Use of therapeutic surfactant lavage in a preterm infant with massive pulmonary hemorrhage

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Abstract

We report a case of a premature infant presenting with recurrent pulmonary hemorrhage in which we performed a therapeutic lavage with diluted surfactant after an acute episode of bleeding with severe intractable hypoxemia. Repeated small aliquots of diluted surfactant (10×2 mL) allowed rapid improvement in oxygenation and reduction of required mean airway pressures during high frequency oscillatory ventilation. This observation may suggest that surfactant lavage could be beneficial in massive pulmonary hemorrhage in infants. A randomized controlled trial might be needed to clarify the potential benefit of this therapeutic intervention on outcome of infants suffering from this life-threatening complication.

Introduction

Pulmonary hemorrhage (PH) is a potentially life-threatening complication occurring shortly after birth in 10-16% of extremely low birth infants, reported to lead to chronic lung disease in 60% of cases.[1] Pulmonary hemorrhage is associated with positive pressure ventilation, patent ductus arteriosus (PDA), thrombocytopenia, intra-uterine growth retardation (IUGR) and surfactant therapy.[2] Blood components act as surfactant inhibitors, with fibrinogen having the strongest inhibitory action.[3] Surfactant is principally used for the management of respiratory distress syndrome in newborns increasing survival rates in treated infants.[4] Bolus surfactant treatment, although still controversial, is also widely used in meconium aspiration syndrome (MAS) after a few studies have shown improved oxygenation and reduction in the need for extracorporeal membrane oxygenation (ECMO).[4] Recently, therapeutic surfactant lavage with diluted surfactant (using various administration protocols) has been reported to improve gas change and oxygenation as well as decrease the need of ECMO in infants suffering from severe MAS.[5,6] In PH, surfactant administration has been mainly proposed in order to reverse blood components' inhibitory effects against endogenous surfactant.[4,7] However, no randomized controlled trial has proven such an intervention to be effective.[8] To our knowledge, surfactant lavage with diluted surfactant has not been described as another potential therapeutic option for severe PH. We report a case of a premature infant presenting with recurrent PH in which we performed in one occasion a therapeutic lavage with diluted surfactant after an acute episode of bleeding because of severe non-responsive hypoxemia.

Case Report

A 26 1/7-week-old male infant, weighting 610 g, was born in our maternity department by caesarian section due to maternal pre-eclampsia. He had a IUGR with abnormal cerebral and umbilical Doppler ultrasounds since 24 weeks of gestation. Apgar scores were 8 (1 min), 9 (5 min), 9 (10 min), but the infant developed rapidly signs of respiratory distress. He was intubated and put electively on high-frequency oscillatory ventilation (HFOV), according to standard practice in our unit[9,10] followed by early rescue surfactant treatment (Curosurf®, Chiesi farmaceutici S.P.A., Parma, Italy, 200 mg/kg). On postnatal day 1, cardiac ultrasound revealed a PDA with left-to-right shunting. Indomethacin treatment was started but was interrupted after 2 doses as the infant developed signs of pulmonary hypertension with a right-to-left shunt in cardiac ultrasound. Inhaled nitric oxide (iNO) was initiated. Repeated cardiac ultrasound 48h later showed spontaneous closure of the PDA and no indirect signs of persisting pulmonary hypertension allowing weaning iNO. On day 3, we noticed for the first time fresh blood in the endotracheal tube associated with transient desaturation (SO_2 74%) and a radiologic image compatible with PH. The infant needed blood and platelet transfusion because of important anemia (Hb 85 g/L) and a low platelet count (25 G/L). Coagulation tests were otherwise normal and further blood tests revealed no additional inborn genetic factors predisposing to coagulopathies. On day 5 a second episode of PH occurred with desaturation (SO_2 66%) and increased oxygen needs (FiO_2 0.43) leading to a transient need to increase mean airway pressures (MAP) up to 18 cm H_2O on HFOV. On day 6, he presented again a PH leading to severe hypoxemia and bradycardia needing resuscitation. Despite administration of surfactant (Curosurf®, 200 mg/kg), a rapid but stepwise elevation of MAP to 35 cm H_2O and a fraction of inspired oxygen concentration (FiO_2) of 100% preductal transcutaneous oxygen saturation remained poor (SO_2 50-60%). He became almost impossible to ventilate on HFOV with severe CO_2 retention (14.1 kPa on an arterial blood gas) and acidosis (pH of 6.97). Small aliquots of 0.5 to 1 mL normal saline boluses through the endotracheal tube (ETT) followed by a suctioning procedure were repeatedly used, showing no effect on the infant's condition.

In this acute situation with severe hypoxia and big difficulties to ventilate we performed a surfactant lavage according recent recommendations[5] using diluted surfactant (Curosurf® diluted in normal saline to reach a concentration of 5 mg/mL). Repeated small aliquots of 2 ml were administered through a small size feeding tube through the ETT with the catheter tip positioned at the ETT tube tip and suctioned out immediately again as the child was too unstable to tolerate larger lavage volumes as have been proposed by several study protocols for MAS.[5,6] Between each lavage cycle, a short period of manual ventilation was used. After 10 lavages (10×2 mL aliquots) the suctioned liquid had cleared and the infant showed rapid clinical stabilization with a decrease in oxygen needs allowing for rapid reduction of MAP to 18 cm H_2O. X-Ray showed much better lung aeration than before surfactant lavage (Figure 1). The evolution of oxygen saturation and CO_2 values before and after the administration of surfactant lavage is given in Figure 2. After that, the infant's situation progressively improved. He presented one last episode of PH one week later, less important, which did not require further intervention.

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Switching back from HFOV to conventional ventilation was possible at 25 days of life. He was finally extubated at 31 days of life. Neurological exams over the first weeks of life revealed no abnormalities, and all of the cerebral ultrasounds performed during his stay were normal, as was the cerebral magnetic resonance imaging at 40 weeks of gestational age.

Discussion

We describe a case of severe pulmonary hemorrhage leading to intractable hypoxemia and a difficult to ventilate situation despite bolus surfactant administration and the use of high frequency oscillation in a premature infant. Bronchoalveolar lavage with diluted surfactant allowed for fast improvement of gas exchange, suggesting that this approach might be considered for such severe cases of pulmonary hemorrhage in the future.

Pulmonary hemorrhage is a life threatening condition occurring to 1-12/1000 live births, with rates increasing to 50/1000 live births in risk groups, such as prematurity, IUGR[2,11] and/or sepsis. Thrombocytopenia and abnormal blood coagulation also appear to contribute to PH pathogenesis.[12] In both preterm and term infants PH has been associated with need of resuscitation and positive pressure ventilation, whereas in term infants meconium aspiration seems to be an important risk factor too.[2] The etiologic role of a PDA in PH remains controversial.[11] Prophylactic administration of synthetic surfactant has been shown to increase the risk of PH, by rapidly decreasing intrapulmonary pressure and thus facilitating left-to-right shunt by the patent ductus arteriosus.[13] Rescue surfactant treatment has not been related to development of this condition.[14] Pulmonary hemorrhage has been shown to be associated with increased mortality, development of chronic lung disease, intraventricular hemorrhage and retinopathy of prematurity.[1] There is no evidence for a significant impact on neurodevelopment outcome of surviving infants.[1] Different approaches have been proposed for the management of PH in newborn infants, including high airway pressures during mechanical ventilation, high frequency oscillation,[15] ECMO,[16] administration of recombinant activated Factor VII[17] and surfactant replacement therapy.[18] Although therapeutic lung lavage has been successfully used in MAS, with or without PH,[5,6,19] resulting in meconium removal from the alveoli and surfactant

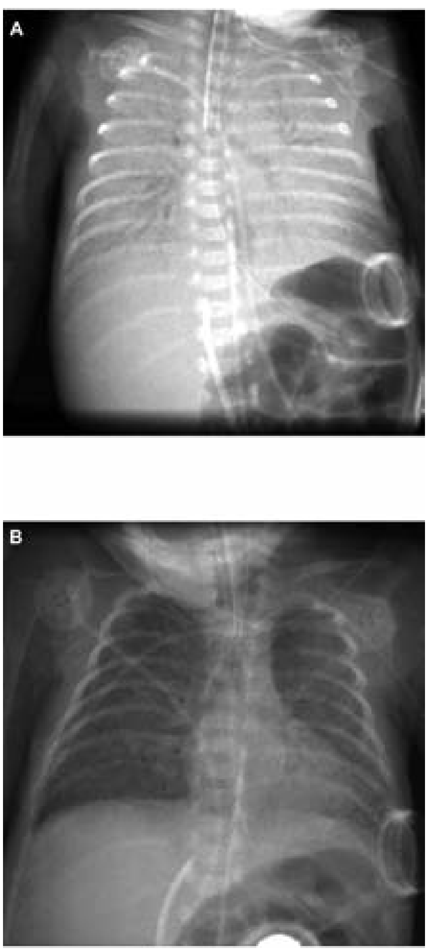

Figure 1. Chest X-Rays of the infant before (A) and after (B) the bronchoalveolar lavage with diluted surfactant. Note that mean airway pressures during high-frequency oscillatory ventilation dropped from 35 cm H_2O before the lavage (A) to 18 cm H2O after (B). The time frame between the two X-rays was 1.5 h.

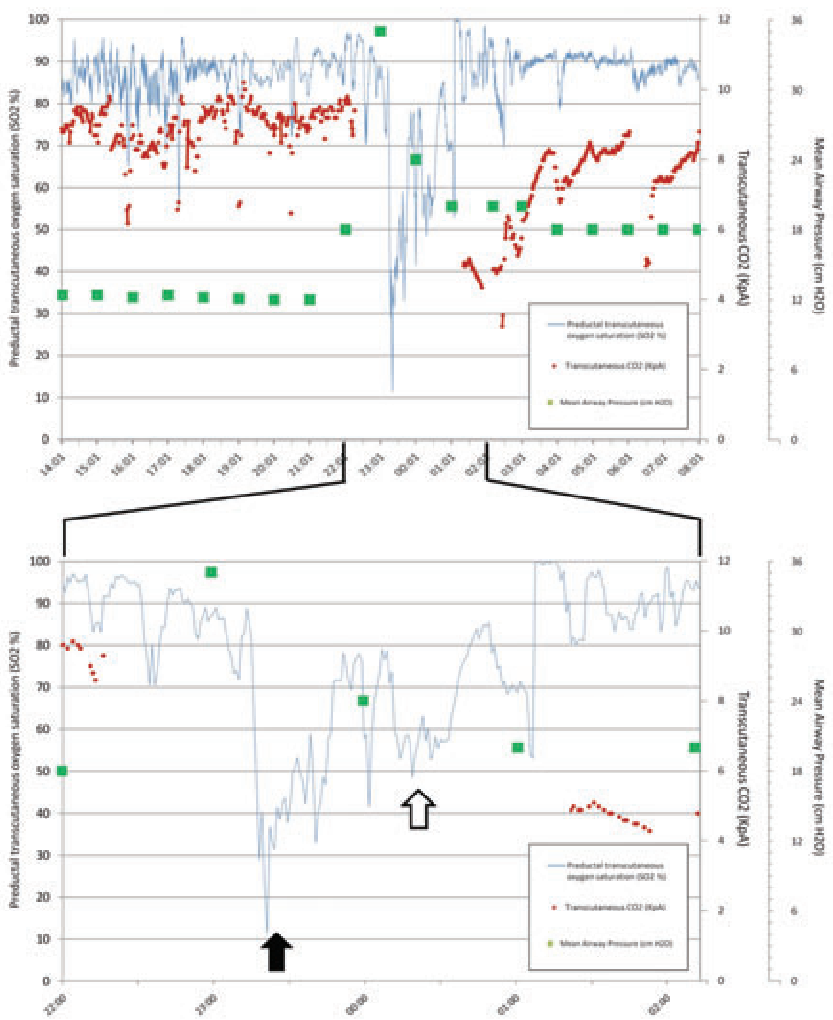

Figure 2. Oxygen saturation (SO_2%), mean airway pressure and CO_2 values before and after the administration of surfactant lung lavage. The black arrow shows the moment of bolus surfactant and prothromplex administration. The white arrow shows the moment of administration of lung lavage.

replacement such an approach has not been described for severe PH that can block central and peripheral airways similar to the situation in MAS. In our case we followed a small volume aliquot protocol, as our patient's extremely critical condition did not allow for the administration of larger lavage volumes as proposed for MAS.[6] We used a surfactant concentration of 5 mg/mL based on our own and current experience in MAS.[5] This intervention resulted in rapid stabilization of the infant's condition with rapid improvement of oxygenation and ventilation efficiency. Whether other surfactant dilution schemes might be more efficient is difficult to know, however obtained results with undiluted surfactant boluses for PH have not been very convincing in the past.[1,4] In our case, administration of an undiluted surfactant bolus showed no effect on gas exchange. In the case of meconium aspiration it has been advocated, based on experimental data and clinical experience, that lung lavage with diluted surfactant solutions can not only remove significant amounts of meconium, alveolar debris and surfactant inhibitors from the alveolar space, but that it also might restore surfactant phospholipid concentration without needing any additional surfactant bolus application.[5] Similar to meconium, blood can not only inhibit surfactant function but also block small airways. Washing-out of blood plugs might therefore become necessary and can explain why bolus application of surfactant might not have been effective in our patient, yet even seemed to worsen the clinical situation. Washing-out the blood plugs only with normal saline could have been an alternative but must probably be considered to be too risky because of eventual further surfactant inactivation and/or depletion, given the fact that normal saline lavage is classically used as the experimental model of neonatal respiratory failure.[20] Washing out blood form the airways with diluted surfactant solutions sounds therefore rational. Nevertheless, to clarify the potential benefit of therapeutic lung lavage with diluted surfactant for severe lung hemorrhage further investigations will be needed.

References

1. Pandit PB, O'Brien K, Asztalos E, et al. Outcome following pulmonary haemorrhage in very low birthweight neonates treated with surfactant. Arch Dis Child Fetal Neonatal Ed 1999;81:F40-4.
2. Berger TM, Allred EN, Van Marter LJ. Antecedents of clinically significant pulmonary hemorrhage among newborn infants. J Perinatol 2000;20:295-300.
3. Finer NN. Surfactant use for neonatal lung injury: beyond respiratory distress syndrome. Paediatr Respir Rev 2004;5 Suppl A:S289-97.
4. Sweet DG, Halliday HL. The use of surfactants in 2009. Arch Dis Child Educ Pract Ed 2009;94:78-83.
5. Dargaville PA, Mills JF. Surfactant therapy for meconium aspiration syndrome: current status. Drugs 2005;65:2569-91.
6. Dargaville PA, Mills JF, Copnell B, et al. Therapeutic lung lavage in meconium aspiration syndrome: a preliminary report. J Paediatr Child Health 2007;43:539-45.
7. Amizuka T, Shimizu H, Niida Y, Ogawa Y. Surfactant therapy in neonates with respiratory failure due to haemorrhagic pulmonary oedema. Eur J Pediatr 2003;162:697-702.
8. Aziz A, Ohlsson A. Surfactant for pulmonary hemorrhage in neonates. Cochrane Database Syst Rev 2008:CD005254.
9. Rimensberger PC, Beghetti M, Hanquinet S, Berner M. First intention high-frequency oscillation with early lung volume optimization improves pulmonary outcome in very low birth weight infants with respiratory distress syndrome. Pediatrics 2000;105:1202-8.
10. Tissieres P, Myers P, Beghetti M, et al. Surfactant use based on the oxygenation response to lung recruitment during HFOV in VLBW infants. Intensive Care Med 2010;36:1164-70.
11. Braun KR, Davidson KM, Henry M, Nielsen HC. Severe pulmonary hemorrhage in the premature newborn infant: analysis of presurfactant and surfactant eras. Biol Neonate 1999;75:18-30.
12. De Carolis MP, Romagnoli C, Cafforio C, et al. Pulmonary haemorrhage in infants with gestational age of less than 30 weeks. Eur J Pediatr 1998;157:1037-8.
13. Soll RF. Prophylactic synthetic surfactant for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2000:CD001079.
14. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2001:CD000510.
15. Pappas MD, Sarnaik AP, Meert KL, et al. Idiopathic pulmonary hemorrhage in infancy. Clinical features and management with high frequency ventilation. Chest 1996;110:553-5.
16. Kolovos NS, Schuerer DJ, Moler FW, et al. Extracorporal life support for pulmonary hemorrhage in children: a case series. Crit Care Med 2002;30:577-80.
17. Grizelj R, Vukovic J, Filipovic-Grcic B, et al. Successful use of recombinant activated FVII and aminocaproic acid in four neonates with life-threatening hemorrhage. Blood Coagul Fibrinolysis 2006;17:413-5.
18. Neumayr TM, Watson AM, Wylam ME, Ouellette Y. Surfactant treatment of an infant with acute idiopathic pulmonary hemorrhage. Pediatr Crit Care Med 2008;9:e4-6.
19. Kaneko M, Watanabe J, Ueno E. Surfactant lavage and replacement in meconium aspiration syndrome with pulmonary hemorrhage. J Perinat Med 2001;29:351-6.
20. Muellenbach RM, Kredel M, Zollhoefer B, et al. Acute respiratory distress induced by repeated saline lavage provides stable experimental conditions for 24 hours in pigs. Exp Lung Res 2009;35:222-33.