Pulmonary haemorrhage in neonates: Systematic review of management

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Abstract

Aim: Pulmonary haemorrhage (PH) is an acute catastrophic event with low incidence yet high mortality among neonates. We aimed to systematically review the management of PH.

Methods: A search was carried out of the PubMed, EMBASE and Cochrane databases according to the PRISMA guidelines. Data were extracted on study design and size, patient demographics, primary and adjunctive treatment methods, and treatment outcomes.

Results: Sixteen studies with 385 newborn infants were included and were significantly heterogeneous regarding treatment methods. Primary treatments included surfactant, high-frequency oscillatory ventilation (HFOV), epinephrine, coagulopathy management, intermittent positive pressure ventilation, cocaine and tolazoline. Adjunctive treatment methods included blood products, HFOV, increased positive end-expiratory pressure, vitamin K, surfactant, adrenaline, vaspressors and inotropes. All five studies using surfactant as primary treatment were effective in improving oxygenation index measures and preventing recurrence of PH, and three studies found no association between surfactant and death or long-term disability. Ventilatory support, epinephrine, management of coagulopathy and tolazoline were all found to be effective primary treatments for PH.

Conclusion: There are several effective methods of managing PH in neonates. Further understanding of the aetiology of PH and ongoing research will allow future prevention and improvements in management of PH.

KEYWORDS
adrenaline, newborn, pulmonary haemorrhage, surfactant

Abbreviations: CMV, conventional mechanical ventilation; ETT, endotracheal tube; FFP, fresh-frozen plasma; HFOV, high-frequency oscillatory ventilation; IPPV, intermittent positive pressure ventilation; MAP, mean arterial pressure; NICU, neonatal intensive care unit; OI, oxygenation index; PDA, patent ductus arteriosus; PEEP, positive end-expiratory pressure; PH, pulmonary haemorrhage; RCT, randomised control trial; RDS, respiratory distress syndrome; VLBW, very low birthweight.

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INTRODUCTION

Pulmonary haemorrhage (PH) can be defined as an acute, catastrophic event which is characterised by discharge of bloody fluid from the upper respiratory tract or the endotracheal tube. The incidence of PH is 1 to 12 per 1,000 live births with PH occurring most commonly within the first few days of life. The most common risk factor associated with PH is prematurity. PH is typically be seen in babies weighing less than 1500g, who often have a patent ductus arteriosus (PDA), have been treated with surfactant and are ventilated. Other risk factors predisposing to PH include intrauterine growth restriction, chorioamnionitis, coagulopathy and respiratory disorders. The typical presentation of the infant with PH is in an extreme premature infant with sudden onset of frothy, pink-tinged secretions or frank bleeding from the endotracheal tube, often requiring increased ventilatory support. If the PH continues, the infant can develop apnoea, generalised pallor, become cyanotic, with concomitant bradycardia and hypotension from hypovolaemic shock. Mortality rates as high as 50% have been reported in extremely premature neonates and there is currently no curative treatment that exists for PH in neonates, although numerous studies have identified treatments that have been shown to increase survival rates. We aimed to synthesise the available evidence on the management of PH.

METHODS

PubMed, EMBASE and Cochrane databases were used to search for relevant articles using the search criteria: ("pulmonary haemorrhage" OR "pulmonary hemorrhage" OR "pulmonary bleeding" OR "pulmonary bleed" OR "lung bleed" OR "lung haemorrhage" OR "lung hemorrhage") AND ("neonate" OR "neonates" OR "newborn infant" OR "newborn" OR "newborns" OR "new born" OR "newborn baby" OR "newborn infants"). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were used to extract data on study design, primary and adjunctive treatment methods and outcomes of treatment. Inclusion criteria included original studies of a neonate population that investigated the effect in the management of pulmonary haemorrhage. A total of 1044 records were identified PubMed (556), EMBASE (456) and Cochrane Database of Systematic Review (12), ranging from the years 1975 to 2020. Titles and abstracts were reviewed, and non-relevant records were excluded if they were not related to the management of PH in neonates. This was performed by two independent reviewers to minimise biases and human error. Animal studies, in vitro studies, studies based on a non-neonate population and studies not published in the English language were also excluded. Full-text analysis was performed on the remaining papers by the same two independent reviewers, and data were extracted from 16 final relevant articles as shown in the PRISMA flow diagram (Figure 1). This systematic review includes a variety of study designs, with levels of evidence ranging from 1b to 4 as per the Oxford Centre for Evidence Based Medicine levels of evidence table.

RESULTS

3.1 Study selection

A total of 1044 studies were obtained from searching the databases PubMed, Cochrane and EMBASE, of which 72 duplicates were identified and removed. Screening of the studies involved exclusion of 774 studies by title and a further 123 by abstract review. The remaining 75 full-text articles were then assessed for eligibility and a further 59 articles were excluded. Sixteen studies remained for final analysis.

3.2 Study characteristics

Four of the sixteen studies identified were published later than 2010. A total of 385 patients were included in this systematic review. The studies were conducted across eleven different countries (USA, UK, Turkey, Taiwan, India, Japan, Canada, Croatia, China, Korea, Norway). Sample sizes ranged from 1 to 97 participants. One Cochrane review examining the effect of surfactant in PH in neonates was identified; however, no randomised or quasi-randomised trials were identified in this study.

3.3 Treatment methods

The treatments for PH were examined under the following outcomes: cessation of PH, improvement of oxygenation index (OI), recurrence of PH, mortality and long-term disability. Adjunctive treatments were also commonly used prior to, concurrent with, or following the primary treatment, although many studies did not evaluate the effectiveness of these methods in controlling PH. Routine intensive care centred on maintenance of airway,
breathing and circulation was discussed in most studies identified, including mechanical ventilation,6–10 suctioning of the endotracheal tube,10–12 fluid therapy,8,9 nutritional support,12 analgesic and sedative drugs.11

3.3.1 Surfactant

In five studies in which surfactant is the primary treatment,8–10,12,13 found it to be effective, both in inducing cessation of PH and improving OI measures. A prospective RCT8 in which VLBW infants in the neonatal intensive care unit (NICU) were randomised to either receive one of two natural surfactants (poractant alfa and beractant; n = 21 each group) found both were equally effective in improving oxygenation and ventilatory indexes following PH. Endotracheal tube (ETT) adrenaline was used as an adjunctive therapy to primary surfactant therapy in this study,8 to all participants. There was a mortality rate of 23 neonates within 72 h of the occurrence of PH and 5 of the 13 surviving infants developed chronic lung disease. However, due to the size of the study groups, no statistically significant conclusions were drawn regarding the mortality or long-term morbidity rate. There was an association between PH and the development of chronic lung disease potentially related to prolonged mechanical ventilation14 but the type of surfactant had no effect on mortality rates or long-term disability.8

A retrospective case series from Amizuka et al.9 found that 21 of 26 neonates treated with single-dose surfactant 3.0 ± 1.3 h after the onset of haemorrhagic pulmonary oedema showed a good response at 1 h following administration. There were no reported deaths or instances of long-term disability in neonates treated with surfactant therapy, although it was unclear at what interval this was recorded.9 Similarly, a retrospective case series by Pandit et al.13 found that all fifteen infants treated with surfactant had an improved ventilatory index and arterial/alveolar ratio.13 Only one death was reported and associated with Staphylococcus aureus sepsicaemia and chronic lung disease. Four of the nine surviving infants in this series subsequently developed chronic lung disease.13

One case report by Neumayr et al.10 reported improved OI within 2 and 5 h of surfactant administration, as well as improved lung compliance and oxygen (O2) saturation. Another case report by Omansky et al. found that two doses of surfactant with adjunctive supports were successful in treating PH.12 Neither of the two case reports10,12 detailed death or long-term disability in the patient cases described. Recurrence of PH did not occur in any of the five studies that used surfactant as the primary treatment method.8–10,12,13

Furthermore, a retrospective cohort study by Yen et al. suggested that surfactant was beneficial in treatment of severe PH. A statistically significant improvement in alveolar-arterial oxygen difference and OI in the 2- to 4-h period post-administration was observed, compared with the group who did not receive surfactant.15
3.3.2 | Ventilation

High-frequency oscillatory ventilation (HFOV)\textsuperscript{16–18} and intermittent positive pressure ventilation (IPPV)\textsuperscript{11} were commonly used as primary treatment methods. Ventilatory support was also used as supportive treatment in five studies, with methods including HFOV (n = 3 studies)\textsuperscript{9,13,19} and increasing MAP by increasing PEEP (n = 3 studies).\textsuperscript{12,13,19} All three studies that used HFOV as primary treatment found it to be effective in treating PH.\textsuperscript{16,17,20} The survival rates with HFOV treatment ranged from 100% (6/6) in the case-control study by Pappas et al.,\textsuperscript{18} 72% (13/18) in the case series by Ko et al.,\textsuperscript{17} to 59% (57/97) in the prospective observational study by Podduttoo et al.\textsuperscript{16} The case series by Ko et al.\textsuperscript{17} also noted that the OI showed rapid and significant improvement following one hour of HFOV use, and subsequent continued improvement in those infants who responded.

In a retrospective cohort study by Yen et al.,\textsuperscript{15} there was a significant decrease in OI and alveolar-arterial gradient during HFOV, following persistent hypoxia or respiratory acidosis during conventional mechanical ventilation (CMV). HFOV was administered to four of nineteen neonates by Bozdag et al. in the RCT of poractant alfa or beractant,\textsuperscript{8} in addition to adjunctive ETT adrenaline therapy. Amizuka et al.\textsuperscript{7} included three neonates who received HFOV before administration of surfactant as the primary treatment method, compared to the remaining twenty-four infants who received CMV. Neither of these studies evaluated the effectiveness of this intervention. However, Podduttoo et al.\textsuperscript{16} concluded that HFOV was a safe and effective adjunctive rescue treatment for neonates with PH and other types of respiratory distress following the failure of CMV.\textsuperscript{16}

Trompeter et al.\textsuperscript{11} concluded that elective IPPV was successful in rapidly controlling PH, in combination with other interventions to correct acidosis and provide adequate oxygenation.\textsuperscript{11} Of the six infants studied, two had already experienced fatal irreversible respiratory failure and were not successfully resuscitated; however, their PH was controlled by IPPV. Three studies\textsuperscript{12,13,19} also focused on increasing PEEP to increase MAP. A retrospective case series by Bhandari et al.\textsuperscript{19} used increased PEEP (increase of 1.7 ± 0.5 cm H\textsubscript{2}O, p < 0.003 for pressure alone; increase of 1.6 ± 0.3 cm H\textsubscript{2}O, p < 0.003 for pressure with epinephrine ± cocaine) as conventional adjunctive therapy as well as the epinephrine and cocaine which were being measured for effectiveness. One of these studies, a case report by Omansky et al.,\textsuperscript{13} noted an improvement in venous blood gas measures of oxygenation following the infant receiving adjunctive PEEP ventilation therapy.

3.3.3 | Adrenaline

ETT adrenaline was the primary treatment method in three studies,\textsuperscript{15,19,21} to utilise its effects of vasoconstriction and increased cardiac output for resuscitation and cessation of PH.\textsuperscript{20} In one retrospective cohort study by Yen et al. (n = 18),\textsuperscript{15} PH was stopped in the majority of neonates following administration of 3–5 doses of 0.5 mL ETT adrenaline (1:10000). This method was not only effective in treating PH, but also avoided the unnecessary use of endotracheal suction. None of the eighteen patients involved in this study died within 24 h of severe PH following adjunctive HFOV therapy and adjunctive ETT adrenaline.\textsuperscript{15}

Bhandari et al. in a retrospective case series (n = 42)\textsuperscript{15} compared adrenaline and cocaine, both alone and in combination, as primary treatments in addition to mechanical. Although the number of neonates in each treatment category was inadequate for appropriate statistical analysis, there was no significant change in survival of the acute episode of PH in neonates whether they were managed with increases in MAP alone or combined with the drugs adrenaline or cocaine.\textsuperscript{19} A case-control study\textsuperscript{21} including 58 neonates administered adrenaline via endotracheal tube (n = 32) or intravenously (n = 8) to treat respiratory distress syndrome (RDS) complicated by PH. Among the infants who survived (n = 29), respiratory status was found to gradually improve after initial therapy; however, treatment-specific survival is not reported in this study.\textsuperscript{21} ETT adrenaline was used as an adjunct to surfactant and HFOV therapy in the RCT by Bozdag et al.,\textsuperscript{8} with all 42 newborns receiving adrenaline. The impact of adrenaline on neonatal outcomes was not reported in this study.\textsuperscript{8}

3.3.4 | Tolazoline

Tolazoline, a nonselective alpha-adrenergic antagonist and vasodilator, used previously in cases of respiratory distress syndrome, meconium aspiration and intrauterine pneumonia that were unresponsive to general supportive treatment. Tolazoline was used in one case report\textsuperscript{7} on a term newborn with neonatal encephalopathy and PH. Following sustained decrease in Hb, hypotension and hypoxia refractory to blood transfusion, intubation and CMV, the infant was given a 6mg bolus of tolazoline and subsequent intravenous infusion. Within 3 min of initiation of infusion, transcutaneous O\textsubscript{2} readings improved and ventilatory support was discontinued 16 h later and the neonate survived without evidence of long-term disability.

3.3.5 | Coagulopathy

Coagulopathy is commonly described in conjunction with PH.\textsuperscript{1} Vitamin K was administered in a prospective RCT\textsuperscript{8} (n = 42) and a retrospective case series\textsuperscript{9} (n = 27) in combination with vasopressors to all neonates studied, although the rationale for this was not described. Neither study evaluated the effectiveness of administration of vitamin K or the vasopressor in inducing cessation of PH or achieving favourable outcomes.

Blood products were also commonly used adjunctive therapies, seen in five studies,\textsuperscript{7,9,11,12,15} including transfusion of fresh-frozen plasma, whole blood, red blood cells and platelets. A retrospective case series by Yen et al.\textsuperscript{15} notes without further discussion that blood component therapy was administered to the affected
neonates if coagulopathy or thrombocytopenia was identified; these terms were not defined in the study. Another retrospective case series by Trompeter et al.\(^4\) reported that six infants (two term, four preterm) received fresh blood transfusion for correction of anaemia following observation of a marked decrease in haematocrit after PH. Coagulation studies were carried out on three of the six infants, and disseminated intravascular coagulation was found in two. A third retrospective case series\(^9\) mentioned that one of the 27 infants involved in the study received packed red blood cell transfusions; however, no further detail was provided. Omansky et al. reported a case of a term infant,\(^12\) suffering PH secondary to RDS, requiring fresh-frozen plasma and dopamine to maintain normal blood pressure. On admission, coagulation studies indicated coagulopathy (prothrombin time of 15.4 seconds and partial thromboplastin time of 32.8 s). Both measures continued to increase until DOL 2 (PT of 16.2 seconds and PTT of 45.6 s) despite administration of a second dose of FFP and continued dopamine infusion. However, the blood present in the ETT began to subside, no further coagulation blood results are reported.

Recombinant FVIIa has been used in a case study by Grizelj et al.\(^20\) with cessation of PH and return to normal haemostasis was achieved in all four infants. rFVIIa increases thrombin activity in a dose-dependent fashion, thus leading to formation of a fibrin clot. However, data from other studies\(^6\) showed that rFVIIa is effective in the cessation of PH in reducing mortality and improving the oxygenation index associated with PH in all six of the studies where it was used. This is in keeping with a retrospective case series which reported no cases of death or long-term disability in neonates treated with surfactant therapy to manage PH.\(^5\) Surfactant administration has a role in PH management, with the low mortality rate and OI improvements demonstrating its importance but more RCTs are needed to support this. One Cochrane review examining the effect of surfactant in PH in neonates was identified; however, no relevant studies were identified in this review\[SO4\].\(^3\)

HFOV is an effective management in treating PH and in improving OI, with a significant decrease in OI seen 1 h post-HFOV in one study,\(^11\) and decreased alveolar-arterial gradient in two studies.\(^11,15\) These effects may be attributed to an increase in MAP,\(^17\) but more evidence is required to identify the exact aetiology of these improvements.

Adjunctive treatments were used in the management of airway, breathing and circulation in NICU babies. They included mechanical ventilation,\(^6\)–\(^10\) suctioning of the ETT,\(^10\)–\(^12\) fluid therapy,\(^8,9\) nutritional support,\(^11\) analgesia and the administration of sedative drugs.\(^11\) Individualised care based on symptoms was evident in all studies.\(^6\)–\(^12\) Other adjunctive therapies include blood products,\(^8,9,13,18,20\) vitamin K,\(^10,13,21\) vasopressors,\(^10,13\) infusion of inotropic drugs including dopamine and digoxin,\(^9,18\) surfactant\(^20\) and ETT epinephrine.\(^10\)

Vitamin K was used in combination with vasopressors in one prospective RCT\(^8\) and one retrospective case study\(^9\) as coagulopathy is commonly described in conjunction with PH. However, neither proved effective in the cessation of PH. The use of recombinant activated factor VII (rFVIIa) to reverse haemorrhagic shock in neonates has also been studied.\(^20\) This case study (n=4) yielded positive results with regard to PH cessation and return to normal haemostasis as rFVIIa increases thrombin activity in a dose-dependent fashion, thus leading to formation of a fibrin clot. However, data from the patients suggest that in a fibrinolytic environment, therapeutic concentrations of rFVIIa may produce insufficient thrombin to facilitate an adequate clot structure and clot stability, resulting in
**TABLE 1** Systematic review table

| Citation               | Study type* | Study group | Key Result                                                                                                                                  | Outcomes                                                                                               | Comments                                      |
|------------------------|-------------|-------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Aziz et al. 2020 USA¹   | Cochrane Systematic Review | 368         | Three observational studies used surfactant therapy as primary treatment strategy                                                          | Observational studies had promising results in physiological variables when surfactant has been used to treat PH | No RCTs identified                            |
| Omansky et al. 2019 USA¹² | Case report Level 4 | 1           | Patient improved and stabilised                                                                                                                | PEEP, surfactant, haemocoagulase interventions were successful and patient discharged on DOL 10       | Small sample size                            |
| Bozdağ et al. 2015 Turkey¹³ | Prospective RCT Level 1b | 42          | Short-term improvement in oxygenation and ventilation was recorded following natural surfactant administration                                 | Exogenous natural surfactants may be used for adjunctive therapy in VLBW infants with pulmonary haemorrhage | Type of surfactant used had no effect on mortality rate No control groups Did not control specifically for severity of illness |
| Yen et al. 2013 Taiwan¹⁴ | Retrospective cohort study Level 2b | 18          | No patient deaths within 24 hours of severe PH using HFOV therapy                                                                             | Active PH stopped after 3–5 instances of epinephrine in the majority of cases                          | Small sample size                            |
| Poddutoor et al. 2011 India¹⁵ | Prospective observational study (cohort study) Level 2b | 97          | 53.33% survival (n = 15) with HFOV                                                                                                           | HFOV safe and effective rescue technique in the treatment of neonates with respiratory failure in whom CMV fails | No control group                             |
| Neumayr et al. 2008 USA (10) | Case Report Level 2b | 1           | OI improved within 2 and 5 hours of surfactant administration                                                                                | Lung compliance improved markedly, and arterial blood gas (O2 saturation) improved No further bleeding occurred | Report is anecdotal in nature                 |
| Grizelj et al. 2006 Croatia¹⁶ | Case study Level 4 | 4           | In 3 patients, the first bolus of rFVIIa completely and immediately stopped the bleeding                                                     | Despite achieving clinically successful haemostasis, fibrinogen levels remained low in all patients with a slightly prolonged prothrombin time | Small sample size No side effects reported using this therapy                                   |
| Shi et al. 2005 China¹⁷  | Case-control Level 3b | 48          | Endotracheal haemocoagulase administered to all 48 patients                                                                                  | Haemocoagulase in addition to mechanical ventilation is effective in newborn infants with pulmonary haemorrhage | Variable between the experimental and control group may contribute to outcomes measured          |
| Amizuka et al. 2003 Japan⁹  | Retrospective case series Level 4 | 27          | Surfactant administration: 26 received a single dose of surfactant at 3.0 ± 1.3h after HPE onset                                               | HPE did not recur after surfactant treatment in any neonate Administration of exogenous surfactant was a useful adjunctive therapy for overcoming inhibitory activity against surfactant | No neonate died or developed chronic lung disease Exogenous surfactant appears to be a useful adjunctive therapy in neonates with HPE |
| Bhandari et al. 1999 USA¹⁰   | Retrospective case series Level 4 | 42          | 12 patients with early gestation PH survived (35%) 6 patients with late gestation PH (>35 weeks) survived (75%)                             | No difference in survival of neonates whether they were managed with MAP/drugs                           | Small sample size The late gestation pulmonary haemorrhage group had much better survival rates independent of treatment |
| Citation               | Study type*          | Study group | Key Result                                      | Outcomes                                                                                                           | Comments                                                                                                          |
|------------------------|----------------------|-------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Tomaszewski et al. 1999| Retrospective case-control study | 58          | Mortality is high (50%)                         | Although mortality is high, PH does not significantly increase the risk of later pulmonary or neurodevelopmental disabilities among those who survive | Small population size Increased risk of neonatal seizures and periventricular leukomalacia |
| Ko et al. 1998 Korea   | Retrospective case series Level 4 | 18          | Survival rate of 72% (13/18)                    | Use of HFOV was both an efficacious and safe method of treating PH                                                  | Small sample size No controls |
| Pappas et al. 1996 USA  | Case-control Study   | 6           | 5/6 infants had improved oxygen index within 6 hours of institution of HFV. | HFV is highly efficacious and safe, rapidly improving gas exchange in this group of infants, rapidly reversing the severe oxygenation and ventilation deficits | Small sample size Patients received CMV prior to the institution of HFV because of persistence of severe respiratory failure |
| Pandit et al. 1995 Canada | Retrospective case series Level 4 | 15          | Increase in FIO2, ventilatory rate, PIP, and PEEP Bovine lipid extract surfactant 14 received a single dose of surfactant following the PH, while 1 patient received two doses No patient deteriorated; none had a recurrence of PH. 1 patient died from Staphylococcus aureus septicemia and BPD 4 had chronic lung disease. | Mean oxygenation index improved post surfactant. All patients improved in their ventilatory status initially. | Small sample size Lack of comparable control group |
| Markestad et al. 1980 Norway | Case Report Level 4 | 1           | Ventilatory support discontinued 16 hrs later after significant improvement | IV Tolazoline (Priscoline); blood transfusion; Bourns infant pressure ventilator in 100% oxygen Significant improvement with interventions used Survival of the neonate without any evidence of permanent damage | Dangerous but a therapeutic trial is justified in the desperately ill child where all other measures have failed |
| Trompeter et al. 1975 England | Retrospective case series Level 4 | 6           | 4/6 survived                                      | Massive PH treated by elective IPPV in combination with vigorous correction of pH, anaemia, and hypovolaemia, by IV alkali and blood transfusion | Small sample size No control |

*Level of evidence from the Oxford CEBM.
continued haemorrhage. Thrombocytopenia prevents complete thrombin generation leading to the formation of a fibrin plug with increased porosity and permeability. Additionally, the structure of the fibrin plug is dependent on both thrombin concentration and on the rate of thrombin formation. Despite these concerns, no adverse effects were reported in this study. Following repeated red blood cell transfusions, a reduction in the concentration of platelets, vitamin K-dependent coagulation proteins, and fibrinogen has been observed.

According to the British Society of Haematology guidelines in preterm infants, the haemoglobin (Hb) should be maintained above 120g/l if requiring ventilatory support or actively bleeding. Platelets should be maintained above 50 if actively bleeding and fresh-frozen plasma (FFP) may be beneficial in clinically significant bleeding or in neonates with an abnormal coagulation profile, defined as a PT or APTT significantly above the normal gestational and postnatal age-related reference range. An additional dose of vitamin K can be administered if the PT is elevated. The fibrinogen level >1.0 g/dl should be maintained using fibrinogen administration. In consultation with haematology recombinant activated factor VII (FVIIa) could be used if there is massive blood loss following correction of other parameters such as thrombocytopenia and hypofibrinogenemia.

ETT epinephrine administration as the primary treatment method was effective in cessation of PH after 3-5 doses. Haemocoagulase reduced the length of PH and the duration of use of mechanical ventilation. In patients who received rFVIIa for treatment of haemorrhagic shock secondary to PH, PH ceased on treatment and clinically successful haemostasis was achieved. No adverse effects were reported. The use of pulmonary vasodilators, tolazoline and cocaine was reported in one case report and resulted in survival without any evidence of long-term disability.

Strengths of this systematic review include a wide publication window in terms of databases searched and the year of publication over 45 years. A variety of search terms were used to capture studies on the management of pulmonary haemorrhage in the neonatal population. There were 2 relevant studies to this subject that were inaccessible. The majority of the data in this review relating to the management of PH came from retrospective case series or case studies. Further randomised control trials would prove beneficial to compare primary treatment methods and deduce the most effective of these.

Pulmonary haemorrhage is a life-threatening catastrophic event which is associated with a high mortality rate in neonates. A multisystem approach is crucial, involving adequate ventilation, persistent monitoring and the use of appropriate interventions. Surfactant therapy, HFOV and increasing MAP were found to be the most successful evidence-based treatment methods. Surfactant therapy was the most commonly cited approach although the timing of administration and number of doses required to achieve optimal outcome is debatable. Evidence supports that surfactant use, as a treatment for PH is associated with reduced mortality, PH cessation and improvements in oxygenation index, regardless of the type of natural surfactant administered. HFOV has also shown efficacy in improving oxygenation index. Understanding the aetiology of PH and optimal standardised management of coagulopathy and circulatory failure are vital to improve outcome by preventative and rescue measures.

**Table 1**

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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