitting, sub-group analyses were planned to determine whether results differed by:

Population:
1. gestational age (e.g. extremely premature [less than or equal to 28 weeks] versus premature [29 to 36 weeks]).
2. birthweight (e.g. very low birth weight infants, <1500 grams, versus infants greater than or equal to 1500 grams or extremely low birth weight infants [<1000 grams] versus infants greater than or equal to 1000 grams).
3. infants with particular illnesses or signs (e.g. oedema, RDS, CLD)
4. hypoalbuminaemia (e.g. less than 30 g/L or less than 25 g/L or less than 20 g/L)

Intervention:
1. dose of albumin infused (e.g. < 1.5 g/kg/dose versus greater than or equal to 1.5 g/kg/dose)
2. type of treatment used in the control group (placebo [e.g. crystalloid] or no treatment)
3. whether albumin is a single infusion on one occasion or a policy of repeated infusions to maintain a serum albumin above a certain level


Types of studies
All randomised controlled trials in which individual patients were allocated to albumin infusion versus control. Cross-over studies were excluded. Quasi randomised trials were excluded.

Types of participants
Preterm infants who had hypoalbuminaemia. Hypoalbuminaemia defined as < 30 g/L, <25 g/L and < 20 g/L.

Types of intervention
Albumin infusion versus placebo (i.e. any other non-colloidal fluid that does not contain albumin) or no treatment. Albumin infusion included any regimen from a single infusion on one occasion to a policy of repeated infusions to maintain the serum albumin above a certain level.

Types of outcome measures
Primary outcomes:
Mortality (neonatal [28 days], before discharge)
Neurodevelopmental outcome at 1 year, 18 months, 2 years, 5 years

Secondary outcomes:
Chronic lung disease (requiring oxygen at 28 days or 36 weeks post-menstrual age)
Intraventricular haemorrhage (any, grade 3-4)
Duration of mechanical ventilation (IPPV) - hours/days
Duration of respiratory support (IPPV or CPAP) - hours/days
Duration of oxygen therapy - hours/days
Septicaemia
Necrotising enterocolitis
Duration of ICN stay - hours/days
Duration of hospital stay - hours/days
Patent ductus arteriosus requiring therapy (medical or surgical)
Cost
Immediate adverse effects (e.g. hypertension, increased ventilation requirements and increased oxygenation)

S E A R C H M E T H O D S F O R I D E N T I F I C A T I O N O F S T U D I E S

See: Neonatal Group methods used in reviews.

The standard search strategy for the Cochrane Neonatal Review Group was used: Searches were made of MEDLINE from 1966 to April 2004, CINAHL from 1982 to April 2004 and the current Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library Issue 1, 2004), using the following strategy:

MeSH search terms ‘serum albumin’, OR ‘albumins’; OR the text words ‘albumin’, OR ‘albumen’, OR ‘hypoalbuminemia’, OR...
'hypoalbuminaemia', OR 'hypo-albuminemia', OR 'hypo-albuminaemia';
AND
MeSH search term 'infant, newborn'
AND
MeSH terms "Albumins / ad [Administration & Dosage]", OR 'Albumins / tu [Therapeutic Use]', OR "Albumins / pd [Pharmacology]", OR the text word phrase "albumin infusion"

Previous reviews (including cross references), and abstracts were also searched. Searches were not restricted to publications in the English language or published data.

**METHODS OF THE REVIEW**

Criteria and methods used to assess the methodological quality of the trials:

Standard methods of the Cochrane Collaboration (Clarke 2002) and its Neonatal Review Group were used. The reviewers worked independently to search for trials for inclusion and to assess methodological quality. Studies were assessed using the following key criteria: blinding of randomisation, blinding of intervention, completeness of follow up and blinding of outcome measurement. However, quality criteria did not determine whether a study was excluded or included from this review. Data were extracted independently by the reviewers. Differences were resolved by discussion and consensus of the reviewers. Investigators were contacted for additional information and data where necessary.

For individual trials, where possible, mean differences (and 95% confidence intervals) were reported for continuous variables. For categorical outcomes, the relative risk and risk difference (and 95% confidence intervals) were reported.

For the meta-analysis, where possible, weighted mean differences (and 95% confidence intervals) were planned to be reported for continuous variables, and the relative risk and risk difference (and 95% confidence intervals) for categorical outcomes. A fixed effects model was planned. Number needed to treat was to be calculated where appropriate.

Given sufficient numbers of included studies we planned to test for heterogeneity where appropriate before deciding to pool the results.

**DESCRIPTION OF STUDIES**

The above search strategy found only three possibly eligible studies of albumin infusions in hypoalbuminaemic preterm infants: two are included in this review.

Kanarek et al (Kanarek 1992) studied the concurrent administration of albumin versus placebo with total parenteral nutrition (TPN) in 24 premature infants (12 in each group). To be eligible the infants had to (1) have respiratory distress requiring assisted ventilation; (2) have had significant hypotension (2 SD below the mean for gestational age, necessitating the use of a plasma expander and/or isotropic agents); (3) have a plasma albumin level below 30 g/L at 48 to 72 hours of life and (4) require TPN for nutritional support. Therefore the population studied in this study was a subset of the population of interest for this review. The albumin was added to the TPN in quantities that were calculated to raise the serum albumin above 30 g/L (maximum 1 g/kg/day).

Greenough et al (Greenough 1993) studied the effect of albumin infusion versus placebo on 40 premature infants (28 - 34 weeks gestational age, 20 in each group). Study subjects were newborn infants who were ventilator dependant at less than seven days of age and had a serum albumin level of ≤30 g/L. Therefore the population studied in this study was once again a subset of the population of interest for this review. Infants were not eligible if they were receiving peritoneal dialysis, had chest drains in situ or were hypotensive (defined as systolic blood pressure less than 40 mmHg). Infants were randomised (the method of randomisation is unknown) to receive either albumin administered as 5 ml/kg of 20% salt-poor human albumin or placebo (5 ml/kg of the infants maintenance fluids). Attempts were made to contact the primary author and no reply was received (we requested clarification of blinding of randomisation, blinding of intervention, completeness of follow up and blinding of outcome measurement; and whether other data were available for any of our primary and secondary outcomes).

The study by Bland et al (Bland 1973) investigated albumin infusions in low birth weight newborn infants at risk for respiratory distress who were acidæmic with a low total serum protein level (whether they were hypoalbuminaemic or not is unknown).

**METHODOLOGICAL QUALITY**

Kanarek et al (Kanarek 1992):
- blinding of randomisation (allocation concealment) - yes
- blinding of intervention - yes
- completeness of follow up - yes
- blinding of outcome measurement - unknown

Greenough et al (Greenough 1993):
- blinding of randomisation (allocation concealment) - unknown
- blinding of intervention - unknown
- completeness of follow up - no (data were analysed and reported for only 15 out of 20 subjects in each group)
- blinding of outcome measurement - unknown
**RESULTS**

We report the results of individual studies. Due to the significant heterogeneity in study quality and the lack of pre-specified outcomes in one of the studies we have not attempted to pool the results.

The results below are organised using our pre-specified primary and secondary outcomes.

**Kanarek et al** (Kanarek 1992)

This study found no significant effect of albumin infusion on any of our pre-specified primary and secondary outcomes.

Primary outcome measures:

- Mortality - there were 3/12 deaths in the experimental group and 2/12 deaths in the control group: RR 1.5 (95% confidence interval 0.3 to 7.43). It is not stated whether mortality is 28 day mortality or at discharge
- Neurodevelopmental outcomes were not assessed or reported

Secondary outcomes:

- There were 5/12 intraventricular haemorrhages (not further defined) in the experimental group and 4/12 in the control group: RR 1.25 (95% confidence interval 0.44 to 3.55)
- There was 0/12 infants with necrotising enterocolitis in the experimental group and 1/12 in the control group: RR 0.33 (95% confidence interval 0.01 to 7.45)
- 5/12 patients in the experimental group and 6/12 in the control group had bronchopulmonary dysplasia (not further defined): RR 0.71 (95% confidence interval 0.31 to 1.63)
- The mean duration of assisted ventilation in the experimental group was 36.9 days (SD 22.9), the mean duration in the control group was 30.8 days (SD 15.2). Mean difference 6.1 days (95% confidence interval -9.45 to 21.65)
- The mean duration of oxygen therapy in the experimental group was 45.7 days (SD 19.1), the mean duration in the control group was 40.4 days (SD 12.5). Mean difference 5.3 days (95% confidence interval -7.62 to 18.22)

The mean arterial blood pressures (MABP) were reported for days three and six. There was no significant differences between the two groups in the first few days of life: the mean (SD) MABP was 35.8 (3.8) mmHg in the albumin group and 34.4 (2.4) mmHg in the control group. When the TPN was commenced on day three the control group’s MABP was unchanged for the rest of the study whereas the albumin group’s MABP continued to rise up until day six when the mean (SD) MABP was 38.9 (4.8) mmHg. No data are given for MABP on day six in the control group; however it is stated that the difference in MABP between the two groups was statistically significant (p < 0.05). Immediate adverse events of albumin infusion including hypertension was one of our secondary outcome measures: none of these data represent hypertension and this reported difference is unlikely to have any clinical significance.

**Other outcomes that were reported in this study that we did not pre-specify include:**

- Time taken to tolerate full feeds - albumin group mean (SD) 16.8 (7.6) days, and control group mean (SD) 18.8 (6.9) days
- Time taken to regain birth weight - albumin group mean (SD) 18.9 (5.9) days, and control group (SD) 24.9 (2.1) days

**Greenough et al** (Greenough 1993)

Primary outcome measures:

- Mortality and neurodevelopmental outcomes were not assessed or reported

Secondary outcomes:

None of our secondary outcomes were reported.

The discussion section of the study report states that there were no adverse effects with albumin in this study (none of the infants required increased oxygen or ventilator support).

Other outcomes (that we did not pre-specify) were reported in this study; these included:

- Fluid input versus output in 12 hour periods preceding infusion, during infusion and post infusion. No significant differences were reported.
- Albumin concentration pre and post infusion. The albumin concentration increased significantly in the albumin group but not in the placebo group.
- Weight pre and post infusion. Weight decreased significantly in the albumin group and increased significantly in the placebo group.
- Peak inspiratory pressures pre and post infusion. There was no significant difference reported.
- Inspired oxygen concentration pre and post infusion. This did fall significantly in the albumin group, and in the placebo group it also fell but not significantly.

**DISCUSSION**

The studies included in our review investigated a small, specific subset of the total number of premature infants receiving albumin infusions. Only one of the studies reported clinically relevant outcomes (Kanarek 1992) - it found no significant differences for our primary outcome measure of death or secondary outcomes of IVH, PDA, NEC, bronchopulmonary dysplasia, duration
of mechanical ventilation and duration of oxygen therapy. There was a statistically significantly higher mean arterial BP in the albumin group at six days of age; however, this is unlikely to have any clinical relevance. The results of this single small study should be treated with caution - the confidence intervals for reported outcomes are wide and a real difference might be masked by a type 2 error. Conversely, any differences seen could easily be due to chance alone. Our second primary outcome (neurodevelopmental outcome) and some of our secondary outcomes weren’t assessed in the included studies (i.e. there were insufficient or no data to assess other clinically important outcomes). The study by Greenough et al (Greenough 1993) did not report any of our primary and secondary outcome measures.

In some neonatal intensive care units albumin is used frequently. For example, at the Grantley Stable Neonatal Unit in Brisbane, Australia, 12% of all preterm infants admitted and 38% of babies <30 weeks GA will get at least one infusion of 20% albumin to increase serum albumin levels or treat oedema [data from the NeoData database, Royal Women’s Hospital, Brisbane for years 2000 to 2002 inclusive]. Such an extensive use of this treatment should be based on better evidence than is currently available.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

There is a lack of evidence from randomised trials to determine whether the routine use of albumin infusion, in preterm neonates with low serum albumin, reduces mortality or morbidity, or is associated with significant side effects.

**Implications for research**

If albumin infusion for hypoalbuminaemic pre-term infants is thought to be worthwhile then there is a need for good quality, double-blind randomised controlled trials to assess the safety and efficacy of this practice.

**POTENTIAL CONFLICT OF INTEREST**

None.

**SOURCES OF SUPPORT**

**External sources of support**

- Department of Health and Ageing, Commonwealth Government, Canberra ACT - Supporting the Centre for Clinical Studies, Mater Hospital AUSTRALIA

**Internal sources of support**

- Grantley Stable Neonatal Unit, Royal Women’s Hospital, Brisbane AUSTRALIA
- Royal Children’s Hospital, Brisbane AUSTRALIA
- Dept of Paediatrics and Child Health, University of Queensland, Brisbane AUSTRALIA
- Centre for Clinical Studies, Mater Hospital, Brisbane AUSTRALIA

**REFERENCES**

**References to studies included in this review**

Greenough 1993 [published data only]

Kanarek 1992 [published data only]

**References to studies excluded from this review**

Bland 1973

**Additional references**

Alderson 2002

Atkinson 1989

Bergstrand 1972

Bunn 2002
Cartlidge 1986

Clarke 2002

Cochrane 1998

Goldwasser 1997

Golub 1994

Green 1993

Greenough 1992

Greenough 1998

Greenough 1999

Kenny 1995

Lay 1980

Margarson 1998

Moison 1998

Osborn 2002

Reading 1990

Stockwell 1992

Vanek 1998

Watkins 1994

Watts 1995

Zlotkin 1987
### Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Greenough 1993</th>
<th>Kanarek 1992</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>A RCT. The method of randomisation is unknown. Whether group allocation was blinded is unknown. Whether the intervention was blinded is unknown. Data is analysed and reported for 30 of the 40 enrolled participants. None of the outcomes reported are said to be blinded.</td>
<td>A RCT. The method of randomisation is unknown. Group allocation was blinded (sealed envelopes). The intervention was blinded. Follow up was complete. It is unknown if outcome measurement was blinded.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Infants between 24 and 34 weeks gestation were eligible for the study if they were ventilator-dependant at less than 7 days of age and had a serum albumin level of less than or equal to 30g/l. They were not eligible if they were receiving peritoneal dialysis, had chest drains in situ or were hypotensive. Hypotension was defined as a systolic blood pressure less than 40 mmHg. 40 infants were entered into the study. Data was incomplete for 5 in each group. The analysis was performed on the remaining 30 participants (15 in each group).</td>
<td>To be eligible the infants had to (1) have respiratory distress requiring assisted ventilation; (2) have had significant hypotension (2 SD below the mean for gestational age, necessitating the use of a plasma expander and/or inotropic agents); (3) have a plasma albumin level below 30 g/L at 48 to 72 hours of life and (4) require TPN for nutritional support. 24 premature (not defined) infants were enrolled (12 in each group).</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>40 patients were randomly allocated to receive either albumin (n=20; 5 ml/kg 20% salt-poor human albumin) or placebo (n=20; 5 ml/kg of infant’s maintenance fluids). The volume of the trial infusion was subtracted from the total daily fluid requirement and given at the maintenance rate.</td>
<td>The albumin was added to the TPN in quantities that were calculated to raise the serum albumin above 30 g/L (maximum 1 g/kg/day). 24 patients were randomised to receive either added albumin to their TPN (n=20) or standard TPN solution (n=20).</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary outcome measures: mortality and neurodevelopmental outcomes were not assessed or reported. Secondary outcomes: none of our secondary outcomes were reported. The discussion section of the study report states that there were no adverse effects with albumin in this study (none of the infants required increased oxygen or ventilator support). Other outcomes (that we did not pre-specify) reported: Fluid input versus output in 12 hour periods preceding infusion, during infusion and post infusion. Albumin concentration pre and post infusion. Weight pre and post infusion. Peak inspiratory pressures pre and post infusion. Inspired oxygen concentration pre and post infusion.</td>
<td>Primary outcome measures: mortality. Secondary outcomes: intraventricular haemorrhages (not further defined).</td>
</tr>
</tbody>
</table>

**Notes**

Allocation concealment  B
Characteristics of included studies (Continued)

Necrotising enterocolitis.
Bronchopulmonary dysplasia (not further defined).
Patent ductus arteriosus (not further defined).
The duration of assisted ventilation.
The duration of oxygen therapy.
The mean arterial blood pressures (MABP) were reported for days 3 and 6.

Other outcomes:
Time taken to tolerate full feeds.
Time taken to regain birth weight.

Notes
Allocation concealment A

Characteristics of excluded studies

Bland 1973  This RCT investigated albumin infusions in low birth weight newborn infants at risk for respiratory distress who were acidaemic with a low total serum protein level (whether they were hypoalbuminaemic or not is unknown).

ANALYSES

Comparison 01. Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined)

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Mortality</td>
<td></td>
<td></td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>02 IVH - any grade</td>
<td></td>
<td></td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>03 Bronchopulmonary dysplasia (not defined)</td>
<td></td>
<td></td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>Subtotals only</td>
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<tr>
<td>04 Necrotising enterocolitis</td>
<td></td>
<td></td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>05 Patent ductus arteriosus</td>
<td></td>
<td></td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>06 Duration of assisted ventilation (days)</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>07 Duration of oxygen therapy (days)</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Subtotals only</td>
</tr>
</tbody>
</table>

INDEX TERMS

Medical Subject Headings (MeSH)
Albumins [*administration & dosage; adverse effects]; Hypoalbuminemia [mortality; *therapy]; Infant Mortality; Infant, Low Birth Weight [blood]; Infant, Newborn; Infant, Premature [*blood]

MeSH check words
Humans

COVER SHEET

Title
Albumin infusion for low serum albumin in preterm newborn infants

Authors
Jardine LA, Jenkins-Manning S, Davies MW
Contribution of author(s)

All three reviewers conducted the search for studies and assessed them for inclusion in this review.
LAJ wrote the review.
MWD and SJM co-wrote the review.

Issue protocol first published

2003/2

Review first published

2004/3

Date of most recent amendment

26 May 2004

Date of most recent SUBSTANTIVE amendment

01 April 2004

What's New

Information not supplied by author

Date new studies sought but none found

Information not supplied by author

Date new studies found but not yet included/excluded

Information not supplied by author

Date new studies found and included/excluded

Information not supplied by author

Date authors' conclusions section amended

Information not supplied by author

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HM-NEONATAL
### Analysis 01.01. Comparison 01 Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined), Outcome 01 Mortality

**Review:** Albumin infusion for low serum albumin in preterm newborn infants  
**Comparison:** 01 Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined)  
**Outcome:** 01 Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Albumin</th>
<th>Placebo</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanarek 1992</td>
<td>3/12</td>
<td>2/12</td>
<td></td>
<td>100.0</td>
<td>1.50 [ 0.30, 7.43 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>100.0</td>
<td>1.50 [ 0.30, 7.43 ]</td>
</tr>
</tbody>
</table>

Total events: 3 (Albumin), 2 (Placebo)  
Test for heterogeneity: not applicable  
Test for overall effect z=0.50  p=0.6

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### Analysis 01.02. Comparison 01 Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined), Outcome 02 IVH - any grade

**Review:** Albumin infusion for low serum albumin in preterm newborn infants  
**Comparison:** 01 Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined)  
**Outcome:** 02 IVH - any grade

<table>
<thead>
<tr>
<th>Study</th>
<th>Albumin</th>
<th>Placebo</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanarek 1992</td>
<td>5/12</td>
<td>4/12</td>
<td></td>
<td>100.0</td>
<td>1.25 [ 0.44, 3.55 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>100.0</td>
<td>1.25 [ 0.44, 3.55 ]</td>
</tr>
</tbody>
</table>

Total events: 5 (Albumin), 4 (Placebo)  
Test for heterogeneity: not applicable  
Test for overall effect z=0.42  p=0.7
Analysis 01.03. **Comparison 01** Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined), **Outcome 03** Bronchopulmonary dysplasia (not defined)

Review: Albumin infusion for low serum albumin in preterm newborn infants

Comparison: 01 Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined)

Outcome: 03 Bronchopulmonary dysplasia (not defined)

<table>
<thead>
<tr>
<th>Study</th>
<th>Albumin n/N</th>
<th>Placebo n/N</th>
<th>Relative Risk (Fixed) 95% CI (%)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanarek 1992</td>
<td>5/12</td>
<td>6/12</td>
<td>0.83 [0.35, 2.00]</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>12</td>
<td>12</td>
<td>0.83 [0.35, 2.00]</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Total events: 5 (Albumin), 6 (Placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=0.41 p=0.7</td>
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<td></td>
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</tr>
</tbody>
</table>

Analysis 01.04. **Comparison 01** Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined), **Outcome 04** Necrotising enterocolitis

Review: Albumin infusion for low serum albumin in preterm newborn infants

Comparison: 01 Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined)

Outcome: 04 Necrotising enterocolitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Albumin n/N</th>
<th>Placebo n/N</th>
<th>Relative Risk (Fixed) 95% CI (%)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanarek 1992</td>
<td>0/12</td>
<td>1/12</td>
<td>0.33 [0.01, 7.45]</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>12</td>
<td>12</td>
<td>0.33 [0.01, 7.45]</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Total events: 0 (Albumin), 1 (Placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Test for overall effect z=0.69 p=0.5</td>
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</tbody>
</table>
Analysis 01.05. Comparison 01 Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined), Outcome 05 Patent ductus arteriosus

Review: Albumin infusion for low serum albumin in preterm newborn infants
Comparison: 01 Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined)
Outcome: 05 Patent ductus arteriosus

<table>
<thead>
<tr>
<th>Study</th>
<th>Albumin</th>
<th>No treatment</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanarek 1992</td>
<td>5/12</td>
<td>7/12</td>
<td>0.71 [ 0.31, 1.63 ]</td>
<td>100.0</td>
<td>0.71 [ 0.31, 1.63 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>12</td>
<td>12</td>
<td></td>
<td>100.0</td>
<td>0.71 [ 0.31, 1.63 ]</td>
</tr>
<tr>
<td>Total events:</td>
<td>5 (Albumin), 7 (No treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect $z=0.80$ $p=0.4$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analysis 01.06. Comparison 01 Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined), Outcome 06 Duration of assisted ventilation (days)

Review: Albumin infusion for low serum albumin in preterm newborn infants
Comparison: 01 Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined)
Outcome: 06 Duration of assisted ventilation (days)

<table>
<thead>
<tr>
<th>Study</th>
<th>Albumin</th>
<th>Placebo</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal (95% CI)</td>
<td>12</td>
<td>12</td>
<td>6.10 [ -9.45, 21.65 ]</td>
<td>100.0</td>
<td>6.10 [ -9.45, 21.65 ]</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect $z=0.77$ $p=0.4$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Analysis 01.07. Comparison 01 Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined), Outcome 07 Duration of oxygen therapy (days)

Review: Albumin infusion for low serum albumin in preterm newborn infants  
Comparison: 01 Albumin vs placebo in infants with plasma albumin <30g/L and requiring assisted ventilation (not defined)  
Outcome: 07 Duration of oxygen therapy (days)

<table>
<thead>
<tr>
<th>Study</th>
<th>Albumin</th>
<th>Placebo</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanarek 1992</td>
<td>12</td>
<td>12</td>
<td>45.70 (19.10)</td>
<td>1200</td>
<td>5.30 [-7.62, 18.22]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>12</td>
<td>12</td>
<td>40.40 (12.50)</td>
<td>1000</td>
<td>5.30 [-7.62, 18.22]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable  
Test for overall effect z=0.80  p=0.4