Role of hemocoagulase in pulmonary hemorrhage in preterm infants: a systematic review

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CRD summary
The review concluded that use of haemocoagulase may reduce the duration of pulmonary haemorrhage in premature infants and reduce mortality but further research was needed. The authors' cautious conclusions reflect the limited evidence base available and may be regarded as reliable.

Authors' objectives
To investigate the clinical efficacy and safety of haemocoagulase therapy in preterm infants with pulmonary haemorrhage.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL and EMBASE were searched up to September 2009 with no language restrictions. Relevant conference proceedings papers (Paediatric Academy Societies, Canadian Paediatric Society) were searched from 1990 to July 2009. Reference lists of retrieved articles were examined. Experts in the field were contacted. Search terms were reported.

Study selection
Observational and randomised controlled trials (RCTs) that compared haemocoagulase therapy with a placebo or with no intervention in preterm infants (less than 37 weeks gestation and less than one month of age) admitted to a neonatal intensive care unit (NICU) were eligible for inclusion. Diagnosis of pulmonary haemorrhage was based on persistence of sanguineous endotracheal tube aspirate and presence of other features including "fluffy" appearance on chest radiograph and a clinical picture of respiratory distress. Primary outcomes of interest were mortality (including infants who died after discharge from NICU), duration of pulmonary haemorrhage and duration of mechanical ventilation.

Haemocoagulase therapy was used as a therapeutic agent in one trial and for prophylaxis in another trial. Included studies were conducted in China. Control groups used routine mechanical ventilation with increased positive end expiratory pressure. The intervention groups used 0.5KU dose of haemocoagulase administered into an endotracheal tube each time and repeated every four to six hours until pulmonary haemorrhage stopped. Mean gestational age ranged from 30.5 to 31.5 weeks. Mean birth weight ranged from 1,380g to 1,490g.

Two researchers independently screened studies for eligibility.

Assessment of study quality
Two reviewers independently evaluated study quality using van Tulder criteria and Cochrane Neonatal Review Group method. The van Tulder scale included 11 items to assess potential for selection, performance, attrition and detection biases. Trials that scored 6 or more were considered high quality trials.

Data extraction
Data were extracted to calculated relative risks (RR) and weighted mean differences (WMD) and their 95% confidence intervals (CI). Two reviewers independently extracted data using the standardised Neonatal Cochrane group data abstraction forms. Any disagreements were resolved by consensus or involvement of a third reviewer.

Methods of synthesis
A fixed-effect model (where there was no evidence of heterogeneity) was used to calculate relative risk, number needed to treat (NNT), weighted mean difference (WMD) and their 95% confidence intervals (CI). Heterogeneity was assessed using X² test and p-values (p<0.05 was considered evidence of heterogeneity). Funnel plots were considered but not presented due to the small number of studies under analysis.

Results of the review
Two RCTs were included in the review (120 infants). The authors could not combine results from both studies for
analysis because one trial (48 infants) used haemocoagulase as an active treatment and the other (72 infants) focused on haemocoagulase as a prophylactic treatment. The included studies were poor quality due to unclear randomisation, allocation concealment, blinding and outcome measure.

**Active treatment:** The trial reported that preterm infants in the haemocoagulase therapy group had a 48% reduction in mortality compared to the control group (RR 0.52, 95% CI 0.31 to 0.89). The absolute risk reduction for mortality was 35.7%. Three preterm infants would need to be treated with haemocoagulase to save one life. Compared to the control group, results showed shorter duration of pulmonary haemorrhage (WMD -1.74, 95% CI -2.22 to -1.26) and a shorter period required for ventilation (WMD -1.55, 95% CI -2.07 to -1.03) with haemocoagulase therapy.

**Prophylaxis:** No statistically significant difference of mortality was found between haemocoagulase and control groups. Analyses showed that infants in haemocoagulase had a shorter duration of pulmonary haemorrhage (WMD -2.22, 95% CI -2.57 to -1.87) and shorter period required for ventilation (WMD -1.84, 95% CI -2.39 to -1.29) compared to the control group.

There were no significant differences between haemocoagulase and controls in both trials for incidence of respiratory distress syndrome, perinatal asphyxia, intracranial haemorrhage, patent ductus arteriosus, bronchopulmonary dysplasia, pneumonia, sepsis and the number of infants who received surfactant.

**Authors’ conclusions**
This systematic review indicated that use of haemocoagulase may reduce the duration of pulmonary haemorrhage in premature infants and reduce mortality. But the role of haemocoagulase in pulmonary haemorrhage needed further evaluation before routine use could be recommended.

**CRD commentary**
The review addressed a clear question and was supported by appropriate inclusion criteria. Relevant sources were searched and no language restrictions were applied to the search, which minimised risks of publication and language biases. Attempts were made to minimise reviewer errors and bias in the review process. A relevant quality assessment tool was applied; it appeared that the quality of the trials was low. Data were appropriately presented in narrative synthesis due to differences in use of the treatment.

The review authors identified methodological weaknesses in the evidence base and drew appropriately cautious conclusions that included calling for further research. The conclusions may be regarded as reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that the role of haemocoagulase in pulmonary haemorrhage needed further evaluation before routine use could be recommended.

**Research:** The authors stated a need for well-planned multicentred randomised controlled trials.

**Funding**
Not stated.

**Bibliographic details**

**PubMedID**
21210254

**DOI**
10.1007/s12098-010-0326-4

**Original Paper URL**
http://www.springerlink.com/content/d34686p3483g8213/
Indexing Status
Subject indexing assigned by NLM

MeSH
Batroxobin /therapeutic use; Hemorrhage /drug therapy /mortality; Hemostatics /therapeutic use; Humans; Infant, Newborn; Infant, Premature; Infant, Premature, Diseases /drug therapy /mortality; Lung Diseases /drug therapy /mortality; Respiration, Artificial /statistics & numerical data; Treatment Outcome

AccessionNumber
12011005094

Date bibliographic record published
20/10/2011

Date abstract record published
14/05/2013

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.