Effect of Hemocoagulase for Prevention of Pulmonary Hemorrhage in Critical Newborns on Mechanical Ventilation: A Randomized Controlled Trial

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Manuscript received: January 18, 2007; Initial review completed: May 1, 2007; Revision accepted: December 4, 2007.

ABSTRACT

Objective: *To investigate the role of hemocoagulase to prevent pulmonary hemorrhage in critical newborns on mechanical ventilation.* ***Design:*** *Randomized controlled trial.* ***Setting:*** *Neonatal Intensive Care Unit of an affiliated hospital of a Medical University.* ***Children:*** *Seventy-two critical newborn infants on mechanical ventilation.* ***Intervention:*** *The involved neonates were divided randomly into two groups. Forty-one patients were treated with prophylactic hemocoagulase(dripped through the endotracheal tube), and other 31 neonates served as controls.* ***Outcome Measures:*** *Incidence of pulmonary hemorrhage, time of ceasing pulmonary hemorrhage if occurred, time of withdrawing of mechanical ventilation in the survivors, and mortality.* ***Results:*** *The incidence of pulmonary hemorrhage (12% vs 42%) and the time of ceasing pulmonary hemorrhage (1.36±0.65 vs 3.58±0.82, days), were significantly less in infants treated with prophylactic hemocoagulase as compared with the controls (P<0.05). The time to withdrawal of mechanical ventilation was less in the intervention group (3.20±0.45 vs 5.04±1.51 days) (P<0.05). The mortality in children who received hemocoagulase was 22.0%, which was significantly less than controls (41.9%)(P<0.05).* ***Conclusion:*** *Prophylactic use of hemocoagulase in mechanically ventilated neonates is effective against pulmonary hemorrhage.*

Key words: *Hemocoagulase, Mechanical ventilation, Newborn infant, Pulmonary hemorrhage.*

INTRODUCTION

Pulmonary hemorrhage is a life-threatening syndrome in critically sick neonates on mechanical ventilation. The incidence approaches 70% in those who die in the first week of life(1). Pulmonary hemorrhage is the principal cause of death in about 9% of neonatal autopsies(2,3). Recent reports have shown that the incidence of pulmonary hemorrhage is increasing in very small infants(4,5).

Hemocoagulase is distilled from the venom of the Brazilian snake *Bothrops atrox*(6). It has been used in plastic surgery, abdominal operation, and human vitrectomy. These patients received venous or muscular administration of 1KU of hemocoagulase 30 min before operation(7-9). It is worth investigating the role of prophylactic hemocoagulase in severely critical neonates in danger of pulmonary hemorrhage. We conducted this trial to investigate the prophylactic effect of hemocoagulase against pulmonary hemorrhage in mechanically ventilated newborn infants.

METHODS

This was a prospective randomized trial. Seventy-two neonates needing mechanical ventilation at the Neonatal Intensive Care Unit of Department of Pediatrics, between July 2000 to June 2004, were enrolled in the study. The mechanical ventilator used in the study was Babylog 8000 plus 5.n. (Dräger, Germany), and Synchronized Intermittent Mandatory Ventilation (SIMV) was the commonly used breath mode.

The Research Institute of Surgery and Daping Hospital affiliated to Third Military Medical University is a center of neonatal transport and a saving network consisting of 48 hospitals in Chongqing. Complete obstetric histories were

obtained and examinations were performed at the time of admission. The neonatal clinical course was followed prospectively and data were recorded on predetermined proforma sheets. The informed consent was obtained from the parents. This study was approved by the Clinical Research Committee of the Institute.

Newborn infants needing mechanical ventilation were included in the study. The indications of mechanical ventilation included repeated apnea episodes, PaO_2 <50mmHg, or/and $PaCO_2$ over 60 mmHg(10). Newborns with severe congenital heart disease, genetic or metabolic disorders, malformations of the mediastinum, lung parenchyma, neoplasia, and other congenital diseases in neurologic, gastrointestinal, hematologic, renal and genitourinary system were excluded.

The diagnosis of pulmonary hemorrhage was based on the continuous presence of blood-stained fluid in the endotracheal tube aspirates; other supporting evidence included: (*i*) chest radiograph showing the fluffy appearance of pulmonary edema in addition to the underlying pathology; (*ii*) increasing respiratory distress; and (*iii*) evidence of systemic deterioration such as shock(11).

Subjects were randomized by simple random number table to receive routine mechanical ventilation in addition to the treatment of the primary diseases (control group), or endotracheal hemocoagulase (0.25 KU) every 4-6 hourly in addition to ventilation (study group). In most subjects, the duration of intervention was 3-5 days.

The hemocoagulase used in this study was Reptilase, prepared and designed from venom of Brazilian snake *Bothrops atrox* (Solco Basle Ltd, Birsfelden-Basle, 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 37ºC *in vitro* within 60±20 seconds.

The data are expressed as mean±standard deviation, or median (range), for descriptive purpose. Chi-square and student *t* test were used to compare categorical and quantitative variables, between the study and control groups respectively.

RESULTS

Seventy-two neonates (42 boys, 30 girls) were enrolled. Their baseline characteristics are shown in ***Table* I**. The study and the controls were comparable with respect to gestational age, birth weight, gender, type of delivery, apgar scores, antenatal steroids, surfactant administration, patent ductus arteriosus, intracerebral hemorrhage, and the disease pattern. There were no complications during the administration of hemocoagulase. The outcome measures *i.e.*, the incidence of pulmonary hemorrhage, time to withdrawal of mechanical ventilation and the mortality are compared between the groups in ***Table* I**.

DISCUSSION

Pulmonary hemorrhage is still fatal in critically newborn infants, especially in those on mechanical ventilation. Outcome is poor because of lack of effective treatment(12). Pulmonary hemorrhage has been associated with a wide variety of predisposing factors, including tiny premature infant, hyaline membrane disease, severe asphyxia, sepsis, intrauterine growth retardation, severe hypothermia, and coagulopathy(13). It has been speculated that the important precipitating factor might lead to the increase of the filtration pressure, and injure the pulmonary capillary endothelium of the lung; this injury is aggravated on mechanical ventilation in the severely critical neonates. Pulmonary hemorrhage might be considered as an extreme form of high permeability pulmonary edema(14). Thus, mechanical ventilation might play a "double-faced" role in pulmonary hemorrhage. On the one hand, mechanical ventilation, which maintains adequate mean airway pressure, particularly end-expiratory pressure, has been suggested to be effective in the treatment of pulmonary hemorrhage; on the other hand, severely critical newborn infants with mechanical ventilation are in danger of pulmonary hemorrhage. In most cases of pulmonary hemorrhage, there is no evidence of coagulation disorders initiating the condition but probably exacerbate it in some cases. The results of this study provide the first evidence that prophylactic

TABLE I COMPARISON BETWEEN THE STUDY (HEMOCOAGULASE) AND CONTROL GROUPS

	Study group (n = 41)	Controls (n = 31)	P-value
A. Clinical data			
Gestational age (wk)	31.5±1.5	31.0±2.3	
Birth weight (g)	1490±830	1460±920	
Gender (Male/Female)	25/16	17/14	
Type of delivery (vaginal/cesarean)	11/30	6/25	
Apgar scores	7.2 ±2.5	7.4±1.9	
Antenatal steroids (%)	10 (24%)	7 (23%)	
Surfactant administration (Curosurf) (%)	6 (15%)	4 (13%)	
Patent ductus arteriosus (%)	4 (10%)	3 (10%)	
Intracerebral hemorrhage (%)	4 (10%)	4 (13%)	
Bleeding time (min)	5.1±2.2	4.9±2.6	
Prothrombin time (s)	14.1±2.7	14.4±2.7	
Partial thromboplastin time (s)	70.1±4.9	68.1±4.8	
B. Primary neonatal morbidity			
Perinatal asphyxia	17	14	
Respiratory distress syndrome	9	6	
Premature infant	8	5	
Sepsis	4	3	
Pneumonia	2	2	
Necrotizing enterocolitis	1	1	
C. Outcome			
Incidence of pulmonary hemorrhage	5(12%)	13(42%)	<0.05
Ceasing pulmonary hemorrhage (days)	1.36±0.65	3.58±0.82	<0.05
Withdrawing of mechanical ventilation in survivors (days)	3.20±0.45	5.04±1.51	<0.05
Number of surviving patients	32/41	18/31	<0.05

administration of hemocoagulase, when given through the endotracheal tube, is effective against pulmonary hemorrhage in mechanically ventilated neonates.

Hemocoagulase has been used in abdominal surgery, plastic surgery, and vitreous surgery. Hemocoagulase is suggested to play a good hemostatic role in the hemorrhagic capillary in abdominal incision, in cases of cleft palate and septum deviation during plastic surgery, and 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 two to three days. The hemostatic effect of hemocoagulase is not associated with any increase of the prothrombin level of the blood and therefore constitutes no danger of thrombosis(15,16). Our recent report also suggested that hemocoagulase could be safely used in the neonates after they suffered from pulmonary hemorrhage and, decreased the mortality(17). Considering the preventive effect of hemocoagulase, prophylactic administration of hemocoagulase in severely critical neonates in danger of pulmonary hemorrhage is worth consideration.

WHAT IS ALREADY KNOWN?

- Hemocoagulase is used as a hemostatic agent in abdominal surgery, vitrectomy, and plastic surgery.

WHAT THIS STUDY ADDS?

- Prophylactic administration of hemocoagulase by endotracheal tube is effective against pulmonary hemorrhage in critically sick newborns on mechanical ventilation.

Contributors: All authors contributed to study design, data acquisition and writing the manuscript.

Funding: None.

Competing interest: None stated.

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