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Aziz A, Ohlsson A

Aziz A, Ohlsson A.
Surfactant for pulmonary haemorrhage in neonates.
Cochrane Database of Systematic Reviews 2020, Issue 2. Art. No.: CD005254.
DOI: 10.1002/14651858.CD005254.pub4.

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[Intervention Review]

Surfactant for pulmonary haemorrhage in neonates

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Editorial group: Cochrane Neonatal Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2020.

Citation: Aziz A, Ohlsson A. Surfactant for pulmonary haemorrhage in neonates. *Cochrane Database of Systematic Reviews* 2020, Issue 2. Art. No.: CD005254. DOI: 10.1002/14651858.CD005254.pub4.

ABSTRACT

Background

In the 1960s and 1970s, pulmonary haemorrhage (PH) occurred mainly in full-term infants with pre-existing illness with an incidence of 1.3 per 1000 live births. Risk factors for PH included severity of illness, intrauterine growth restriction, patent ductus arteriosus (PDA), coagulopathy and the need for assisted ventilation. Presently, PH occurs in 3% to 5% of preterm ventilated infants with severe respiratory distress syndrome (RDS) who often have a PDA and have received surfactant. The cause of PH is thought to be due to rapid lowering of intrapulmonary pressure, which facilitates left to right shunting across a PDA and an increase in pulmonary blood flow. Retrospective case reports and one prospective uncontrolled study have shown promising results for surfactant in treating PH.

Objectives

To evaluate the effect of surfactant treatment compared to placebo or no intervention on mortality and morbidities in neonates with PH.

Search methods

For this update *The Cochrane Library*, Issue 2, 2012; MEDLINE; EMBASE; CINAHL; Clinicaltrials.gov; Controlled-trials.com; proceedings (2000 to 2011) of the Annual Meetings of the Pediatric Academic Societies (Abstracts2View) and Web of Science were searched on 8 February 2012.

Selection criteria

Randomised or quasi-randomised controlled trials that evaluated the effect of surfactant in the treatment of PH in intubated term or preterm (< 37 weeks) neonates with PH. Infants were included up to 44 weeks' postmenstrual age. The interventions studied were intratracheal instillation of surfactant (natural or synthetic, regardless of dose) versus placebo or no intervention.

Data collection and analysis

If studies were identified by the literature search, the planned analyses included risk ratio, risk difference, number needed to treat to benefit or to harm for dichotomous outcomes, and mean difference for continuous outcomes, with their 95% confidence intervals. A fixed-effect model would be used for meta-analyses. The risk of bias for included trials would be assessed. Heterogeneity tests, including the I^2 statistic, would be performed to assess the appropriateness of pooling the data and the results would be reported.

Main results

No trials were identified.

Authors' conclusions

No randomised or quasi-randomised trials that evaluated the effect of surfactant in PH were identified. Therefore, no conclusions from such trials can be drawn. In view of the promising results from studies with less strict study designs than a randomised controlled trial, there is reason to conduct further trials of surfactant for the treatment of PH in neonates.

PLAIN LANGUAGE SUMMARY

Surfactant for pulmonary haemorrhage in neonates

Bleeding into the lungs (pulmonary haemorrhage) occurs mainly in infants born before term (37 weeks' gestation) because of severe lung disease (particularly respiratory distress syndrome, a disease caused by the lack of the normal lining chemicals of the lung (surfactant)) and the need for a breathing machine (assisted ventilation). The risk factors for pulmonary haemorrhage include preterm birth, poor growth while in the womb (intrauterine growth restriction), respiratory problems, abnormal blood flow around the blood vessels in the lungs (patent ductus arteriosus), bleeding problems (coagulopathy), the need for a breathing machine and surfactant treatment. The underlining cause of pulmonary haemorrhage is thought to be a rapid increase in pulmonary blood flow due to a patent ductus arteriosus. Some studies have shown promising results with the use of surfactant treatment in infants with pulmonary haemorrhage. However, no randomised controlled trials were identified in this review. Currently, no recommendation for clinical practice based on randomised controlled trials can be presented; further research is needed.

BACKGROUND

Description of the condition

In the late 1960s and early 1970s, the incidence of pulmonary haemorrhage (PH) was quoted as 1.3 per 1000 live births (Cole 1973). Currently, PH complicates the hospital course of 3% to 5% of preterm infants with respiratory distress syndrome (RDS) (Wiswell 2001). PH occurs mainly in preterm ventilated infants with severe RDS, who often have a patent ductus arteriosus (PDA) and who have received surfactant (Papworth 2001). Risk factors for PH include severity of associated illness, intrauterine growth restriction, PDA, coagulopathy and surfactant therapy (Papworth 2001).

In the early 1970s, Cole et al (Cole 1973) conducted a study on 15 infants with sudden clinical deterioration associated with blood-stained liquid flowing from their tracheas. The investigators performed clinical observations, coagulation studies, and analyses of simultaneously obtained samples of lung effluent and arterial or venous blood for haematocrit and protein composition. In most cases, the haemorrhagic effluent was oedema fluid and not whole blood. The most important precipitating factor for PH was acute left ventricular failure due to asphyxia. Coagulation disorders probably served to exacerbate the condition, but did not appear to be the initiating factor (Cole 1973).

PH appears to be a complication of surfactant therapy. In a meta-analysis of seven placebo-controlled trials using synthetic surfactant and four trials using animal-derived surfactant given either as prophylaxis or treatment of RDS, surfactant therapy was associated with an increased risk of PH (typical risk ratio (RR) 1.47; 95% confidence interval (CI) 1.05 to 2.07) indicating an increased risk for PH with surfactant treatment (Raju 1993). In five multicentre, placebo-controlled trials of the synthetic surfactant Exosurf Neonatal in infants weighing at least 700 g, the incidence of clinical PH was 1.9% in treated infants and 1.0% in control infants (Van Houten 1994).

There are several Cochrane reviews on the use of surfactant in neonates that report on PH (Soll 1997; Soll 2009; Stevens 2007). The RR for PH was statistically significantly increased with the use of prophylactic synthetic surfactant versus control treatment (intratracheal administration of normal saline or air placebo) (typical RR 3.28; 95% CI 1.50 to 7.16) (Soll 1997) but not for treatment of established RDS versus control (intratracheal administration of air placebo) (typical RR 1.44; 95% CI 0.68 to 3.05) (Soll 1997). In contrast to clinical diagnosis, the pathological diagnosis of PH at postmortem was not more common in infants treated with Exosurf Neonatal (Van Houten 1994). Surfactant therapy may be a contributing factor, causing PH by inducing a rapid lowering of intrapulmonary pressure, which facilitates left-to-right shunting across a PDA and an increase in pulmonary blood flow (Wiswell 2001). Surfactant may be associated with in-vitro cytotoxicity. The degree of cytotoxicity differs for different surfactants and different dosages (Findlay 1995). These activities may be initiated at the two-cell interface of the alveolar-capillary membrane barrier, with PH occurring as a result of disruption of membrane integrity at this interface (Findlay 1995). In a postmortem study, infants treated with surfactant who developed PH were shown to have more extensive intra-alveolar haemorrhage compared to infants with PH who were not treated with surfactant (Pappin 1994). In neonates treated with surfactant, moderate and severe PH is associated with an increased risk of death and short-term morbidity, but not with increased long-term morbidity (Pandit 1999).

Description of the intervention

Although surfactant therapy may be a contributing to factor leading to PH, PH has been effectively managed using surfactant instillation, including in those infants who have previously been treated with surfactant (Pandit 1995; Amizuka 2003; Finer 2004). It may seem counterintuitive that surfactant therapy should be suggested for treatment of this disorder (Wiswell 2001). However, haemoglobin, plasma proteins and cell membrane lipids (molecular components in haemorrhagic pulmonary oedema) can inactivate endogenous lung surfactant and adversely affect lung mechanics (Holm 1987). Exogenous surfactant replacement can reverse this process even in the continued presence of inhibitor molecules (Holm 1987) and thus has potential utility in the therapy of PH in preterm infants. Surfactant treatment has been suggested in the context of other lung aspirations such as meconium (Finer 2004; El Shahed 2007). In a Cochrane systematic review El Shahed et al (El Shahed 2007) identified four trials including 326 infants testing the effect of surfactant in infants with meconium aspiration syndrome. The authors concluded that: "In infants with meconium aspiration syndrome, surfactant administration may reduce the severity of respiratory illness and decrease the number of infants with progressive respiratory failure requiring support with ECMO [extracorporeal membrane oxygenation]. The relative efficacy of surfactant therapy compared to, or in conjunction with, other approaches to treatment including inhaled nitric oxide, liquid ventilation, surfactant lavage and high frequency ventilation remains to be tested".

How the intervention might work

In a retrospective case series of 15 neonates treated with surfactant following PH, Pandit et al (Pandit 1995) noted improvement in the oxygen index three to six hours following surfactant treatment. No infant deteriorated following surfactant treatment. The primary respiratory diagnosis was RDS in eight infants (all had received surfactant prior to the PH), meconium aspiration syndrome in three infants, and isolated PH in four infants. Amizuka et al (Amizuka 2003) treated 26 out of 27 neonates with haemorrhagic pulmonary oedema/PH occurring at 1.5 hours ± 0.1 hours (mean ± standard error of the mean (SEM)) after birth with surfactant. Treatment was at 3.0 hours ± 1.3 hours after the onset of PH. A good response to exogenous surfactant, defined as ventilatory index < 0.047 at one hour after surfactant administration, was seen in 82% of cases. Both Pandit et al (Pandit 1995) and Amizuka et al (Amizuka 2003) recommended further investigations, including randomised controlled trials to evaluate the effectiveness of surfactant for PH.

Why it is important to do this review

Based on case reports and case series it is suggested that surfactant has the potential to reduce mortality and morbidity from PH. No systematic review of randomised controlled trials has been conducted justifying this review according to Cochrane criteria.

Cochrane reviews that address trials of pulmonary surfactant in neonates

Meta-analyses of the original randomised controlled trials of surfactant for the treatment and prevention of RDS were first published in *Effective Care of the Newborn* (Sinclair 1992). Since

then, multiple systematic reviews have been published in *The Cochrane Library* including reviews of protein-free synthetic surfactant for the prevention and treatment of RDS (Soll 1998; Soll 2010 (updated 2011)) and reviews of animal-derived surfactant for the prevention and treatment of RDS (Soll 1997 (updated 2010); Seger 2009). Reviews that compare different surfactant preparations (Soll 2001; Pfister 2007; Pfister 2009; Singh 2011 (non-Cochrane review)) as well as different treatment strategies (Soll 1999; Stevens 2007; Soll 2009; Rojas-Reyes 2012) have been published.

Reviews have addressed the method of instillation of surfactant (Abdel-Latif 2010; Abdel-Latif 2011; Abdel-Latif 2011a) as well as the use of surfactant replacement therapy in conditions other than RDS (Dargaville 2002; El Shahed 2007; Tan 2012).

The previous published version of this review was last updated in 2008 (Aziz 2008).

OBJECTIVES

Primary objective

To evaluate the effect of surfactant on mortality in neonates with PH compared to placebo or no intervention.

Secondary objective

To evaluate the effect of surfactant on neonatal morbidities associated with PH compared to placebo or no intervention.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials that evaluated the effect of surfactant in the treatment of PH in neonates.

Types of participants

Preterm (< 37 weeks) or term (≥ 37 weeks) intubated infants with PH during initial hospitalisation after birth. Infants would be included up to 44 weeks' postmenstrual age (PMA). Infants would be included regardless of prior treatment with surfactant.

Types of interventions

Intratracheal instillation of surfactant (animal-derived or synthetic regardless of dose) versus placebo or no intervention. Conventional resuscitative measures could be used in both groups.

Types of outcome measures

Primary outcomes

1. All-cause mortality during initial hospital stay.
2. Mortality due to PH during initial hospitalisation.
3. All-cause mortality during the neonatal period.

Secondary outcomes

1. Bronchopulmonary dysplasia (BPD) at 28 days (supplemental oxygen at 28 days of age).
2. BPD at 36 weeks' PMA (supplemental oxygen at 36 weeks' PMA).
3. Retinopathy of prematurity (ROP) (any stage and stage > 3 or more).
4. Sepsis (clinical symptoms and signs of sepsis and bacteraemia).
5. Necrotising enterocolitis (NEC) (Bell's stage II or more).
6. Intraventricular haemorrhage (IVH) (all grades and grades III and IV).
7. Periventricular leukomalacia (PVL); cystic changes in the periventricular areas.
8. Length of hospital stay (days).
9. Duration of assisted ventilation (days).
10. Duration of oxygen requirement > 0.21 (days).
11. Pneumothorax (after PH has occurred).
12. Long-term outcomes assessed at any age beyond one year of age by a validated cognitive, motor, language or behavioural/school/social interaction/adaptation test.
13. Any side effects reported in the trials.

Search methods for identification of studies

Electronic searches

For this update *The Cochrane Library*, Issue 2, 2012; MEDLINE; EMBASE' CINAHL; Clinicaltrials.gov; Controlled-trials.com' proceedings (2000 to 2011) of the Annual Meetings of the Pediatric Academic Societies (Abstracts2View) and Web of Science were searched on 8 February 2012.

For the original review (Aziz 2008) the following databases were searched:

- the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 4, 2007),
- using the OVID interface: MEDLINE from 1966 and EMBASE from 1980 to time of full review (January 2008).

Surfactant search terms in EMBASE were the EMTREE terms 'lung surfactant' and 'surfactant', and in MEDLINE, the MeSH term 'pulmonary surfactants'. To ensure that all potentially relevant references would be retrieved, additional search terms were identified by looking at the 'Used For' sections of the scope notes of each EMTREE and MEDLINE term. All additional terms were then searched in both EMBASE and MEDLINE using the command '.mp,hw.' to designate the fields in which the search should be conducted. The resultant search sets were combined using the Boolean operator 'OR' to create a single set of results.

Alveolar haemorrhage search terms used in EMBASE were the EMTREE term 'lung haemorrhage' and additional terms identified by looking at the 'Used For' sections of the scope notes for the EMTREE term. The truncation symbol colon ":" was used to replace the last letter 'e' in each instance of the word haemorrhage or haemorrhage to account for variations in word endings. The additional terms identified for the EMBASE search, as well as the phrase 'lung haemorrhage' were used to search MEDLINE. In both databases, to ensure that all potentially relevant references were retrieved, the search command '.mp,hw.' was used to designate the fields in which the search for terms should be conducted. The resultant search sets were combined using Boolean operator 'OR' to create a single set of results. The set of surfactant terms were combined with the set of alveolar search terms using the Boolean operator 'AND'. This final set of results was not limited by age or language.

Science Citation Index (Web of Science) was searched for authors quoting the publications by Pandit et al (Pandit 1995; Pandit 1999).

We did not apply any language restrictions.

Searching other resources

We searched the proceedings of the Annual Meetings of the Pediatric Academic Societies and the European Society for Paediatric Research published in *Pediatric Research* or electronically on their websites from 1994 to time of the full review in January 2008.

Data collection and analysis

Selection of studies

We used the standard review methods of the Cochrane Neonatal Review Group.
All abstracts and published studies identified as potentially relevant by the literature search were assessed for inclusion in the review by the two review authors (AA, AO).

Data extraction and management

If studies were identified, each review author would extract data separately on a data abstraction form. The information would then be compared and differences would be resolved by consensus. One review author (AO) would enter data into RevMan 5.1 (RevMan 2011) and the other review author (AA) would cross check the printout against his own data abstraction forms and errors would be corrected. For the studies identified as an abstract, the primary study author would be contacted to obtain further information if needed.

The primary analysis would include infants with PH.

The two review authors would abstract data from the identified trials to pre-designed data-abstraction forms. One review author (AO) would enter the data into RevMan 5.1 (RevMan 2011) and the other review author (AA) would have checked for accuracy.

Assessment of risk of bias in included studies

The following headings and associated questions (based on the questions in the 'Risk of bias' table) would be evaluated by the two review authors and entered into the 'Risk of bias' table if we had identified at least one trial for inclusion.

- Selection bias (random sequence generation and allocation concealment).

Adequate sequence generation?

For each included study, we would categorise the risk of selection bias as:

Low risk - adequate (any truly random process, e.g. random number table; computer random number generator);
High risk - inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
Unclear risk - no or unclear information provided.

Allocation concealment?

For each included study, we would categorise the risk of bias regarding allocation concealment as:

Low risk - adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
High risk - inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
Unclear risk - no or unclear information provided.

Blinding?

- Performance bias

For each included study, we would categorise the methods used to blind study personnel from knowledge of which intervention a participant received. (As our study population consisted of neonates they would all be blinded to the study intervention.)

Low risk - adequate for personnel (a placebo that could not be distinguished from the active drug was used in the control group);
High risk - inadequate - personnel aware of group assignment;
Unclear risk - no or unclear information provided.

- Detection bias

For each included study, we would categorise the methods used to blind outcome assessors from knowledge of which intervention a participant received. (As our study population consisted of neonates they would all be blinded to the study intervention.) Blinding would be assessed separately for different outcomes or classes of outcomes. We would categorise the methods used with regards to detection bias as:

Low risk - adequate; follow-up was performed with assessors blinded to group;
High risk - inadequate; assessors at follow-up were aware of group assignment;
Unclear risk - no or unclear information provided.

Incomplete data addressed?

- Attrition bias

For each included study and for each outcome, we would describe the completeness of data including attrition and exclusions from the analysis. We would note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we would re-included missing data in the analyses. We would categorise the methods with respect to the risk of attrition bias as:

Low risk - adequate (< 10% missing data);
High risk - inadequate (> 10% missing data);
Unclear risk - no or unclear information provided.

Free of selective reporting?

- Reporting bias

For each included study, we would describe how we investigated the risk of selective outcome reporting bias and what we found. We would assess the methods as:

Low risk - adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

High risk - inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
Unclear risk - no or unclear information provided (the study protocol was not available).

Free of other bias?

- Other bias

For each included study, we would describe any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We would assess whether each study was free of other problems that could put it at risk of bias as:

Low risk - no concerns of other bias raised;
High risk - concerns raised about multiple looks at the data with the results made known to the investigators, difference in number of patients enrolled in abstract and final publications of the paper;
Unclear - concerns raised about potential sources of bias that could not be verified by contacting the authors.

- Overall risk of bias

We would make explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We would assess the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We would explore the impact of the level of bias through undertaking sensitivity analyses - see 'Sensitivity analysis'.

Measures of treatment effect

If studies were identified, the planned statistical methods would include risk ratio (RR), risk difference (RD), number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) for dichotomous outcomes, and mean difference (MD) for continuous outcomes, with their 95% CI. A fixed-effect model would be used for meta-analysis.

Unit of analysis issues

The unit of analysis would be the individual patient.

Dealing with missing data

If we had identified trials with missing data, we would approach the study authors to provide us with additional information.

Assessment of heterogeneity

Heterogeneity tests would be performed to assess the appropriateness of pooling the data. Results of the I^2 statistic would be reported.

Assessment of reporting biases

If at least 10 trials were included in one meta-analysis we would perform a funnel plot. If there was asymmetry, we would try and explain it based on study characteristics.

Data synthesis

We planned to perform statistical analyses according to the recommendations of the Cochrane Neonatal Review Group (neonatal.cochrane.org/en/index.html). We planned to analyse all infants randomised on an intention-to-treat basis. We planned to analyse treatment effects in the individual trials. We planned to use a fixed-effect model for meta-analysis in the first instance to combine the data. Where substantial heterogeneity existed, the potential cause of heterogeneity would be examined in subgroup and sensitivity analyses. When we judged meta-analysis to be inappropriate, we planned to analyse and interpret individual trials separately. For estimates of typical RR and RD, we would use the Mantel-Haenszel method. For measured quantities, we would use the inverse variance method.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses would be conducted for preterm and term infants and, within these subgroups, for infants who had received surfactant or not prior to PH. Subgroup analyses would be conducted based on birthweight ≤ 1500 g and > 1500 g and on gestational age < 37 weeks and ≥ 37 weeks at birth.

Sensitivity analysis

Sensitivity analyses would be conducted excluding information from abstracts.

RESULTS

Description of studies

No randomised or quasi-randomised controlled trials were identified through an extensive literature search conducted in July 2007 and February 2012. One review made no reference to any randomised controlled trials (Lacaze-Masmonteil 2007). All studies referred to in that review are included in the background of this review. One case report of an 11-week-old boy with severe unilateral PH after iatrogenic lung injury during corrective surgery for congenital heart defects was identified (Haas 2006). The study design and the age of the infant at the time of treatment prevented inclusion of the report in this review.

Risk of bias in included studies

As no studies were included methodological quality was not assessed.

Effects of interventions

No randomised or quasi-randomised studies were identified and included in the review. No results can be presented.

DISCUSSION

Summary of main results

No trials were identified for inclusion in this review.

Observational studies have shown promising results in physiological variables when surfactant has been used to treat PH. In a retrospective case series of 15 neonates treated with surfactant following PH, Pandit et al (Pandit 1995) noted improvement in the oxygen index following surfactant treatment. One infant died from infection and BPD and an additional four infants developed

BPD. Amizuka et al (Amizuka 2003) gave surfactant to 26 of a total of 27 neonates with PH occurring soon after birth. A good response to exogenous surfactant, defined as ventilatory index < 0.047 at one hour after surfactant administration, was seen in 82% of cases. No neonate died or developed BPD. These observations need to be confirmed in well-designed and conducted randomised controlled trials, which include the primary and secondary outcomes identified in this review. Until such trials have been conducted, no recommendations for clinical practice based on evidence from randomised clinical trials can be made.

It should be noted that in a Cochrane systematic review El Shahed et al (El Shahed 2007) identified four trials involving 326 infants that tested the effect of surfactant in infants with meconium aspiration syndrome. The authors concluded: "In infants with meconium aspiration syndrome, surfactant administration may reduce the severity of respiratory illness and decrease the number of infants with progressive respiratory failure requiring support with ECMO. The relative efficacy of surfactant therapy compared to, or in conjunction with, other approaches to treatment including inhaled nitric oxide, liquid ventilation, surfactant lavage and high frequency ventilation remains to be tested". Surfactant could potentially be an effective treatment of aspiration of a number of substances such as antenatal aspiration of meconium, blood, vernix and amniotic fluid or postnatal aspiration of blood.

AUTHORS' CONCLUSIONS

Implications for practice

No guidance for clinical practice based on evidence from randomised clinical trials can be provided at the present time.

Implications for research

The data available from retrospective and prospective uncontrolled studies that have shown a potential benefit of surfactant for PH justify the conduct of randomised controlled trials. Infants enrolled in such trials should be stratified by preterm/term status. The primary outcome should be all-cause mortality during initial hospital stay. Secondary outcomes should include those listed in this review.

ACKNOWLEDGEMENTS

We are grateful to Ms. Tamsin Adams-Webber, Librarian, The Hospital for Sick Children, Toronto, who assisted us with developing the search strategy for this protocol/review and conducted the search according to that strategy on 30 July 2007. Ms. Yolanda Montagne conducted the searches in February 2012.

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Lacaze-Masmonteil 2007	Review article

WHAT'S NEW

Date	Event	Description
27 January 2020	New citation required but conclusions have not changed	Contact author changed, and contact details updated.
27 January 2020	Amended	Arne Ohlsson deceased.

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 2, 2008

Date	Event	Description
15 March 2012	New citation required but conclusions have not changed	No new trials for inclusion or exclusion were identified. The conclusions did not change.
15 March 2012	New search has been performed	This updates the review "Surfactant for pulmonary hemorrhage in neonates" (Aziz 2008). Updated literature search was done on February 8, 2012.
9 January 2008	New citation required but conclusions have not changed	No new trials for inclusion or exclusion were identified. The conclusions were not changed.

CONTRIBUTIONS OF AUTHORS

Drs Aziz and Ohlsson contributed to all sections of the protocol. Dr Ohlsson wrote the full review.

Both review authors evaluated the literature searches conducted in February 2012 for any studies that met inclusion criteria.

Dr Ohlsson updated the review to the most current Cochrane format in 2012.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Mount Sinai Hospital, Canada.

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA.

  Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Premature; Hemorrhage [*drug therapy]; Lung Diseases [*drug therapy]; Pulmonary Surfactants [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn