

CASE REPORT

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Treatment of Acute Pulmonary Hemorrhage in Neonates with Endotracheal Ankaferd Blood Stopper Use

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Introduction: Neonatal pulmonary hemorrhage (PH) is a clinical picture with various risk factors playing a role in its etiology and has a high neonatal mortality and morbidity rate. In this paper, we share the results of Ankaferd blood stopper (ABS) use in the treatment of neonatal PH.

Materials and methods: In this retrospective cross-sectional study, data were obtained using the patient file and automation systems. Two patients whose pulmonary bleeding was stopped by administering ABS between July 2018 and July 2020 in the neonatal intensive care unit were included in the study.

Results: The first patient was a male baby born by cesarean section at 38 3/7 weeks of gestation and weighing 3320 g. Massive PH was detected in the patient who developed cyanosis at the 3rd hour of maternal side follow-up. Despite endotracheal tube (ETT) aspiration, pulmonary bleeding continued, and the bleeding stopped immediately after ABS was used. The other patient was a male baby born by cesarean section at 33 6/7 weeks of gestation. Postpartum prematurity, respiratory distress syndrome, and neonatal sepsis were diagnosed and massive PH developed on the 9th day of follow-up. The bleeding stopped immediately after ABS was administered.

Conclusion: There is still no effective drug or method to treat PH in the neonatal period. ABS, a new treatment option, may be beneficial in reducing mortality and morbidity.

Keywords: Ankaferd Blood Stopper (ABS), pulmonary hemorrhage treatment, neonate

Introduction

First described in 1855, pulmonary hemorrhage (PH) is a well-known condition in term and preterm newborns. It is often a sign of a worsening clinical condition (1). It refers to the appearance of fresh blood in the endotracheal tube or trachea. Severe (massive) PH is an acute, life-threatening event that occurs in

approximately 10% of extremely preterm neonates. It is associated with injury of the premature lung caused by the treatment of respiratory distress syndrome, mechanical ventilation, and disturbances in the pulmonary circulation (2). PH may develop less frequently in term infants than in preterm infants. The incidence of clinical PH is estimated to be 1–12

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per 1000 live births, whereas the rate of PH in very low birth-weight infants varies from 4% to 12%. The variation in its incidence is mainly due to the unclear etiology and diagnostic criteria of PH. PH occurs most commonly in the first few days after birth. The mortality rate of severe PH is approximately 50% (3). Its pathogenesis is thought to be due to pulmonary edema with a hemorrhagic component, as analysis of the hemorrhagic fluid has shown a lower hematocrit than the infants' blood. Infants with severe PH typically present with an acute decline in clinical status, often with hypotension, hypoxia, bradycardia, and pallor. Signs and symptoms of heart failure may also be noted including tachycardia, hepatosplenomegaly, heart murmur, and peripheral edema (4).

Ankaferd Blood Stopper (ABS) is a standardized herbal extract obtained from the following five plants: *Thymus vulgaris*, *Glycyrrhiza glabra*, *Vitis vinifera*, *Alpinia officinarum*, and *Urtica dioica*. Ankaferd represents its unique local hemostatic effect by promoting the very rapid, i.e., in <1-second formation of a protein network, which acts as an anchor for vital physiological erythrocyte aggregation, covering the classical cascade model of the clotting system without independently acting on coagulation factors and platelets (5-6). The safety and effectiveness of ABS have been proven in traumatic dermal bleeding, postoperative bleeding such as tonsillectomy, and dental bleeding (7-8). Previous studies have shown the effect of ABS on stopping bleeding in the lung tissue and preventing air leakage (9).

In this paper, we report two cases in which ABS was used as a new treatment option for neonatal PH. This study is possibly the first to report that ABS application can be life-saving in stopping bleeding in neonatal PH.

Materials and Methods

We included two newborns who were treated with ABS for acute PH in the neonatal intensive care unit (NICU) between July 2018 and July

2020. Patient information, X-rays, blood gas, complete blood count, and other bleeding-related laboratory results were obtained from patient files and automation systems. In patients with PH in whom the bleeding could not be stopped despite classical treatment methods such as administration of adrenaline through ETT, high positive end-expiratory pressure, and tracheal aspiration, 1 ml ABS was diluted in 1 ml isotonic solution (total 2 ml) and administered via a 6 French nasogastric tube through ETT under sterile conditions. After the drug was administered, positive pressure ventilation was applied for 30 seconds.

Ethical Statement

Ethics committee approval was not obtained because the study was retrospective and a case report. Consent was obtained from the parents of the patients.

Case Presentation

Case - 1

The second child of a 21-year-old mother, who was not consanguineous with her husband, was a male baby born at 38 3/7 weeks of gestation with repeated cesarean section, weighing 3320 g. There was no history of maternal disease. Birth Length was 51 cm, head circumference was 34 cm, Apgar scores at 1st minute was 8, Apgar score at the 5th minute was 9. The baby did not need postnatal aspiration and/or positive pressure ventilation. The baby was administered vitamin K and hepatitis B vaccine and had no problems, and was administered to the mother. The baby developed cyanosis at the 3rd hour of the mother's side follow-up and respiration were found to be superficial. The baby was admitted to the NICU and intubated mechanical ventilator support was started. During the intubation procedure, the patient developed progressive respiratory failure, and massive PH was detected in the airway. Fresh and abundant blood was aspirated from the airway. The bleeding could not be stopped even though the adrenaline was administered 3

times through the ETT at a dose of 0.1 ml/kg (1/10,000 dilution) due to its vasoconstrictive effect. The bleeding stopped immediately after ABS was administered with 6 French aspiration catheters through the ETT. Respiratory support was administered with mechanical ventilation in High-Frequency Oscillatory (HFO) mode. There was no active bleeding in gastric lavage. Examinations during hemorrhage revealed that arterial blood gas pH was 7.18, pO_2 was 35 mmHg, pCO_2 was 65 mmHg, HCO_3 was 17.8 mmol/L, and the base deficit was -4.8 mmol/L.

In coagulation tests, prothrombin time (PT) was 17 seconds, active partial thromboplastin time (aPTT) was 33.6 seconds, and international normalized ratio (INR) was 1.43. Complete blood count was as follows: hemoglobin 18 g/dL, Hct 54%, leukocyte 18,500/mm³, platelet 266,000/mm³. Furthermore, 1 hour later, pH in arterial blood gas was 7.30 pO_2 was 79 mm/hg, pCO_2 was 46.6 mm/hg, HCO_3 was 21 mmol/L, the base deficit was -2.7 mmol/l, serum reactive protein (CRP) was 9.5 mg/dl (normal <1 mg/dl), hemoglobin was 10.1 g/dl, HCT was 30.5%, and other biochemical tests were normal. The patient was administered 1 mg of vitamin K, erythrocyte suspension, and fresh frozen plasma supplementation once.

Transthoracic echocardiography (TTE) revealed a patent foramen ovale without hemodynamic significance and thin patent ductus arteriosus. The patient was extubated on the postnatal 4th day and was discharged on the 13th day without complications. Transfontanel and abdominal ultrasonography were normal. Lung radiograph during PH and after recovery are seen in figure 1.

Case 2

The second child of a 23-year-old mother, who was not consanguineous with her husband, was a male baby born at 33 6/7 weeks of gestation by emergency cesarean section due to pre-eclampsia, weighing 2150 g. Birth height was 45 cm, head circumference was 33 cm, Apgar score at 1st minute was 7, and Apgar scores at 5th minute was 8. There was no need for postpartum aspiration and positive pressure ventilation. Mechanical ventilator support was started with nasal Continuous positive airway pressure after less invasive surfactant treatment (LISA) due to preterm respiratory distress syndrome and prematurity. The case developed cutis marmoratus, tachycardia, and cyanosis on the postnatal 4th day. Examination results were as follows: Leukocyte 3000/mm³, hemoglobin: 13.4 g/dl, hematocrit 40.2%, platelet: 131,000/mm³, CRP: 37 mg/dl, procalcitonin 3 ng/dl.

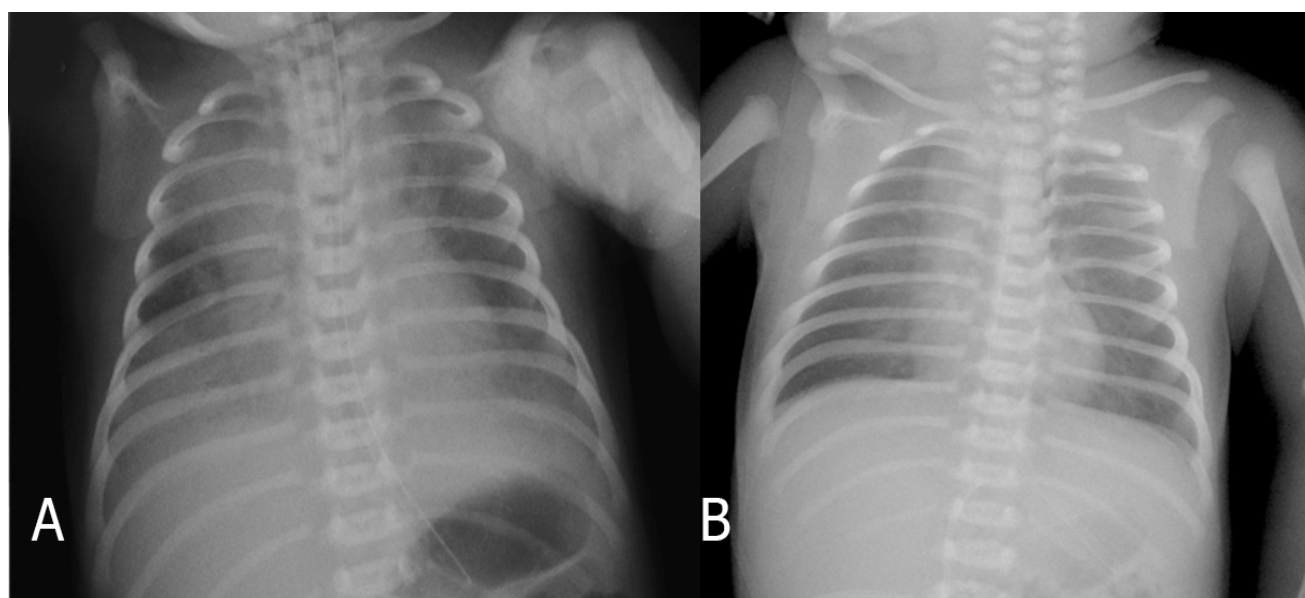


Figure 1. Chest radiographs of the first patient during pulmonary hemorrhage and before discharge

Antibiotic treatment was started for late neonatal sepsis and the patient was followed up with intubated mechanical ventilation. No patent ductus arteriosus was detected in TTE. On the 9th day of follow-up, massive PH, and progressive respiratory failure developed. To manage PH, the patient was aspirated through the ETT, adrenaline was administered 3 times, and surfactant was administered 1 time with no success. The bleeding stopped immediately after ABS was administered to the patient through the ETT. However, after the procedure, reintubation was required because the ETT tip was clogged with a clot. Ventilation support was provided with mechanical ventilation in HFO mode. 1 mg of vitamin K was administered; fresh frozen was administered once. Post-bleeding hematocrit decreased from 35.2% to 21%. Erythrocyte and platelet (platelet count $19,000/\text{mm}^3$) suspension were administered once. During bleeding, arterial blood gas pH was 7.08, pO_2 was 33.2 mmHg, pCO_2 was 59.2 mmHg, HCO_3 was 16.4 mmol/L, and the base deficit was -8.8 mmol/l. After 1-hour, arterial blood gas pH was 7.18, pO_2 was 82.5 mmHg, pCO_2 was 46.7 mmHg, HCO_3 was 18.3 mmol/L, and the base deficit was -4.7 mmol/l. Clinical picture improved during the follow-up, cranial and abdominal ultrasonography outcomes were normal, and the patient was extubated

on the postnatal 22nd day. Retinopathy of prematurity examination was also normal, and the patient was discharged on the postnatal 37th day. Chest X-ray taken during and after hemorrhage is shown in Figure 2.

Discussion

Acute massive PH represents the end of the spectrum of pulmonary edema in the neonate. The etiology of PH is still unknown, but it is stated that there are some risk factors such as a low gestational week, intrauterine growth restriction, resuscitation in the delivery room, surfactant treatment, asphyxia, lack of antenatal steroids, patent ductus arteriosus, infection, and coagulopathy (10). In the present study, the first case had no risk factors in antenatal history, and a small patent ductus arteriosus, which was not hemodynamically significant, was detected at the postnatal 3rd hour. The second case had risk factors such as prematurity, respiratory distress syndrome, surfactant administration, and postnatal 4th-day neonatal sepsis. In the cases, bleeding time was normal, factor 7 and 13 levels, PT, activated PTT, INR, liver, and kidney function tests and other biochemical tests were within normal limits. There were hypoxia, metabolic acidosis hypercarbia and respiratory in blood gas analyses during PH. The standard therapy is to raise the Positive End-Expiratory Pressure to 6 to 8 cm H_2O .

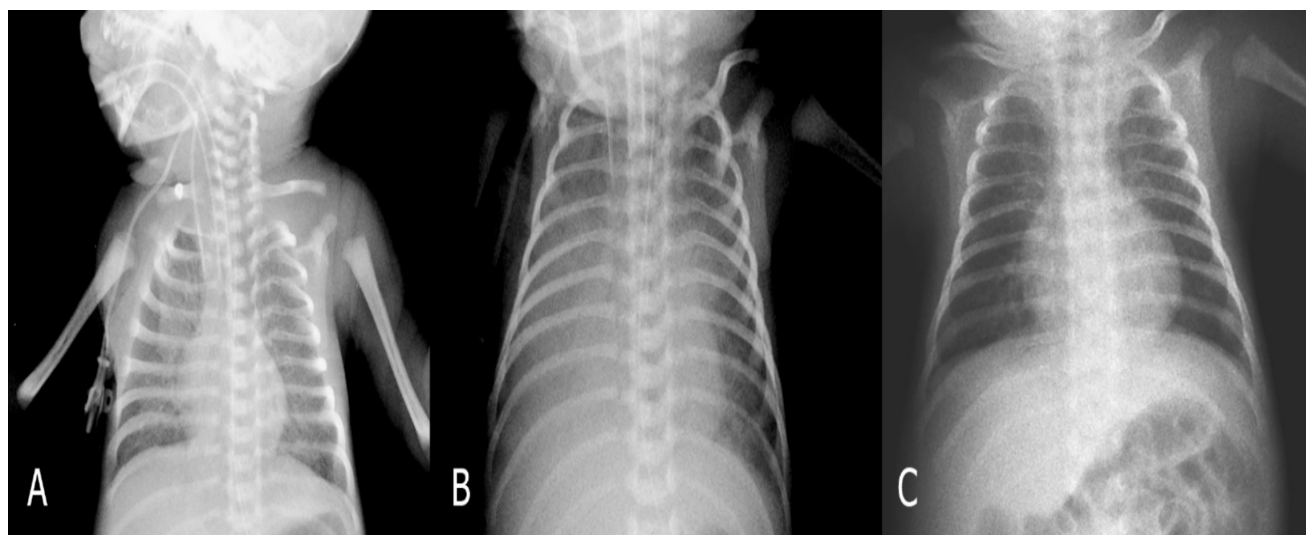


Figure 2. Chest radiographs of the second patient before and during pulmonary hemorrhage and before discharge

To decrease PH, the mean airway pressure should be increased in an attempt to reverse or slow down hemorrhagic pulmonary edema. Endotracheal or nebulized epinephrine has been used in the treatment of PH because of its vasoconstrictive and inotropic effects. In some cases, HFO mod ventilation may be needed to increase the mean airway pressure. This is probably the first study to report that ABS application can be lifesaving in stopping bleeding in neonatal PH.

The basic mechanism of action for ABS is the formation of an encapsulated protein network that provides focal points for vital erythrocyte aggregation. ABS-induced protein network with blood cells, particularly erythrocytes, covers the primary and secondary hemostatic system without disturbing coagulation factors. Metin et al. investigated pulmonary parenchymal damage in rabbits and reported that ABS, which was used as a topical hemostatic agent, reduces the amount of postoperative bleeding and air leakage when applied in lung surgery procedures, and it can be used as an effective and harmless pleurodesis agent thanks to the pleural fibrosis and adhesion it provides (11). The effectiveness of ABS in preventing air leakage and bleeding in the lung was investigated in Wistar-Albino rats. It was shown that ABS use was effective in preventing air leakage in the lung parenchyma and significantly stopped pulmonary bleeding (9).

Arslan et al. reported that in an adult patient with lung cancer who presented with severe hemoptysis, hypoxemia, and hemodynamic instability, the bleeding was successfully controlled with the endoscopic application of 2 ml ABS (12). In the present study, it was observed that acute massive PH stopped in a short time in both patients who received ABS via ETT. The bleeding did not recur afterward, a second dose of ABS was not applied. The patients were discharged in good health after respiratory support in HFO mode and other

treatments. There is no information about the usage dose of ABS in neonates and how it should be diluted, and it was administered to our cases as a total of 2 milliliters after dilution with 0.9% saline at a one-to-one ratio. After the procedure, positive pressure ventilation support was administered for 30 seconds. After the procedure, no complications developed in the patients except ETT occlusion in the second case.

In acute severe PH, with significant mortality in the neonatal period, application of ABS through ETT successfully stopped pulmonary bleeding in two cases. Further studies are needed on this subject.

Conflicts of Interest

The authors declared no conflict of interest for the present article. All authors contributed equally to the present manuscript and read and approved the final version.

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