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Case Reports

Massive Pulmonary Haemorrhage Presumably Following Surfactant Administration in Very Preterm Neonates in Lagos, Nigeria: Report of Two Cases with Fatal Outcomes and Review of the Literature.

Peter Odion Ubuane,[1,2] Zainab O. Imam,[1] Ayodeji Olusola Akinola,[1] Omolara Adeolu Kehinde,[1,2] Ekaete Alaje,[1] Amotunur Lamina,[1] Gbenga Akinyosoye,[1] Bridget Fagbuji,[1] Oluwabukola Jeje,[1] Elizabeth Aruma Disu,[1,2] Fidelis Olisamedua Njokanma [1,2]

[1]Dept of Paediatrics, Lagos State University Teaching Hospital (LASUTH), Ikeja, Lagos, Nigeria. [2]Dept of Paediatrics & Child Health, Lagos State University College of Medicine (LASUCOM), Ikeja, Lagos, Nigeria.

Abstracts

Pulmonary haemorrhage (PH) is bleeding from the lungs manifesting as bloodstained or pink frothy secretions from the trachea, often with acute clinical and respiratory deterioration. It is a rare but highly fatal complication of prematurity, often following surfactant replacement therapy (SRT), mechanical ventilation, coagulopathy and other risk factors. Despite having one of the highest burdens of global preterm births, there is paucity of reports on PH in Nigeria. Thus, we report two cases with fatal outcomes, aimed at raising awareness of PH among neonatal care providers in the context of increasing utilisation of SRT and advanced respiratory support in preterm care. **Case 1** is a 29-week 5 day preterm who had surfactant therapy and continuous positive airway pressure but later had a massive PH resulting in death despite intubation, suctioning and resuscitation. Additional risk factors included sepsis, intraventricular haemorrhage and suspected coagulopathy. **Case 2** is a 28-week preterm who was referred from a private hospital at the 18th hour of life and was mechanically ventilated and had SRT. He developed PH the following day and died despite transfusion and intratracheal adrenaline. Other risk factors were severe thrombocytopaenia and severe hyponatraemia. PH can be fatal. These cases highlight the need for early detection of PH before symptoms, especially in the context of SRT and MV, while also ensuring prompt and optimal management of sepsis, coagulopathy and electrolytes.

Keywords: Alveolar bleeding, surfactant therapy, sub-Saharan Africa, case report, minimally-invasive surfactant therapy (MIST), less-invasive surfactant administration (LISA)

Correspondence

Dr Peter Odion Ubuane
Department of Paediatrics & Child Health,
Lagos State University Teaching Hospital/Lagos State University College of Medicine,
Ikeja, Lagos State, Nigeria
Email: peterubuane@gmail.com

Introduction

Together with antenatal corticosteroid therapy, caffeine citrate therapy and gentler ventilation, exogeneous surfactant replacement therapy (SRT) has revolutionalised outcomes among preterm infants since the 1980s.[1–3]

However, SRT is associated with increased risk of complications such as pulmonary haemorrhage (PH)[4] which is defined pathologically as the presence of extravasated erythrocytes in the pulmonary alveoli, septa or both, and clinically as bloodstained or pink frothy secretions, emanating or aspirated from the trachea, often

associated with acute clinical and respiratory deterioration of the infants.[5,6] It is thought that the rapid lowering of intrapulmonary pressure which occurs with SRT results in shunting of blood from the left to the right through a patent ductus arteriosus (PDA), increased pulmonary flow and rupture of pulmonary blood vessels.[7] Other factors associated with neonatal PH include prematurity (immature lungs), intrauterine growth restriction (IUGR), PDA, coagulopathy, perinatal asphyxia, sepsis, hypoxia, mechanical ventilation (MV), low birthweight, anaemia, blood transfusion, amongst others.[5,7–12]

PH is a rare but potentially catastrophic complication of preterm infants, with case fatality of over 50%.[4,7,10] The incidence of PH varies globally, generally increasing inversely with gestational age (GA) (see Figure 1).[4] Ahmad *et al*[4] in a retrospective cohort report from a network of 340 neonatal intensive care units (NICUs) across the US reported a 10-year incidence of 0.47% among all admitted neonates. In Brazil, Ferreira *et al.,*[8] reported a prevalence of 6.7 per 1,000 live births, with rates of 8% and 11% among infants <1,500g and <1,000g respectively.

Recently, Gezmu *et al.,*[10] in a prospective cohort study, reported an incidence of 4% among neonates admitted into a neonatal unit in Botswana. A preliminary report from our unit in Lagos, Nigeria, reported an incidence of 0.5% among preterm infants.[13] With increasing access to interventions like SRT and assisted ventilation in Nigeria, there may be increased risk of adverse events like PH.[3,14] However, we found no case reports of PH in Nigeria despite being the third largest contributor of preterm births worldwide.[15] Perhaps there is limited recognition of PH as a distinct respiratory morbidity especially when it occurs in the context of coagulopathy. Appropriate proactive respiratory care of preterm infants would be better data-informed when there is adequate description of the spectrum of preterm-associated respiratory morbidities including PH.[13] To enhance awareness, we report two cases of massive PH with fatal outcomes, along with a narrative review of current literature.

Case 1

AB was a male baby born operatively at GA 29 weeks 5 days (birthweight 965g) to a 32-year-old booked mother admitted into our Hospital's Obstetric Unit due to poorly-controlled pre-eclampsia with superimposed chronic hypertension. Her routine antenatal tests were normal but for a 28-week Doppler-velocitometry which showed "high resistant flow with absent end-diastolic flow suggesting foetus at moderate risk with tendency to asymmetric IUGR." There were no maternal risk factors for sepsis. The mother had two doses of antenatal dexamethasone. Post-resuscitation (stimulation and suctioning only), he was commenced on delivery-room CPAP, aminophylline, vitamin K, incubator care. He had prophylactic bovine-lipid exogenous surfactant (5mL/kg) administered intratracheally with a feeding tube under direct laryngoscopy (unit protocol).

Following instillation, he went apnoeic necessitating a brief bag-mask ventilation. His SpO_2 improved from 91% pre- to 97% post-instillation on FiO_2 of 21%, CPAP 5 cmH_2O. Thereafter, he was stable except for intermittent fever despite antibiotics, necessitating change to the Unit's second line antibiotics regimen. By day 3, he had another apnoea, with bradycardia and cyanosis, and started bleeding profusely from the nostrils and mouth. Apnoea and bleeding persisted despite intravenous vitamin K and resuscitation which included suctioning, bag-mask ventilation and endotracheal intubation for suctioning and MV. Profuse intratracheal bleeding was visualised through the endotracheal tube (ETT). Resuscitation was unsuccessful. Unfortunately, his platelets/blood counts sample was lost-in-transit and coagulation studies were not requested. Post-mortem screening cranial USS showed IVH.

Case 2

BB is a male preterm (GA 28-weeks) who was third of a set of quadruplets, conceived via in-vitro fertilization. Following operative birth at a private hospital, he was referred along with the fourth sibling to our outborn neonatal unit and admitted at the 18th hour life (after demise of the first two babies). His mother was a 45-year-old primigravida who had cervical cerclage at 8 weeks but developed preterm contractions at 27 weeks 5 days. She had no history of fever, hypertension, diabetes, antepartum haemorrhage, premature rupture of membrane, urinary tract infection or abnormal vaginal discharge. Postnatally, the baby was commenced on intravenous caffeine and ceftazidime before referral.

At presentation, he was apnoeic and hypothermic (35.5∘C), necessitating provision of warmth and resuscitation with bag-and-mask ventilation. He regained spontaneous respiration, and was commenced on intranasal oxygen. However, he had another episode of apnoea about 30 minutes later, and was bagged again before regaining spontaneous but slow shallow respiration, necessitating intubation and MV at the 21st hour of life. On day 2, his vitals remained stable. On day 3, he had exogeneous surfactant therapy via ETT. The next day, he began to desaturate on MV, and became pale with reduced activity. Bright red blood started flowing out through the ETT. He continued to desaturate despite endotracheal suctioning.

Results of investigations were: sodium 85mmol/L (severe hyponatraemia), potassium 5.7mmol/L, chloride 68mmol/L (hypochloaraemia), bicarbonate 14mmol/L; urea 9.6mg/dl, creatinine 1.3mg/dl; C- reactive protein: 5mg/L; WBC 1.3x 10^9/l, neutrophils 11.4%, platelets 11x109/l (severe thrombocytopaenia). Endotracheal instillation of adrenaline was followed by reduced bleeding and improvement of SpO_2 to 98%. He also had fresh whole blood (20ml/kg), IV tranexamic acid (10mg/kg);

unfortunately, platelet concentrate was not immediately available. About 30 minutes after, he became apnoeic and paler, with copious flow of blood mixed with clots through the ETT. Repeat of endotracheal suctioning and adrenaline instillation was unsuccessful in resuscitating him.

Discussion

Perhaps this is the first case reports of pulmonary haemorrhage in the context of SRT and MV in preterm care in Nigeria. Our report becomes pertinent with increasing drive for surfactant therapy and advanced neonatal ventilation in neonatal care in Nigeria,[14,16–20] while paying attention to bundled holistic care that encompassese optimal infection control, haemostatic care, fluids and electrolytes balance and thermoregulation. Although the clinical manifestation of PH may range from mildly symptomatic presentation to frank massive fatal bleeding, our cases exemplify the rarer extreme catastrophic forms, in the setting of SRT, MV, sepsis and coagulopathy.

While this by no means imply that we have no cases that present with milder forms and survived, we have highlighted these two to reinforce recent advocacy and drive for early detection of PH, even before clinical manifestation, in order to enhance survival, as well as cautious and gentle respiratory care for the preterm lung.[21] As illustrated by our cases, PH is potentially catastrophic with marked and rapid clinical deterioration, cardiopulmonary decompensation and collapse.

Clinical Manifestations

Based on the time of onset, PH may be classified as early (within seven days of life) or late (after seven days).[4] As observed in our cases, PH most commonly occurs in the first week of life, often between the second and fourth day.[4] Clinically, the onset of massive PH was heralded or associated in both cases by sudden deterioration of the infant with pallor or apnoea. Affected babies are usually hypotensive, frequently limp and unresponsive, although term babies may occasionally be active and restless secondary to hypoxemia. Occasionally, cardiovascular collapse antedates the overt haemorrhage by an hour or two and, rarely, the baby may look surprisingly well despite the production of copious blood-stained pulmonary oedema. The rapid deterioration and high case fatality associated with PH calls for early and accurate diagnosis before onset of obvious external bleeding.

Although chest auscultation may reveal widespread crepitations and reduced breathe sounds[22] and chest radiography may show multilobar infiltrates,[23] neither of these is helpful in PH diagnosis. Recently, chest ultrasonography shows promise in detecting PH before symptoms. Li and colleagues[24] demonstrated that ultrasonographic signs of lung consolidation combined with fluid bronchograms and pleural effusion has sensitivity, specificity and positive predictive index of 81.0%, 98.4% and 94.4%, respectively, in detecting pre-symptomatic PH. Additionally, Ren *et al.*[21] showed that ultrasononographic *shred sign* is highly sensitive and specific for diagnosis of PH. Our unit is currently integrating point-of-care ultrasonographic screening into neonatal care which could assist early PH detection.

Management of Pulmonary Haemorrhage

The goals of management of PH is to quickly restore and sustain optimal haemodynamic status by replacing blood loss; restore and improve optimal respiration, gaseous exchange and oxygenation; stop or control bleeding and treat the underlying cause.[25] Measures to enhance gaseous exchange include tracheal suctioning to remove blood and blood clots as was done in our cases. Optimising gaseous exchange include gentle increase of positive end-expiration pressure to tamponade pulmonary bleeding and splint the airway, with or without increase of FiO_2 to enhance oxygenation.[7]

High-frequency oscillatory ventilation has been recommended in the management of severe PH to stop bleeding through pressure effect.[25] Treatment of the underlying causes of PH may include the administration of blood products like platelet concentrates in cases of thrombocytopaenia as was required for Case 2. Unfortunately, platelet concentrate was not promptly available before his demise. The alternative use of fresh whole blood was inadequate to address the thrombocytopaenia. Although we could not retrieve the platelet counts for Case 1, the concomitant presence of IVH may suggest coagulopathy too.

However, the role of the association of thrombocytopaenia with PH may be uncertain partly because the normal range of platelet counts for neonates is not truly known. Physiologically, the often low platelets counts and coagulation factors seen in neonates, especially preterm infants, is somewhat counterbalanced by higher procoagulant factors such as von-Willebrand factors.[26] Albeit, there is fair agreement that neonatal bleeding in the presence of thrombocytopaenia, as in our Case 2, warrants platelet transfusion.[26]

Bleeding control is a cornerstone goal in the management of PH. However, the most appropriate specific treatment for arresting bleeding in PH is still largely unknown because of the lack of adequately-designed and -powered clinical trials.[25] Limited observational studies or expert opinion suggest that intra-tracheal or nebulised adrenaline may control bleeding by inducing vasoconstriction.[25,27] The administration of adrenaline to case 2 resulted in an initial control which was unfortunately followed later by torrential bleeding.

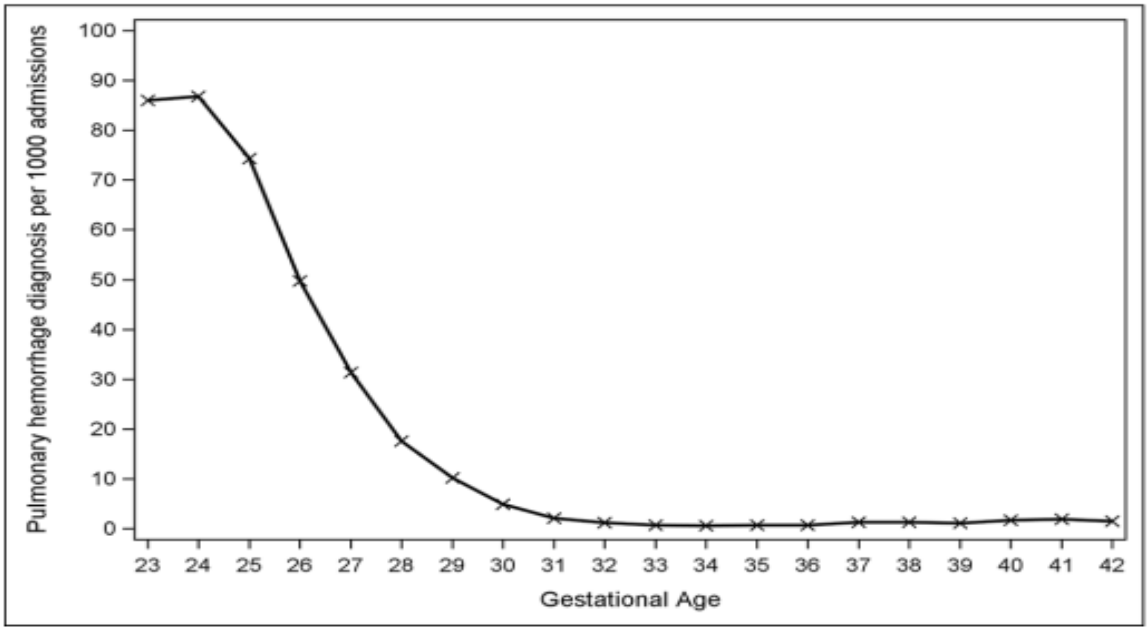
Although SRT has been associated with increased risk of PH, SRT itself is paradoxically employed as a treatment modality for PH, aimed at replacing surfactant molecules deactivated by the haemorrhage. The most recent (2020) Cochrane systematic review on the potential use of SRT in PH, while acknowledging that limited observational studies suggest the efficacy of SRT

in PH treatment, concluded that there was need for further randomized controlled trials to establish the use of SRT for PH treatment.[6] However, Barnes *et al.*,[25] in a more recent systematic review on the management of PH, noted that all five studies which evaluated surfactant as the primary treatment for PH reported its positive effect in controlling bleeding and improving oxygenation.

Our two cases deteriorated too rapidly to allow for possible repeat of SRT, reinforcing the need for anticipatory ultrasonographic assessment. Other substances that have also shown potential in reducing bleeding in PH include haemocoagulase,[28] activated factor VII,[29] heparin[30] or vitamin K.[25] Treatment of underlying causes or risk factors include the surgical or medical treatment of PDA.[31,32] Tatiana and Patrick[32] reported that the early treatment of haemodynamically-significant PDA with ibuprofen among extremely preterm infants resulted in less incidence of PH, but was associated with higher incidence of neonatal enterocolitis.

Prevention

Our cases highlight the need for closer haemodynamic and cardiorespiratory monitoring and prompt management of thrombocytopaenia, electrolytes abnormalities and sepsis in critically-ill preterm infants, especially after surfactant therapy or while undergoing advanced respiratory support. Preventing PH requires understanding and appropriately managing intra- to extra-uterine haemodynamic transition of the newborn. Interventions such as delayed cord clamping (or umbilical cord milking in those > 28 weeks), close haemodynamic and cardiopulmonary monitoring, cautious blood pressure management, careful management of haemodnamically-significant PDA and infection control may minimise PH occurrence among preterm infants.[4,33] The acknowledged clinical care gap in the two cases, namely unavailability of platelet concentrates and delayed availability or absence of laboratory results, highlight the enormous challenge neonatal care practitioners in low-resource sub-Saharan African settings with largely out-of-pocket healthcare financing face in the care of very premature babies.[34,35] Thus our report lends advocacy 'voice' for enhanced support for neonatal care.



CASES

Figure 1. Reducing incidence of pulmonary haemorrhage with increasing gestational age. (Source: BMJ. Used with

Limitation and Conclusion

We report two preterm infants with massive PH with fatal outcomes in the context of SRT and MV, with challenging supportive, diagnostic and haemodynamic care in a low-resource setting. Typical of case reports, our cases are selectively-biased towards an extreme spectrum of PH with fatal outcomes and by no means representative of the population of preterm infants in our care or of the spectrum of PH seen in our unit. Moreover, our report does not validate or refute causal association of PH with surfactant therapy or mechanical ventilation. Larger studies are needed to elucidate risk factors and outcomes of PH in low-resource settings.

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Conflicts of interest: None

Ethical Considerations: As part of a larger prospective study of preterm-associated Respiratory morbidities with nested case series, this retrospective case report was approved by the Health Research Ethics Committee of the Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria (LREC/06/10/2042).

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