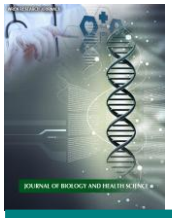

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Case Report

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Pharmaceutical Monitoring of a Case of Pulmonary Hemorrhage with Coagulation Dysfunction in a 680 g Extremely Low Birth Weight Infant at 25+1 Weeks Gestation

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Abstract

Objective: To conduct pharmaceutical monitoring for a case of Pulmonary Hemorrhage (PH) accompanied by coagulation dysfunction in a 680 g Extremely Low Birth Weight (ELBW) infant at 25+1 weeks of gestation and to provide a reference for the clinical treatment of PH in ELBW infants.

Methods: The patient's bleeding treatment regimen was optimized. Interventions included the use of tranexamic acid for antifibrinolytic hemostasis, transfusion of fresh frozen plasma (9 times) and cryoprecipitate (4 times), vitamin K_1 supplementation to improve coagulation function, subcutaneous injection of heparin calcium for anticoagulation (2 times) and administration of human fibrinogen to elevate fibrinogen levels (2 times).

Results: The patient's bleeding was successfully controlled. Following two administrations of human fibrinogen, the infant's coagulation function and Platelet count (PLT) were essentially restored to normal.

Conclusion: When coagulation dysfunction occurs in ELBW infants, vigilance for the onset of pulmonary hemorrhage is crucial. The use of fibrinogen-containing interventions can improve coagulation function and mitigate risk factors for pulmonary hemorrhage in these patients.

Keywords: Extremely low birth weight infant; Neonatal pulmonary hemorrhage; Coagulation disorders; Human fibrinogen

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Introduction

Neonatal Pulmonary Hemorrhage (NPH) pre-dominantly occurs in the early neonatal period and represents a major cause of mortality, with high incidence and fatality rates, particularly among preterm infants in the Neonatal Intensive Care Unit (NICU). Literature indicates that the incidence of PH is inversely correlated with birth weight and gestational age, affecting approximately 1-12 per 1000 neonates annually [1]. Due to immature lung development, many preterm infants are susceptible to respiratory conditions such as respiratory distress syndrome, apnea and pulmonary hemorrhage, often necessitating mechanical ventilation. Extremely Low Birth Weight (ELBW) infants, with their smaller gestational ages and birth weights, are at heightened risk for pulmonary hemorrhage, potentially leading to respiratory failure and death [2]. While some studies exist on PH in Very Low Birth Weight (VLBW) infants, clinical research specifically focusing on PH in ELBW infants is limited. In clinical practice, managing ELBW infants with PH is particularly challenging due to their lower weight, susceptibility to infections and other comorbid risk factors. Current research on PH in ELBW and VLBW infants predominantly

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concentrates on identifying risk factors, with fewer studies dedicated to treatment strategies and pharmaceutical monitoring [3]. This case analysis aims to contribute to the clinical management of PH in ELBW infants by detailing the treatment approach.

Case Summary

The patient, a male infant born at $25+^{1}/_{7}$ weeks gestation *via* spontaneous vaginal delivery on November 28, 2024, at 08:26, due to maternal cervical insufficiency and type 1 placental abruption. Birth weight was 680 g. Following delivery, immediate interventions included placement under a radiant warmer with plastic film wrapping, airway positioning and continuous positive airway pressure *via* T-piece resuscitator through an endotracheal tube. Apgar scores were 3 at 1 minute, 7 at 5 minutes and 9 at 10 minutes. Postnatal presentation was characterized by poor responsiveness, weak spontaneous respiration and critical condition, without fever, seizures or high-pitched cry.

Admission physical examination: Temperature 36.0°C, heart rate 128 bpm, respiratory rate 20-30/min (on T-piece ventilation), blood pressure 55/30 mmHg, percutaneous oxygen saturation 83%. Weight: 680 g. Appearance consistent with preterm infant; poor responsiveness, absent cry (intubated), weak respiration. Cyanosis noted on forehead skin; facial and lip color slightly pale with mild perioral cyanosis; skin gelatinous, no petechiae or ecchymosis. Anterior fontanelle flat and normotensive. Pupils bilaterally round and equal, sluggish light reflex. Neck supple. Chest symmetrical without deformity; nipples difficult to identify, no areolae, no palpable breast buds. Breath sounds decreased in left lung and nearly inaudible in right lung; scattered moist rales audible bilaterally. Regular cardiac rhythm with muffled heart sounds; no significant pathological murmurs auscultated. Abdomen soft; umbilical cord dry. Liver and spleen not palpable. Bowel sounds weak. Both testes undescended. No lower limb edema. Generalized hypotonia. No plantar creases. Nails do not reach fingertips/toe tips. Primitive reflexes not elicited.

Treatment Course

Following admission on November 28, the infant received supportive care including airway maintenance and continuous invasive mechanical ventilation *via* endotracheal tube. Exogenous pulmonary surfactant (Poractant alfa, 136 mg (1.7 ml)) was administered intratracheally. Caffeine citrate (intravenous infusion, 13.6 mg, Qd) was given for respiratory stimulation. Minimal enteral feeding with breast milk/preterm formula was initiated. Vitamin K_1 (intravenous, 1mg, Qd) was administered for hemorrhage prophylaxis. Parenteral nutrition, glucose management and fluid therapy were provided for metabolic stability. On November 29, elevated CRP (8.4 ↑ $mg{\cdot}L^{-1}$) prompted antibiotic therapy with cefotaxime (0.03 g, intravenous infusion, Q12 h). Due to worsening inflammatory markers on November 30 (WBC: 1.99 ↓ $*10^{9}{\cdot}L^{-1}$, PLT: 90 ↓ $*10^{9}{\cdot}L^{-1}$, CRP: 8.37 ↑ $mg{\cdot}L^{-1}$), antibiotic therapy was switched to piperacillin-tazobactam (0.05 g, intravenous infusion, Q12 h). Progressive jaundice was treated with phototherapy. Supportive medications included enteral zinc-iron-calcium supplement, vitamins A and D, lactase, probiotics and ambroxol.

On December 1, severe anemia of prematurity (HGB 115 $g{\cdot}L^{-1}$) was diagnosed and treated with one transfusion of O Rh(D)+ leukocyte-reduced red blood cells, followed by furosemide to prevent fluid overload. Subsequent hemoglobin normalized (December 4: HGB 155 $g{\cdot}L^{-1}$).

On December 4, approximately 3ml of fresh blood was observed in the endotracheal tube, suggesting coagulopathy. Ventilator settings were increased and hemostatic therapy was initiated with intravenous hemocoagulase (from *Deinagkistrodon acutus* venom, 0.50U, Q12h) and intratracheal administration of 1:10,000 epinephrine and hemocoagulase (0.20U). Bleeding was temporarily controlled. Labs showed WBC $11.15*10^{9}{\cdot}L^{-1}$, HGB 155 $g{\cdot}L^{-1}$, PLT $159*10^{9}{\cdot}L^{-1}$, CRP 2.1 $mg{\cdot}L^{-1}$ and coagulation panel: APTT 66.30S ↑, PT 12.70S ↑, fibrinogen (FBI) 2.28 $g{\cdot}L^{-1}$, D-Dimer 1.69 ↑ $\mu g{\cdot}mL^{-1}$.

On December 9, scant pink-tinged sputum was noted on suctioning, with labs showing APTT >170s, FBI 0.12 $g{\cdot}L^{-1}$. Tranexamic acid was added. On December 10 (FBI 0.19 $g{\cdot}L^{-1}$), fresh frozen plasma (FFP) transfusion was initiated. On December 12 (FBI 0.32 $g{\cdot}L^{-1}$), cryoprecipitate was added. Following two cryoprecipitate transfusions (Dec 14 & 16), FBI remained low, indicating limited efficacy. On December 17, following pharmacy consultation, hemocoagulase was discontinued. Human fibrinogen (0.1 g) was administered, with a second dose (0.136 g) on December 21. The infant ultimately received 9 FFP transfusions, 4 cryoprecipitate transfusions, vitamin K_1, 2 doses of subcutaneous heparin calcium and 2 doses of human fibrinogen. After the two human fibrinogen doses, coagulation function and PLT largely normalized, suggesting effective therapy.

On December 23, vitamin K_1 and tranexamic acid were discontinued. Coagulation function returned to near-normal levels.

Discussion

Extremely low birth weight infants (ELBWI, birth weight <1000 g) are highly susceptible to Pulmonary Hemorrhage (PH), a complication associated with significant mortality and morbidity. Studies indicate that earlier onset of PH correlates with lower survival rates [4]. PH is recognized as the second leading direct cause of death in preterm infants [5]. Its etiology remains incompletely understood [6]. Research by Chen D, et al. suggests that a higher 5-minute Apgar score may be

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protective against Massive PH (MPH) in ELBWIs, while the presence of Patent Ductus Arteriosus (PDA) and Early-Onset Sepsis (EOS) increases the risk [7]. Longer mechanical ventilation duration in ELBWIs with MPH is associated with higher mortality and increased incidence of VAP and intracranial hemorrhage.

The reported incidence of PH varies. For VLBW infants, estimates range from 4%-12%. One study reported an 8.3% incidence, while another found 8.7% [8]. Cao ZL, et al. reported a PH incidence of 5.90% in VLBW infants, with a mortality rate of 43.2% [8]. The median day of PH onset has been reported as day 3 (IQR 2,6), occurring earlier in non-survivors (median day 2.0) compared to survivors (median day 6.0) [8]. A US multicenter study found the highest PH incidence in infants born at 23-24 weeks gestation, predominantly within the first 7 days of life [9]. PH onset in this case occurred on day 7.

A single-center study of 599 preterm infants identified coagulation dysfunction as a risk factor for PH, with a positive predictive value of 70.4% [10]. The neonatal coagulation system is immature, particularly in ELBWIs compared to term infants. Coagulation function correlates positively with gestational age and birth weight; smaller, more premature infants exhibit poorer coagulation, higher bleeding risks and higher incidence of coagulopathy and DIC [11]. Multivariate analysis by Zhu W, et al. demonstrated that infants with PT ≥ 30 seconds had a 47.7-fold higher mortality risk than those with PT <30 seconds [11]. On December 16, this patient's PT exceeded 160 seconds. Prolonged exposure to a hemodynamically significant PDA can lead to pulmonary over circulation and systemic hypoperfusion, increasing PH risk; this patient's PDA was a likely contributing factor [12].

The relationship between neonatal PH and coagulation factor replacement is complex, with limited research. Some studies suggest that early, aggressive FFP transfusion might be a risk factor for PH in ELBWIs [13]. Routine prophylactic plasma use is not recommended as platelet counts and coagulation tests may not accurately predict clinical bleeding events [14]. Given the critical role of coagulation factors in PH pathogenesis, factor replacement is considered a key treatment component, but strategies must be individualized. In this case, despite FFP transfusions, coagulopathy persisted and scant bloody secretions continued.

Research by Zhang ZZ, et al. indicated that plasma or cryoprecipitate therapy might improve survival in ELBWI with PH, but did not significantly reduce PH incidence [3]. Conversely, other studies propose plasma transfusion as an independent risk factor for PH, potentially due to interference with neonatal platelet function by adult donor plasma, prolonging bleeding time [14,15]. High-quality RCTs on plasma/cryoprecipitate efficacy in neonatal bleeding are scarce. Recommendations often extrapolate from adult studies or expert consensus, which may not be directly applicable to the heterogeneous neonatal population. Thus, the widespread use of plasma and cryoprecipitate remains debated, underscoring the need for more targeted clinical research.

Prolonged use of hemocoagulase (from snake venom) can lead to fibrinogen depletion, potentially causing bleeding even at standard doses [16,17]. The proposed mechanism involves the batroxobin component specifically hydrolyzing fibrinogen, directly converting FBI to fibrin, leading to its sustained consumption. The resulting fibrin clots are unstable and prone to fibrinolysis, further accelerating FBI clearance. Chronic rapid consumption may overwhelm hepatic synthesis capacity, decreasing plasma FBI concentration. Hyperglycemia has also been identified as a PH risk factor possibly reflecting physiologic instability and stress severity, though the mechanism requires further study [18].

In this case, hemocoagulase was used for 8 days. It was discontinued on December 17, replaced by tranexamic acid, plasma/cryoprecipitate and human fibrinogen. Following this change, fibrinogen levels gradually increased, reaching 1.68 $g{\cdot}L^{-1}$ five days after hemocoagulase cessation, consistent with previous reports. Consensus increasingly targets fibrinogen levels of (1.5-2) $g{\cdot}L^{-1}$ in bleeding patients [19]. Studies suggest that combining fibrinogen with tranexamic acid can improve coagulation in trauma-induced coagulopathy [20].

While the hemocoagulase dose used (0.5U) was within standard range, it may have contributed to FBI depletion. For this patient, FFP and cryoprecipitate were utilized. Data on human fibrinogen use in neonates is limited and package inserts note the lack of systematic pediatric references. However, early fibrinogen supplementation is considered crucial for maintaining hemostasis. In this case, when coagulopathy was uncontrolled, human fibrinogen was administered based on literature review. Fibrinogen is essential for stable clot formation; a platelet plug alone is fragile and fibrinogen, by binding to platelet IIb/IIIa receptors, promotes stable platelet aggregation. After initiating human fibrinogen on December 17, PLT count rose from 25 to 127. Fibrinogen is the most abundant coagulation factor and its deficiency often reaches critical levels earlier than other factors.

In neonatal PH with low FBI, direct FBI supplementation can raise plasma levels and promote effective hemostasis. Early research identified an association between neonatal PH, low fibrinogen levels and impaired thrombin-fibrinogen reaction [21]. Therefore, for neonates with confirmed fibrinogen deficiency, fibrinogen replacement offers direct hemostatic benefit, potentially reducing the need for RBC, FFP and platelet transfusions and avoiding complications like volume overload. However, fibrinogen concentrate lacks other clotting factors. In multi-factor deficiency, isolated fibrinogen supplementation may not fully correct coagulopathy, as upstream coagulation cascade defects can

impair thrombin generation and subsequent fibrin formation. In this case, combining fibrinogen with FFP effectively improved coagulation. Studies indicate that combining FFP with fibrinogen concentrate can increase fibrinogen levels approximately five times faster than FFP alone, reducing FFP volume requirements and associated complications like pulmonary edema [22].

Conclusion

ELBWIs represent one of the most challenging populations in neonatal care due to high morbidity, mortality and long-term sequelae. This case report details the successful management of PH with coagulation dysfunction in an ELBWI using human fibrinogen, contributing clinical data to inform treatment strategies. Through close collaboration among clinical pharmacists, physicians and nursing staff, the infant was discharged after 117 days of intensive care, with a weight of 2.86 kg.

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