Short Communication

Biology of the Neonate

Biol Neonate 2005;88:118–121
DOI: 10.1159/000085826

Received: December 2, 2004
Accepted after revision: February 14, 2005
Published online: May 17, 2005

New Treatment of Neonatal Pulmonary Hemorrhage with Hemocoagulase in Addition to Mechanical Ventilation

Yuan Shi Shifang Tang Huangqiang Li Jinning Zhao Feng Pan

Department of Pediatrics, Research Institute of Surgery and Daping Hospital, Third Military Medical University, Chongqing, China

Key Words
Hemorrhage, neonatal pulmonary · Hemocoagulase · Ventilation, mechanical

Abstract
Objective: To investigate the effect of a new treatment for neonatal pulmonary hemorrhage with hemocoagulase in addition to mechanical ventilation. ***Methods:*** Forty-eight newborn infants with pulmonary hemorrhage were included and divided randomly into 2 groups. Among them, 28 patients were treated with hemocoagulase in addition to mechanical ventilation, and the other 20 neonates served as controls and were treated with mechanical ventilation only. ***Results:*** Both the length of pulmonary hemorrhage and the duration of mechanical ventilation in the survivors were significantly shortened in the infants treated with hemocoagulase in addition to mechanical ventilation as compared to controls ($p < 0.05$). Moreover, all infants that were unable to remain in the neonatal intensive care unit died after discharge, and when their outcome was estimated as non-survivors, the mortality in the patients with this new treatment was 39.3% (11/28), which was significantly lower than in controls (75.0%, 15/20; $p < 0.05$). When the discharged infants were not included in the statistics, the mortality in the hemocoagulase group was 10.7% (3/28), which was also significantly lower than in controls (40.0%, 8/20; $p < 0.05$). ***Conclusions:*** The new treatment with hemocoagulase in addition to mechanical ventilation is effective in newborn infants with pulmonary hemorrhage.

Pulmonary hemorrhage is still a life-threatening complication in newborn infants. It was present in the lungs of 68% of the neonates who died in the 1st week of life, and is one of the most significant clinical casualties associated with the need for cardiopulmonary resuscitation in the neonatal intensive care unit (NICU) [1]. It has been found to be the principal cause of death in about 9% of neonatal autopsies. Pulmonary hemorrhage has also been suggested to be an important risk factor for mortality in meconium aspiration syndrome [2]. Overall, 74% of liveborn infants had histological evidence of pulmonary hemorrhage upon autopsy [3]. Pulmonary hemorrhage occurred in 5.7% of the total population of very-low-birth-weight infants and the associated mortality was rather high [4]. A recent report indicated that pulmonary hemorrhage in very small infants has tended to increase since 1998. Nevertheless, there has been no great improvement in the treatment of neonatal pulmonary hemorrhage in recent years [5].

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0006–3126/05/0882–0118$22.00/0

Accessible online at:
www.karger.com/bon

Yuan Shi, MD
Department of Pediatrics, Research Institute of Surgery and Daping Hospital
Third Military Medical University
Chongqing 400042 (China)
Tel. +86 23 68757345, Fax +86 23 68819756, E-Mail petshi530@hotmail.com

Hemocoagulase, introduced in 1966 from the venom of the Brazilian snake *Bothrops atrox*, was used clinically [6]. It has been used in plastic and abdominal surgery, and human vitrectomy [7–9]. The aim of this study is to investigate the clinical effect of hemocoagulase on newborn infants with pulmonary hemorrhage.

Patients and Methods

The study population comprised newborn infants with pulmonary hemorrhage admitted between January 2001 and January 2004 to the NICU, Department of Pediatrics, Research Institute of Surgery and Daping Hospital, Third Military Medical University, Chongqing, China. The neonates were identified clinically to have suffered from pulmonary hemorrhage when blood-stained fluid effused from endotracheal tube aspirates, especially if repeated suctioning showed an increase in the amount of hemorrhagic fluid, in addition to some primary diseases such as hyaline membrane disease and severe bacterial sepsis. Other supporting evidence included: (1) radiograph of the infant chest showing the fluffy appearance of pulmonary edema in addition to the underlying pathology; (2) increased respiratory distress, and (3) systemic deterioration such as shock [10].

The NICU, Department of Pediatrics, Research Institute of Surgery and Daping Hospital, Third Military Medical University is the center of neonatal transport and a saving network consisting of 32 hospitals in Chongqing. The infants were immediately transported into the NICU when the primary diseases had been diagnosed.

Complete obstetric histories were obtained and examinations were performed upon admission. The neonatal clinical course was followed prospectively and data were recorded on predetermined performance sheets. Written parental consent was obtained prior to enrolling the subjects. This study was approved by the Clinical Research Committee of Daping Hospital and Research Institute of Surgery, Third Military Medical University.

Because of financial difficulties or worry about severe sequelae of the infants, some parents decided to abandon active life-saving measures, so that these infants were discharged from the NICU. These infants were followed up after discharge and estimates of their outcomes were made.

Therapeutic Methods

Once the neonatal patients had been diagnosed with pulmonary hemorrhage, they were divided randomly into 2 groups based on the method of random number table: the hemocoagulase group, and the control group. In the control group, the neonates were treated with mechanical ventilation, keeping an adequate mean airway pressure, particularly end-expiratory pressure. The mechanical ventilator used in the study was Babylog 8000 newborn infant ventilator (Dräger, Germany), and synchronized intermittent mandatory ventilation was the commonly performed breath mode in addition to the positive end-expiratory pressure levels from 5 to 7 cm H_2O.

Other routine methods included: (1) clearing the airway of blood to allow ventilation; (2) resisting the temptation to administer large volumes of blood; (3) evaluation of the possibility of coagulopathy and administration of vitamin K and platelets if appropriate, and (4) treatment of the primary diseases. In the therapeutic group, in addition to the methods mentioned for the controls, the neonates received treatment with hemocoagulase. The hemocoagulase was dripped through the endotracheal tube.

The hemocoagulase used in this study was Reptilase, which is prepared from the venom of the Brazilian snake *B. atrox*. Repilase is the isolated, purified hemocoagulase, and is completely free of neurotoxins and toxic substances. Each batch is carefully controlled biologically, and is produced by Solco Basel Ltd. (Birsfelden, Switzerland). Each vial contains 1 Klobusitzky unit (KU) of hemocoagulase in lyophilized form. One KU is the quantity of the enzyme hemocoagulase which coagulates standard human plasma incubated at 37°C in vitro within 60 ± 20 s.

Hemocoagulase was dripped through the endotracheal tube at a dosage of 0.5 KU each time. It was repeated every 4–6 h until pulmonary hemorrhage had stopped and the critical condition had stabilized.

Bleeding time, prothrombin time, and partial thromboplastin time were assayed just after pulmonary hemorrhage had started in all newborns.

Statistical Analysis

The data are expressed as mean ± standard deviation, or median (range), for descriptive purpose. The χ^2 test or Wilcoxon two-sample test were used to analyze the difference between groups.

Results

Forty-eight neonates (26 boys, 22 girls) were involved. The main perinatal data of these neonates are shown in table 1. No differences were found between the hemocoagulase group and the controls regarding gestational age, birth weight, gender, type of delivery, patent ductus arteriosus, intracerebral hemorrhage, bronchopulmonary dysplasia, and the time of occurrence of pulmonary hemorrhage. The administration of surfactant, platelet transfusion, plasma transfusion, or red blood cell transfusion were not different between the 2 groups. There were also no differences in bleeding time, prothrombin time, and partial thromboplastin time between the 2 groups. Table 2 shows the primary diseases of the neonates, and there was no difference between the groups. Prophylactic vitamin K was the standard treatment for each infant with a single dose of 0.5–1 mg intramuscularly at birth, with a subsequent dose for breastfed neonates. Values for bleeding time, prothrombin time, and partial thromboplastin time were within the normal range for newborns.

As table 3 shows, both the length of pulmonary hemorrhage and the duration of mechanical ventilation in the survivors were significantly shortened in the infants treated with hemocoagulase in addition to mechanical venti-

Table 1. Clinical data of the newborn infants with pulmonary hemorrhage

	Hemocoagulase group	Controls	p value
Gestational age, weeks	30.5 ± 1.8	30.9 ± 2.9	>0.05
Birth weight, g	1,380 ± 630	1,410 ± 720	>0.05
Gender (male/female)	15/13	11/9	>0.05
Type of delivery (vaginal/cesarean)	9/19	5/15	>0.05
Surfactant administration (Curosurf), %	11 (3/28)	10 (2/20)	>0.05
Plasma infusion, %	96 (27/28)	100 (20/20)	>0.05
Red blood cell or platelet transfusion, %	18 (5/28)	15 (3/20)	>0.05
Patent ductus arteriosus, %	7 (2/28)	10 (2/20)	>0.05
Intracerebral hemorrhage, %	11 (3/28)	15 (3/20)	>0.05
Bronchopulmonary dysplasia, %	7 (2/28)	5 (1/20)	>0.05
Time of pulmonary hemorrhage, h	48.1 ± 19.9	50.3 ± 26.9	>0.05
Bleeding time, min	5.2 ± 2.3	4.9 ± 2.5	>0.05
Prothrombin time, s	14.2 ± 2.1	14.5 ± 2.5	>0.05
Partial thromboplastin time, s	70.3 ± 4.8	68.9 ± 3.8	>0.05

Table 2. Primary disease of the neonates with pulmonary hemorrhage

Primary disease	Hemocoagulase group	Controls
Perinatal asphyxia	13	8
Respiratory distress syndrome	9	6
Sepsis	3	3
Pneumonia	2	2
Cold injury syndrome	1	1

Table 3. Length of pulmonary hemorrhage and duration of mechanical ventilation

Group	Hemocoagulase	Control
Number of surviving patients	17	5
Length of pulmonary hemorrhage, days	1.86 ± 0.85	3.60 ± 0.88*
Duration of mechanical ventilation in the survivors, days	2.50 ± 0.95	4.05 ± 1.01*

* $p < 0.05$ vs. hemocoagulase group.

lation as compared with the controls. Eight of 28 infants in the hemocoagulase group (28.6%) and 7 of 20 controls infants (35.0%) were unfortunately discharged from the NICU, but there was no significant difference between these 2 groups ($p > 0.05$). All these infants died after leaving the NICU, and when their outcome was estimated as non-survivors, the mortality in the patients with this new treatment was 39.3% (11/28), which was significantly lower than in the controls (75.0%, 15/20; $p < 0.05$). When the discharged infants were not included in the statistics, the mortality in the hemocoagulase group was 10.7% (3/28), which was also significantly reduced compared to the controls (40.0%, 8/20; $p < 0.05$).

Discussion

Pulmonary hemorrhage is still a critically fatal disease in newborn infants, and lacks effective treatment [11]. In China as well as in other developing countries, the reported mortality from neonatal pulmonary hemorrhage is high (40–50%) [12]. Parents' inability to support the ongoing neonatal intensive care might be a major reason for the relatively higher mortality compared with the current statistics in the United States and Europe [13, 14]. Pulmonary hemorrhage usually occurs between the 2nd and 4th day of life in neonates who mostly suffer from some severe primary diseases. It has been associated with a wide variety of predisposing factors including prematurity, hyaline membrane disease, asphyxia, severe sepsis, intrauterine growth retardation, severe hypothermia, and coagulopathy [15].

In most cases of pulmonary hemorrhage, there is no evidence that coagulation disorders initiate the condition but they probably serve to exacerbate it in some cases. It was postulated that the important precipitating factor might increase the filtration pressure and so injure the capillary endothelium of the lung. Pulmonary hemorrhage might be considered as an extreme form of high permeability pulmonary edema [16]. Thus mechanical ventilation, which maintains an adequate mean airway pressure, particularly end-expiratory pressure, was performed in all neonatal patients with pulmonary hemorrhage. Nevertheless, in most cases, pulmonary hemorrhage seems to be very difficult to control once it happens.

The results of this study provide the first evidence that hemocoagulase, when given through the endotracheal tube, is effective in the treatment of neonatal pulmonary hemorrhage. Hemocoagulase has been used in plastic and abdominal surgery, and in human vitrectomy. In cases of cleft palate and septum deviation, primary studies have suggested that hemocoagulase plays a good hemostatic role in the hemorrhagic capillary in abdominal incision during plastic surgery, and also appears to be a useful agent in the control of intraocular bleeding during vitreous surgery. Twenty minutes after the parenteral administration of 1 KU of hemocoagulase, the normal bleeding time in healthy adults sinks to half or one third. This tendency towards elevated coagulability is maintained for 2–3 days. The hemostatic effect of hemocoagulase is not associated with any increase in the prothrombin level of blood and therefore constitutes no danger of thrombosis [17, 18]. Our present study also indicates that the clotting system of neonatal patients seems impervious during local hemocoagulase treatment, and the danger of cerebral hemorrhage is not increased.

In conclusion, the present study indicates that, in addition to mechanical ventilation, treatment with hemocoagulase can be safely performed in newborns with pulmonary hemorrhage and reduce the associated mortality.

References

1 Kostelanetz AS, Dhanireddy R: Survival of the very-low-birth-weight infants after cardiopulmonary resuscitation in neonatal intensive care unit. J Perinatol 2004;24:279–283.
2 Lin HC, Su BH, Lin TW, Peng CT, Tsai CH: Risk factors of mortality in meconium aspiration syndrome: Review of 314 cases. Acta Paediatr Taiwan 2004;45:30–34.
3 Coffin CM, Schechtman K, Cole FS, Dehner LP: Neonatal and infantile pulmonary hemorrhage: An autopsy study with clinical correlation. Pediatr Pathol 1993;13:583–589.
4 Tomaszewska M, Stork, E, Minich NM, Friedman H, Berlin S, Hack M: Pulmonary hemorrhage: Clinical course and outcomes among very-low-birth-weight infants. Arch Pediatr Adolesc Med 1999;153:715–721.
5 St-John EB, Carlo WA: Respiratory distress syndrome in VLBW infants: Changes in management and outcomes observed by the NICHD Neonatal Research Network. Semin Perinatol 2003;27:288–292.
6 Valvo A: New treatment of ophthalmic herpes zoster with the hemocoagulating fraction of *Bothrops jacaraca* venom (hemocoagulase) (in Italian). Ann Ottalmol Clin Ocul 1968;94:1011–1026.
7 Zhu M, Cao J, Jia Z, Duan Z, Liu G, Wei J, Long H: Hemocoagulase in abdominal operation and its effect on hemoagglutination (in Chinese). Zhonghua Wai Ke Za Zhi 2002;40:581–584.
8 Palmisano PA: Klobusitsky's hemocoagulase in plastic surgery (in Italian). Minerva Chir 1975;30:686–692.
9 Kim SH, Cho YS, Choi YJ: Intraocular hemocoagulase in human vitrectomy. Jpn J Ophthalmol 1994;38:49–55.
10 Hansen T, Corbet A: Pulmonary physiology of the newborn; in Taeusch HW, Ballard RA (eds): Avery's Diseases of the Newborn, ed 7. Singapore, Harcourt Asia, 2001, pp 574–575.
11 Narayan S, Aggarwal R, Upadhyay A, Deorari AK, Singh M, Paul VK: Survival and morbidity in extremely low birth weight (ELBW) infants. Indian Pediatr 2003;40:130–135.
12 AlKharfy TM: High-frequency ventilation in the management of very-low-birth-weight infants with pulmonary hemorrhage. Am J Perinatol 2004;21:19–26.
13 Yam BM, Au SK: Comparison of the experiences of having a sick baby in a neonatal intensive care unit among mothers with and without the right of abode in Hong Kong. J Clin Nurs 2004;13:118–119.
14 Wong VC, Chiu SW: Health-care reforms in the People's Republic of China – Strategies and social implications. J Manag Med1998;12:270–286.
15 Berger TM, Allred EN, Van-Marter LJ: Antecedents of clinically significant pulmonary hemorrhage among newborn infants. J Perinatol 2000;20:295–300.
16 Cole VA, Norman ICS, Reynolds EOR, et al: Pathogenesis of hemorrhagic pulmonary edema and massive pulmonary hemorrhage in the newborn. Pediatrics 1973;51:175–177.
17 Ozawa H, Abiko Y, Akimoto T: A 50-year history of new drugs in Japan – The development and trends of hemostatics and antithrombotic drugs (in Japanese). Yakushigaku Zasshi 2003;38:93–105.
18 Pupita F, Di-Placido V, Zini R, Pupita P: Clinical pharmacology of the hemocoagulase isolated from *Bothrops jararaca* venom (in Italian). Clin Ter 1982;101:629–638.