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SPECIAL ARTICLE

Role of Hemocoagulase in Pulmonary Hemorrhage in Preterm Infants: A Systematic Review

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Abstract Pulmonary hemorrhage (PH) in neonates is associated with significant morbidity and mortality. IIemocoagulase is an established hemostatic agent and may be beneficial in neonates with severe PH.This systematic review was performed to investigate the clinical efficacy and safety of hemocoagulase therapy in preterm infants with Pulmonary hemorrhage (PH). The search strategy of the Cochrane Neonatal Review Group was used to determine outcomes following PH in neonates. The primary outcomes were mortality, duration of PH and length of mechanical ventilation. Other morbidities included: Respiratory Distress Syndrome, sepsis, intraventricular hemorrhage, necrotizing enterocolitis and bronchopulmonary dysplasia. The Cochrane Library, MEDLINE, EMBASE and CINAHL and bibliographies of identified trials were searched. The standard methods of the Cochrane Neonatal Review Group and van Tulder's guidelines were followed independently by the authors to assess study quality, enter data and report outcomes. Typical treatment effects were calculated using fixed confidence intervals (CI). Heterogeneity tests were performed. Two 'randomized' controlled studies related to the role of hemocoagulase in neonates were identified: One for treatment of PH and the other for prevention of PH. All preterm infants' of gestational age≤32 weeks and birth weight≤1500 g with PH were included in the study. A total of 48 and 72 preterm infants were enrolled and randomized into two groups in trial 1 and trial 2 respectively. Mortality risk was significantly lower in the treatment group (RR 0.52; 95%CI 0.31, 0.89, p<0.02) when hemocoagulase was used as therapy compared to prophylactic use in neonates (RR 0.52; 95%CI 0.26, 1.07, p=0.07). Duration of PH and mean duration of ventilation were shorter in both treatment and prophylactic groups. Use of hemocoagulase appeared to be effective in preventing PH in premature infants and reduced mortality. However, the potential risks of use of hemocoagulase including adverse effects and the effectiveness of hemocoagulase still remain uncertain due to the lack of good quality large randomized controlled studies. This needs further evaluation, before routine use can be recommended.

Keywords Pulmonary hemorrhage · Prematurity · Hemocoagulase · Mechanical ventilation

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Introduction

Pulmonary hemorrhage (PH) also known as hemorrhagic pulmonary edema can be a catastrophic event in preterm infants. PH is associated with significant morbidity and mortality [1–3]. The incidence of PH has been reported to be 11.9% in a population of very low-birth weight infants [4]. PH in 68% of neonates remains the major cause of

mortality in the first week of life [5–7]. Etiologies in preterm infants that have been reported to cause PH include: patent ductus arteriosus, use of surfactant, sepsis, disseminated intravascular coagulation and neurological insults including intraventricular hemorrhage [2, 8]. The four main mechanisms of PH are: increased pulmonary microvascular pressure, reduced intravascular oncotic pressure, reduced lymphatic drainage and increased microvascular permeability [9]. The pathological changes that occur in the lungs depend on the cause of PH. Management of PH varies according to the underlying etiology. One of the common practices in management of PH is optimizing ventilation by increasing positive end expiratory pressure. However, this strategy may not always be effective. Recently, the role of hemocoagulase has been studied in neonates with PH [10, 11].

Hemocoagulase is a mixture of purified enzymes isolated from the venom of a South American viper, *Bothrops atrox* [12–14]. It is free of neurotoxins and reduces blood loss. Hemocoagulase has two different enzymatic activities, one which promotes blood coagulation by converting prothrombin to thrombin (thromboplastin like enzymes) and the other which causes a direct transformation of fibrinogen to fibrin monomer. Hemocoagulase shortens the bleeding time and clotting time, by promoting coagulation locally at the site of bleeding.

The main contraindications for use of hemocoagulase are arterial thrombotic disorders and hypersensitivity [15, 16]. The potential side effects include anaphylactic reaction and or allergy [15, 16]. There is paucity of information related to the use of hemocoagulase and any associated adverse effects in newborns.

The primary objective was to perform a systematic review to investigate the clinical efficacy and safety of hemocoagulase therapy in preterm infants with PH.

The key characteristics of this review were: a clearly predefined objective and eligibility criteria for inclusion and exclusion of studies, an explicit reproducible methodology, a systematic literature search, an assessment of the validity and systematic presentation.

Material and Methods

Identification of Studies

Types of Studies

A literature search was carried out to identify studies that evaluated the role of hemocoagulase in neonatal pulmonary hemorrhage. The authors searched observational and randomized controlled trials with *a priori* inclusion and exclusion criteria. The literature search for identification of studies was based on the search strategy described in this paper.

Type of Participants

Inclusion Criteria

The main *a priori* inclusion criteria for consideration of the randomized controlled trials were:

- Preterm infants <37 weeks and less than 1 month of age admitted to the NICU
- PH (Diagnosis of PH was based on persistence of sanguineous endotracheal tube aspirate and presence of other features including 'fluffy' appearance on chest radiograph, and a clinical picture of respiratory distress).

Exclusion Criteria

- Major life threatening congenital anomalies including congenital heart disease
- Malformations of the mediastinum, lung parenchyma and neoplasia

Hemocoagulase was compared with a placebo or with no intervention.

Outcome Measures

Primary Outcomes

- Mortality (including infants who die after discharge from the NICU)
- Duration of PH in days
- Duration of mechanical ventilation in days

Other common conditions like RDS, PDA, ICH, perinatal asphyxia [Umbilical Cord pH <7.0, APGAR score <3 at >5 min, clinical neurological conditions (like seizures or signs of hypoxic ischaemic encephalopathy), evidence of multiorgan failure], pneumonia (radiological findings of pneumonia and increased respiratory distress), sepsis (positive blood culture), cold injury, NEC, BPD and DIC (abnormal PT and PTT tests) were compared between hemocoagulase and control groups in both studies. Respiratory distress syndrome (RDS) was defined by clinical criteria, radiological findings consistent with RDS, requirement for surfactant and mechanical ventilation for 24 h. Necrotizing enterocolitis was defined according to Bell's criteria (stage ≥ 2) and was classified as medical or surgical [17]. Patent ducts arteriosus (PDA) was diagnosed on the basis of clinical findings with or without echocardiography. Chronic lung disease (BPD) was defined as supplemental oxygen dependency at 36 weeks corrected age [18]. If an infant was discharged home or transferred to another medical facility before 36 weeks corrected GA on supplemental

oxygen, a diagnosis of BPD was made. Diagnosis and severity of intraventricular hemorrhage (IVH) was determined using criteria of the Canadian Paediatric Society statement on the use of cranial ultrasound screening [19].

Frequencies of anaphylactic reaction and or allergy were also compared among both groups.

Search Strategy for Identification of Studies

The search strategy of the Cochrane Neonatal Review Group was used. The following databases were searched: Medline (1966 to September 2009), Cochrane Central Register of Controlled Trials (The Cochrane Library, issue 3 2009), CINAHL (1982 to September 2009) and EMBASE (1980 to September 2009). In addition, the authors searched abstracts from the Pediatric Academy Societies' annual meetings published in Pediatric Research (1990 to July 2009) and the Canadian Paediatric Society's annual meeting proceedings (1990 to July 2009). No language restrictions were applied. Relevant trials were also identified by tracking citations. Experts in the field were also contacted to improve the search strategy.

Search Strategy Controlled vocabulary (MeSH terms), keywords and text words used: randomized controlled trial (RCT) (1), newborn infant (limited to human, birth to 1 month) (2), combined 1 and 2 (3), lung disease/or hemorrhage or pulmonary hemorrhage (4), combined 3 and 4 (5), Hemocoagulase or Batroxobin (6), combined 5 and 6 (7), treatment or therapies (8), combined 6 and 8 (9), combined 9 and 2 (10), prevention (11), combined 2 and 11 (12), combined 6 and 12 (13)

Study Selection and Data Extraction All abstracts and published studies were independently identified and assessed for inclusion by two reviewers (title, abstract, keywords). Full papers were reviewed according to inclusion criteria. Individual reviewer separately extracted data using the Standardized Neonatal Cochrane group data abstraction forms.

One reviewer entered data into RevMan 5.0 (Update Software Oxford, UK) and the other reviewer cross-checked the printout against the data abstraction forms. Errors were corrected.

The third and fourth reviewers examined all results, scientific contents and conclusions. The information was compared and all differences were resolved by consensus. In the event consensus could not be reached, the third reviewer entered data separately and resolved the disagreement.

The choice between qualitative and quantitative (meta-analysis) pooling was based on the available data and homogeneity.

Methodological Quality

Two reviewers assessed the methodological quality according to van Tulder's guidelines [20] and Cochrane Neonatal Review Group method. Van Tulder scale includes 11 items to assess internal validity of clinical trials. Trials which have six or more items were considered to be high quality [20]. It was impractical to mask the reviewers to the authors, institutions or journals.

Statistical Analysis

RevMan 5.0 software is the software used for preparing and maintaining Cochrane reviews (The Information Management System, 2008) was used to analyse the data. Heterogeneity was assessed using *Chi-Square* test and P-values lower than 0.05 were considered to be statistically significant. Where there was no statistically significant difference in the results, a fixed effect model was used for meta-analysis. Relative risk (RR), number needed to treat (NNT) for dichotomous outcomes and weighted mean difference (WMD) for continuous outcomes were used. All estimates of treatment effects were reported with 95%CI. As hemocoagulase was used either as a therapeutic agent or a prophylactic agent in the two RCTs [10, 11], the authors could not combine results from both studies [10, 11] for analysis.

Results

Description of Studies There were no observational studies on the use of hemocoagulase in PH in neonates. Two randomized controlled studies assessing the effects of hemocoagulase vs control for the treatment of PH were identified [10, 11].These studies were performed in the tertiary referral NICU affiliated with Third Military Medical University which caters to 48 hospitals in Chongqing, China. In the Shi et al study, hemocoagulase was used as a therapeutic agent [10] and in another RCT, hemocoagulase was used for prophylaxis [11]. A detailed description of both studies is presented in Table 1.

Hemocoagulase is marketed in the trade name of Slounase in China by Lee's Pharma (www.leespharm.com).

In a randomized controlled trial on hemocoagulase for treatment of PH in neonates, all preterm infants eligible for the study were randomized into two groups based on random number table (Table 1) [10]. The control group was managed with routine mechanical ventilation maintaining an adequate mean airway pressure and positive end-expiratory pressure of 5 to 7 cm H_2O. Toxicity due to hemocoagulase was also monitored

Table 1 Characteristics of included studies

Study ID	Methods	Participants	Interventions	Outcome	Notes	Allocation concealment
Shi et al. 2005	RCT, Treatment study Intention to treat basis-No Masking of allocation-Yes Masking of intervention-No Masking of outcome assessment-No Completeness of follow-up-Yes	Total 48 neonates eligible for the study Total 48 neonates enrolled, of which 28 preterm infants in the hemocoagulase group and 20 preterm infants in the control group	Study group: Hemocoagulase was instilled into endotracheal tube at a dose of 0.5 KU each time, and repeated every 4–6 h until pulmonary hemorrhage stopped Control group: Mechanical ventilation with increased positive end expiratory pressure	Primary outcomes-Cessation of PH, mortality, duration of mechanical ventilation Secondary outcome-Coagulopathy	Definition of PH means blood stained fluid effused from endotracheal tube aspirates with fluffy changes on chest radiograph, increased respiratory distress, systematic deterioration such as shock Coagulopathy: abnormal prothrombin time, partial thromboplastin time, bleeding time (Study period: January 2001 to January 2004) Funding: Unclear	Grade B: Unclear
Shi et al. 2008	RCT, Prophylactic study Intention to treat basis-No Masking of allocation-Yes Masking of intervention-No Masking of outcome assessment-No Completeness of follow-up-Yes	Total 72 neonates eligible for the study Total 72 neonates enrolled, of which 41 subjects in the Hemocoagulase group and 31subjects in the control group	Study group: Hemocoagulase was instilled into endotracheal tube at a dose of 0.5 KU each time, and repeated every 4–6 h until pulmonary hemorrhage stopped Control group: Mechanical ventilation with increased positive end expiratory pressure	Primary outcomes-Incidence of PH, cessation of PH, withdrawing of mechanical ventilation in survivors (days), number of surviving patients Secondary outcome-Coagulopathy	Definition of PH means continuous presence of blood stained fluid in the endotracheal tube aspirates with fluffy changes on chest radiograph, increased respiratory distress, evidence of cardiorespiratory failure Coagulopathy: abnormal prothrombin time, partial thromboplastin time, bleeding time (Study period: July 2000 to June 2004) Funding: None	Grade B: Unclear

in all preterm infants. The administration of surfactant and blood products was not different between the two groups.

In another randomized controlled trial to determine the role of hemocoagulase as a prophylactic agent to prevent PH, preterm infants were randomized by simple random number table to receive routine mechanical ventilation and hemocoagulase in the treatment group and only mechanical ventilation in the control group (Table 1) [11].

Due to the differences in the intention to use hemocoagulase, these two studies were not combined in the final analysis (Table 1) [10, 11]. Details about study population characteristics, clinical data and morbidities are shown in Tables 1 and 2. The numbers of infants in both studies were small and the dose of hemocoagulase was different (Table 1) [10, 11]. It is possible that a smaller dose was used for prophylaxis. The patients' characteristics were similar in both treatment and control groups in both studies (Table 2). Clinical data from both studies is presented in Table 2 [10, 11].

Analysis revealed a 48% reduction (RR 0.52; 95%CI 0.31, 0.89, P<0.02) in mortality rates in the hemocoagulase group compared to the control group in the treatment study (Fig. 1) [10]. This gives an absolute risk reduction (35.7%) of mortality due to PH from 75% to 39.3%, which yields a number needed to treat equal to 3 (95% CI 1.6, 10.5) [10]. In the prophylaxis study [11], there was a 48% reduction (RR 0.52, 95%CI 0.26, 1.07, *P*=0.07) in mortality in the hemocoagulase group compared with the control group (Fig. 1). This gives an absolute risk reduction of mortality (20%), which yields a number needed to treat equal to 5 (95% CI 2.4, -65.9.) [11]. In the first study [10] where hemocoagulase was used as a treatment, there was a shorter duration of PH (weighted mean difference -1.74; 95%CI -2.22, -1.26, P <0.00001) and a shorter period was required for ventilation (weighted mean difference -1.55; 95%CI -2.07, -1.03, P <0.00001) compared to the control group (Fig. 2). In the second study [11] where hemocoagulase was used as a prophylactic agent to prevent PH, there was a shorter duration of PH (weighted mean difference -2.22, 95%CI -2.57, -1.87, P<0.00001) and a shorter period was required for ventilation (weighted mean difference -1.84, 95% -2.39, -1.29, P<0.00001) compared to the control group (Fig. 2).

The incidence of RDS, perinatal asphyxia, ICH, PDA, BPD, pneumonia, sepsis and the number of infants who received surfactant were not statistically significant between the study and control groups in both studies (Table 2) [10, 11].

In both studies, the hemocoagulase group had a shorter duration of PH [11]. Neither study stated whether additional doses of surfactant were administered at time the PH occurred.

The funnel plot which examines the publication bias has not been included in this review as its value is limited based

Table 2 Comparison between the hemocoagulase and control groups

Study	Treatment study (Shi et al, 2005)		Prophylaxis study (Shi et al, 2008)	
	Hemocoagulase (*n*=28)	Control (*n*=20)	Hemocoagulase (*n*=41)	Control (*n*=31)
Gestational age, wks	30.5±1.8	30.9±2.9	31.5±1.5	31.0±2.3
Birth weight, g	1380±630	1410±720	1490±830	1460±920
Vaginal delivery/Cesarean section	9/19	5/15	11/30	6/25
RDS	9/28	6/20	9/41	6/31
PDA	2/28	2/20	4/41	3/31
ICH	3/28	3/20	4/41	4/31
Perinatal Asphyxia	13/28	8/20	17/41	14/31
Pneumonia	2/28	2/20	2/41	2/31
Sepsis	3/28	3/20	4/41	3/31
Cold injury	1/28	1/20	No data	No data
NEC	No data	No data	1/41	1/31
Death	11/28	15/20	9/41	13/31
Surfactant	3/28	2/20	6/41	4/31
PRBC/Platelet transfusion	5/28	3/20	No data	No data
Duration of PH (days)	1.86±0.85	3.60±0.88*	1.36±0.65	3.55±0.6*
Bleeding time, min	5.2±2.3	4.9±2.5	5.1±2.2	4.9±2.6
Prothrombin time, seconds	14.2±2.1	14.5±2.5	14.1±2.7	14.4±2.7
Partial thromboplastin time, seconds	70.3±4.8	68.9±3.8	70.1±4.9	68.1±4.8

*p<0.05

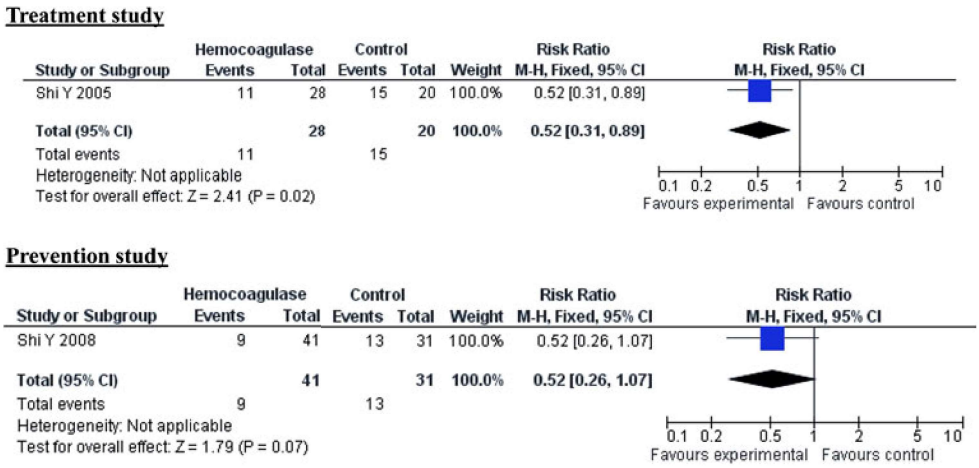

Fig. 1 The role of hemocoagulase in PH: Mortality

on one single study included in each treatment and prophylaxis studies.

Discussion

Pulmonary hemorrhage is a common problem in extremely premature infants in NICUs and can be life threatening. It is associated with increased morbidity and mortality in VLBW infants [1–3, 21]. The higher incidence of PH in the two studies reviewed may have been due to the increased incidence of central nervous system insults associated with perinatal asphyxia and/or ICH. Definitive and effective therapies to treat PH in neonates are still lacking. Hemocoagulase is a new therapy for PH in neonates, but has not been studied in a large multicentre clinical trial.

In this systematic review, the authors found hemocoagulase to be effective in reducing mortality associated with PH, the total duration of PH and duration of mechanical ventilation when used for treatment of PH. In contrast, the role of hemocoagulase for the prevention of PH was not associated with a reduction in mortality compared to the control group. In both studies, there was no evidence of anaphylactic or allergic reaction in neonates who received hemocoagulase.

The incidence of various morbidities in premature infants in both groups was not different.

In both studies the authors identified several methodological flaws including the following:

- The studies were carried out by the same investigator for treatment and prevention of PH using different doses of hemocoagulase.
- The method of randomization is not well described, and the studies did not reveal how randomization numbers were concealed or how infants were counted.
- The number of infants was unequal in the two groups. It is unclear if the unequal numbers arose from deliberate unbalanced randomization and raises the question of possible selection bias. However, imbalance in one or more trials has no effect on standard meta-analysis [22]. Separate estimates are obtained from each trial that take correct account of the numbers per arm. This is a form of Simpson's paradox [22]. This study also has a potential source of performance and detection bias.
- Sample size was also not calculated in both studies.

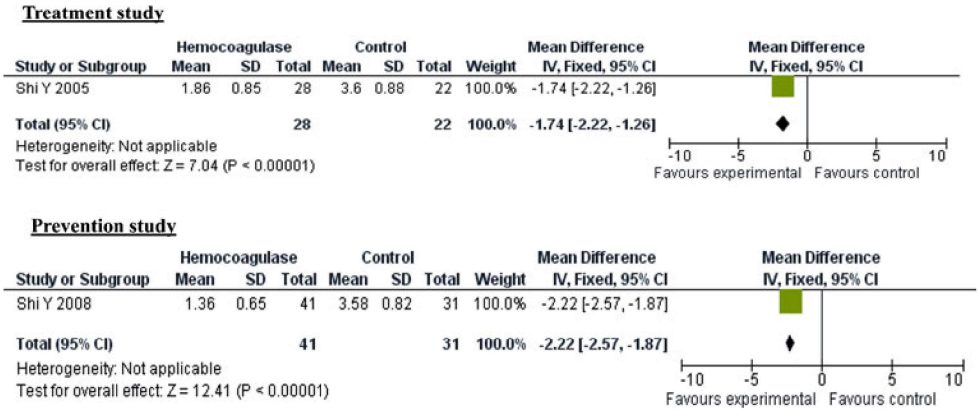

Fig. 2 The role of hemocoagulase in PH: Duration of PH

- Neither study mentions how blinding of intervention and outcome measurement was performed. Lack of blinding of the intervention may have impacted reporting of the duration of PH and time of cessation of PH.
- Coagulation tests were performed but fibrinogen levels, fibrinogen degradation products, thrombin time, blood counts and platelets were not reported but assumed normal.
- The time course of PH did not permit baseline ultrasound evaluations on all patients but post intervention head ultrasound scans were not systematically performed to clearly delineate the presence/absence or progression of intracranial hemorrhage, infarction and ischemia.
- Hemorrhagic complications in other sites are not reported.
- The definitions of RDS, BPD, PDA, NEC, cold injury, severity of perinatal asphyxia in the original trials were also lacking. The first trial [10] includes the mortality of patients who were discharged from the NICU whereas the second trial [11] was less clear regarding this end-point.
- The causes of death in infants enrolled in the studies are unclear. It is also unclear if any of the deaths were attributable to the intervention (hemocoagulase).
- No long term follow-up data is available for analysis.

These methodological issues raise the concern that the quality of the two selected trials was not of a sufficiently high standard and may have possibly influenced the differences in outcomes attributed to hemocoagulase as the primary intervention. Therefore, the results of the systematic review cannot be generalized due to methodological flaws in the included studies [10, 11].

Conclusions

This systematic review indicates that the use of hemocoagulase may possibly reduce the duration of PH in premature infants and reduce mortality. However, the role of hemocoagulase in PH needs further evaluation before routine use can be recommended. The authors recommend a well planned, multicentre randomized controlled trial to determine the efficacy and safety of hemocoagulase therapy in preterm neonates with PH.

Contributions All authors contributed to study design, data acquisition and writing the manuscript

Conflict of Interest None.

Role of Funding Source None.

References

1. Lin TW, Su BH, Lin HC, et al. Risk factors of pulmonary hemorrhage in very-low-birth-weight infants: a two-year retrospective study. Acta Paediatr Taiwan. 2000;41:255–58.
2. Lodha A, Shah PS, Hellmann J. Pulmonary haemorrhage associated with neonatal neurological disease. Heart Lung Circ. 2009;18:45–8.
3. Sly PD, Drew JH. Massive pulmonary haemorrhage: a cause of sudden unexpected deaths in severely growth retarded infants. Aust Paediatr J. 1981;17:32–4.
4. Pandit PB, Dunn MS, Colucci EA. Surfactant therapy in neonates with respiratory deterioration due to pulmonary hemorrhage. Pediatrics. 1995;95:32–6.
5. Berger TM, Allred EN, Van Marter LJ. Antecedents of clinically significant pulmonary hemorrhage among newborn infants. J Perinatol. 2000;20:295–300.
6. 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;153:715–21.
7. Kostelanetz AS, Dhanireddy R. Survival of the very-low-birth-weight infants after cardiopulmonary resuscitation in neonatal intensive care unit. J Perinatol. 2004;24:279–83.
8. Berger TJ, Chavez C, Tew RD, Navasca FT, Ostrow DH. Biological indicator comparative analysis in various product formulations and closure sites. PDA J Pharm Sci Technol. 2000;54:101–9.
9. Snashall PD. Pulmonary oedema. Br J Dis Chest. 1980;74:2–22.
10. Shi Y, Tang S, Li H, Zhao J, Pan F. New treatment of neonatal pulmonary hemorrhage with hemocoagulase in addition to mechanical ventilation. Biol Neonate. 2005;88:118–21.
11. Shi Y, Zhao J, Tang S, et al. Effect of hemocoagulase for prevention of pulmonary hemorrhage in critical newborns on mechanical ventilation: a randomized controlled trial. Indian Pediatr. 2008;45:199–202.
12. Kim SH, Cho YS, Choi YJ. Intraocular hemocoagulase in human vitrectomy. Jpn J Ophthalmol. 1994;38:49–55.
13. Palmisano PA. Klobusitsky's hemocoagulase in plastic surgery. Minerva Chir. 1975;30:686–92.
14. Valvo A. New treatment of ophthalmic herpes zoster with the hemocoagulating fraction of Bothrops jacaraca venom (Hemocoagulase). Ann Ottalmol Clin Ocul. 1968;94:1011–26.
15. Slounase. http://www.leespharm.com/en/product_launched_detail.php?id=3
16. Kornalik F. The influence of snake venom enzymes on blood coagulation. Pharmac Ther. 1985;29:353–405.
17. Kliegman RM, Walsh MC. Neonatal necrotizing enterocolitis: pathogenesis, classification, and spectrum of illness. Curr Probl Pediatr. 1987;17:213–88.
18. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics. 1988;82:527–32.
19. Fetus and Newborn Committee of Canadian Pediatric Society: Routine screening cranial ultrasound examinations for the prediction of long term neurodevelopmental outcomes in premature infants. *J Paediatr Child Health* 2001; 39–52. Available at, 6.
20. van Tulder M, Furlan A, Bombardier C, Bouter L. Updated method guidelines for systematic reviews in the cochrane collaboration back review group. Spine (Phila Pa 1976). 2003;28:1290–9.
21. Pappin A, Shenker N, Hack M, Redline RW. Extensive intra alveolar pulmonary hemorrhage in infants dying after surfactant therapy. J Pediatr. 1994;124:621–6.
22. Altman DG, Deeks JJ. Meta-analysis, Simpson's paradox, and the number needed to treat. BMC Med Res Methodol. 2002;2:3.