Surfactant for pulmonary hemorrhage in neonates (Review)

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[Intervention Review]

Surfactant for pulmonary hemorrhage in neonates

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ABSTRACT

Background

In the late 1960's and 1970's, pulmonary hemorrhage (PH) occurred mainly in full term infants with severe pre-existing illness. The incidence of PH was quoted as 1.3 per 1,000 live births. In the older medical literature, the risk factors associated with PH included the severity of the associated illness, intrauterine growth restriction, patent ductus arteriosus (PDA), coagulopathy, and the need for assisted ventilation. Presently, PH occurs mainly in preterm ventilated infants with severe respiratory distress syndrome (RDS) who often have a PDA and have received surfactant. Currently, PH complicates the hospital course of 3-5% of preterm infants with RDS. Although not clear, the cause of PH is thought to be due to a rapid lowering of intrapulmonary pressure, which facilitates left to right shunting across a patent ductus arteriosus and an increase in pulmonary blood flow. Retrospective case reports and one prospective uncontrolled study that used surfactant for PH in neonates have shown promising results in treating PH.

Objectives

To evaluate the effect of surfactant treatment compared to placebo or no intervention on mortality in neonates with pulmonary hemorrhage. In addition, the review will evaluate the effect of surfactant treatment on neonatal morbidities associated with PH compared to placebo or no intervention.

Search methods

The following databases were searched in January 2008: The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2007) and MEDLINE from 1966 and EMBASE from 1980 to the time of the full review using the OVID interface. The proceedings of the Annual Meetings of the Pediatric Academic Societies and the European Society of Pediatric Research published in Pediatric Research or electronically on their web sites were searched from 1994 to the time of the full review. Science citation index (Web of Science) was searched for authors quoting key references of observational studies.

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. Infants were included regardless of prior treatment with surfactant. The interventions studied were intratracheal instillation of surfactant (natural or synthetic, regardless of dose) vs. placebo or no intervention.

Data collection and analysis

If studies were identified by the literature search, the planned analyses included calculation of the relative risk (RR), risk difference (RD), number needed to treat (NNT) or number needed to harm (NNH) for dichotomous outcomes, and weighed mean difference (WMD) for continuous outcomes, with their 95% confidence intervals (CI). A fixed effects model would be used for meta-analyses. Heterogeneity tests, including the I- squared (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 randomized or quasi-randomized 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 randomized controlled trial, there is reason to conduct further trials of surfactant for the treatment of PH in neonates.

PLAIN LANGUAGE SUMMARY

Surfactant for pulmonary hemorrhage in neonates

Bleeding into the lungs (pulmonary hemorrhage) 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 hemorrhage include prematurity, 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 hemorrhage 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 hemorrhage. However, no randomized controlled trials were identified in this review. Currently, no recommendation for clinical practice based on randomized controlled trials can be presented; further research is needed.

BACKGROUND

In the late 1960's and early 1970's, the incidence of pulmonary hemorrhage (PH) was quoted as 1.3 per 1,000 live births (Cole 1973). Currently, PH complicates the hospital course of 3% to 5% of preterm infants with respiratory distress syndrome (RDS) (Wiswell 2001). Pulmonary hemorrhage occurs mainly in preterm ventilated infants with severe respiratory distress syndrome (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 1970's, 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 hematocrit and protein composition. In most cases, the hemorrhagic effluent was edema 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).

Pulmonary hemorrhage 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 relative risk (RR) 1.47 (95% confidence interval 1.05, 2.07)] indicating an increased risk for PH with surfactant treatment (Raju 1993). In five multicenter, placebo-controlled trials of the syn-

thetic surfactant Exosurf Neonatal in infants weighing at least 700 grams, 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 2004a; Soll 2004b; Stevens 2004; Yost 2004). The RR for PH was statistically significantly increased with the use of prophylactic synthetic surfactant vs. control treatment (intratracheal administration of normal saline or air placebo) (typical RR 3.28; 95% CI 1.50, 7.16) (Soll 2004b) but not for treatment of established RDS vs. control (intratracheal administration of air placebo) (typical RR 1.44; 95% CI 0.68, 3.05) (Soll 2004a). In contrast to clinical diagnosis, the pathological diagnosis of PH at autopsy 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 patent ductus arteriosus (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 an autopsy study, infants treated with surfactant who developed PH were shown to have more extensive intra-alveolar hemorrhage 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).

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 (Finer 2004, Pandit 1995, Amizuka 2003). It may seem counterintuitive that surfactant therapy should be suggested for treatment of this disorder (Wiswell 2001). However, hemoglobin, plasma proteins and cell membrane lipids (molecular components in hemorrhagic pulmonary edema) 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. 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".

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 hemorrhagic pulmonary edema/PH occurring at 1.5 +/- 0.1 hours (mean +/- SEM) after birth with surfactant. Treatment was at 3.0 +/- 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 randomized controlled trials to evaluate the effectiveness of surfactant for PH.

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 hospitalization after birth. Infants would be included up to 44 weeks postmenstrual age. Infants would be included regardless of prior treatment with surfactant.

Types of interventions

Intratracheal instillation of surfactant (animal derived or synthetic regardless of dose) vs. 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

(1) Mortality due to PH during initial hospitalization.

(2) All cause mortality during the neonatal period.

SECONDARY OUTCOMES:

(3) Bronchopulmonary dysplasia (BPD) at 28 days (supplemental oxygen at 28 days of age).

(4) Bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age (supplemental oxygen at 36 weeks postmenstrual age).

(5) Retinopathy of prematurity (ROP) (any stage and stage > 3 or more).

(6) Sepsis (clinical symptoms and signs of sepsis and bacteremia).

(7) Necrotizing enterocolitis (NEC) (Bell's stage II or more).

(8) Intraventricular haemorrhage (IVH); all grades and grades III and IV.

(9) Periventricular leukomalacia (PVL); cystic changes in the periventricular areas.

(10) Length of hospital stay (days).

(11) Duration of assisted ventilation (days).

(12) Duration of oxygen requirement > 0.21 (days).

(13) Pneumothorax (after PH has occurred).

(14) 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.

(15) Any side effects reported in the trials.

Search methods for identification of studies

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 hemorrhage search terms used in EMBASE were the EMTREE term 'lung hemorrhage' 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 hemorrhage or haemorrhage to account for variations in word endings. The additional terms identified for the EMBASE search, as well as the phrase 'lung hemorrhage' 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.

The proceedings of the Annual Meetings of the Pediatric Academic Societies and the European Society of Pediatric Research published in Pediatric Research or electronically on their web sites were searched from 1994 to time of the full review. Science citation index (Web of Science) was searched for authors quoting the publications by Pandit et al (Pandit 1995, Pandit 1999).

No language restrictions were applied.

Data collection and analysis

The standard review methods of the Cochrane Neonatal Review Group were used.

All abstracts and published studies identified as potentially relevant by the literature search were assessed for the inclusion in the review by one review author (AO). 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 and the other (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 author would be contacted to obtain further information if needed. The quality of included trials would be evaluated independently by the review authors, using the following criteria:

Blinding of randomisation

Blinding of intervention

Blinding of outcome measure assessment

Completeness of follow up

There are three potential answers to these questions: yes, no, cannot tell

If studies were identified, the planned statistical methods would include relative risk (RR), risk difference (RD), number needed to treat (NNT) or number needed to harm (NNH) for dichotomous outcomes, and weighed mean difference (WMD) for continuous outcomes, with their 95% confidence intervals (CI). A fixed effects model would be used for meta-analysis.

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

The primary analysis would include infants with PH. 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 $\leq$ 1500 g and > 1500 g and on gestational age < 37 weeks and $\geq$ 37 weeks at birth.

Secondary analyses would be conducted excluding information from abstracts.

RESULTS

Description of studies

See: Characteristics of excluded studies.

No randomized or quasi-randomized controlled trials were identified through an extensive literature search conducted in July 2007. A recent review made no reference to any randomized controlled trial (Lacaze-Masmonteil 07). All studies referred to in that review are included in the background of this review. One case report of an 11 weeks old boy with severe unilateral PH after iatrogenic lung injury during corrective surgery for congential 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 randomized or quasi-randomized studies were identified and included in the review. No results can be presented.

DISCUSSION

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 randomized 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 randomized 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 July 30, 2007.

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Wiswell 2001

Wiswell TE. Expanded uses of surfactant therapy. *Clinics in Perinatology* 2001;**28**:695–711.

Yost 2004

Yost CC, Soll RF. Early versus delayed surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2004, Issue 3.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Lacaze-Masmonteil 07	Review article

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 22 January 2008.

Date	Event	Description
9 January 2008	Amended	Converted to new review format

HISTORY

Protocol first published: Issue 2, 2005

Review first published: Issue 2, 2008

CONTRIBUTIONS OF AUTHORS

Drs Aziz and Ohlsson contributed to all sections of the protocol.

Dr Ohlsson wrote the full review.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Mount Sinai Hospital, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Hemorrhage [*drug therapy]; Infant, Newborn; Infant, Premature; Lung Diseases [*drug therapy]; Pulmonary Surfactants [*therapeutic use]

MeSH check words

Humans