Original Article doi: 10.2176/nmc.oa.2019-0062

Neurol Med Chir (Tokyo) 59, 371–378, 2019 Online July 6, 2019

Initial Results of Empirical Cryoprecipitate Transfusion in the Treatment of Isolated Severe Traumatic Brain Injury: Use of In-house-produced Cryoprecipitate

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Abstract

Acute coagulopathy is common after traumatic brain injury (TBI), particularly in severe cases of acute subdural hemorrhage (ASDH). Although acute coagulopathy is associated with poor outcomes, the optimal treatment strategy remains unknown. Here, we report the initial results of an empirical cryoprecipitate transfusion strategy that we developed as an early intervention for acute coagulopathy after TBI. We performed chart reviews of adult patients (aged ≥18 years) who received early cryoprecipitate transfusion after admission to our institution with a diagnosis of severe TBI (Glasgow Coma Scale ≤8) and ASDH from March 2013 to December 2016. We compared the outcomes of these patients with those who were treated before the implementation of the cryoprecipitate transfusion strategy (January 2011–February 2013). During the study period, 33 patients received early cryoprecipitate transfusion and no acute transfusion-related adverse event was reported. The rate of coagulopathy development within 24 h after admission was lower in these patients (23%) than in the controls (49%), but the difference was not significant ($P = 0.062$). The in-hospital mortality rate was 36% in patients receiving early cryoprecipitate transfusion and 52% in controls. After adjusting for confounding factors, the in-hospital mortality rate was significantly lower in the intervention period [adjusted odds ratio: 0.25, 95% confidence interval (CI): 0.08–0.78, $P = 0.017$]. In summary, we analyzed initial results of a cryoprecipitate transfusion strategy in patients with severe isolated TBI and ASDH. No acute transfusion-related adverse event was observed, and early transfusion of the in-house-produced cryoprecipitate may have reduced rates of coagulopathy development and in-hospital mortality.

Key words: coagulopathy, cryoprecipitate, mortality, transfusion, traumatic brain injury

Introduction

Traumatic brain injury (TBI) is a leading cause of death after trauma.[1)] Acute coagulopathy developing after TBI has been recognized as a major complication contributing to secondary brain injury and impaired outcomes.[2–5)] The reported incidence of acute coagulopathy in isolated TBI varies widely between 10% and 90%; this incidence is especially elevated in patients with severe TBI, such as those with acute subdural hemorrhage (ASDH).[3,6,7)]

Therefore, early correction of coagulopathy after TBI is crucial for reducing mortality rates, particularly among those with severe TBI. One common option for the treatment of acute coagulopathy is the plasma component, and the use of cryoprecipitate can theoretically recover the normal values of fibrinogen faster than the use of fresh frozen plasma (FFP).[8)] However, the benefits of using cryoprecipitate on the outcomes of patients with isolated TBI have not been established,[9)] and the optimal transfusion strategy to treat acute coagulopathy after TBI has only been investigated in a few clinical studies.

Based on the high prevalence of coagulopathy in severe TBI that results in increased mortality and decreased fibrinogen levels at the early phase after injury,[10)] we hypothesized that early transfusion of cryoprecipitate helps to prevent the development of coagulopathy and to reduce mortality in patients with severe TBI and ASDH. We then implemented a cryoprecipitate transfusion strategy, in which

Received April 6, 2019; Accepted May 29, 2019

empirical transfusion of cryoprecipitate was allowed if the attending physician was certain of the benefit of the transfusion in each case.

In this study, we aimed to report the initial results of our strategy of transfusion with in-house-produced cryoprecipitate, including data on both efficacy and safety in patients with severe TBI and ASDH.

Materials and Methods

Study setting

This retrospective cohort study was performed at the Tertiary Emergency Medical Center, Metropolitan Bokutoh Hospital, which is located in eastern Metropolitan Tokyo, Japan. Following our institutional protocol, blood tests were performed immediately after arrival and within the first 24 h after admission. In our 24-bed intensive care unit, patients were managed by full-time physicians, including neurosurgeons and intensivists. Rehabilitation was actively introduced as soon as the patient was fit for the therapy.

We performed a chart review of a prospectively maintained database of all trauma patients who were admitted to our institution from January 2011 to December 2016. This study was divided into two periods. The first period was the observational control period in which the cryoprecipitate transfusion protocol had not yet been implemented (January 2011–February 2013). The second period was the intervention period (March 2013–December 2016), in which we implemented the cryoprecipitate transfusion strategy that allowed attending physicians to empirically transfuse three packs of in-house cryoprecipitate to patients who were diagnosed with severe TBI with ASDH, even before the results of the coagulation tests were available. This was considered only if the physician was certain of the benefit of the transfusion. Except for the cryoprecipitate transfusions during the interventional period, blood components were transfused with reference to the established guidelines.[11–13]

Patient cohort

We included adult patients (aged ≥18 years) who were diagnosed with severe TBI with ASDH after blunt head injury, and who received cryoprecipitate transfusion under the implemented strategy. Their outcomes were compared with those of adult patients who were diagnosed with severe TBI with ASDH after blunt head injury, but whose diagnoses occurred before the implementation of the cryoprecipitate transfusion strategy. Patients were excluded if they were not transported directly from the scene to our institution or had major extra-cranial injury, as indicated by an Abbreviated Injury Scale (AIS) score of ≥3. The diagnoses were based on the results of whole-body computed tomography scans. Severe TBI was defined as TBI with a Glasgow Coma Scale (GCS) score of ≤8 on admission.

Cryoprecipitate and blood products in our hospital

Blood products, such as red blood cell (RBC) solution, FFP, and platelet concentrate (PC), were supplied by the Japanese Red Cross Society (Tokyo, Japan). While both RBC solution (one unit: 140 mL, two units: 280 mL) and FFP (one unit: 120 mL, two units: 240 mL) were produced from donated whole blood, PC and four units FFP (480 mL) were obtained via apheresis from donors.

Fibrinogen concentrate is not available in Japan, and cryoprecipitate is not produced by the Japanese Red Cross Society. Thus, cryoprecipitate is prepared in hospitals in Japan where patients with acquired hypofibrinogenemia are admitted. In this study, cryoprecipitate was produced by our staff from the Department of Transfusion Medicine using a modified method as previously described.[14] In brief, one pack of cryoprecipitate was prepared from type AB RhD-positive FFP (480 mL) by collecting the precipitate formed during controlled thawing at 4°C and re-suspending in 30–50 mL plasma. The cryoprecipitate can be stored up to a year at temperatures of −20°C or lower. Each pack of cryoprecipitate produced by our hospital contains 1500–2500 mg/dL of fibrinogen, 500–600% activity of factor VIII, 1000–1200% activity of von Willebrand factor, and 200–300% activity of factor XIII.

At least 20 packs of cryoprecipitate are readily available for use in our hospital. A pack of cryoprecipitate can be thawed within 9 min using recirculating water bath thawing system at 37°C (FF-40, Kawasumi Laboratories Incorporated, Oita, Japan). Although the methods of manufacturing may vary in different facilities, the cryoprecipitate products have relatively similar components.[15]

Data collection

We assessed the patient's medical history, age, sex, mechanism of injury, GCS score on admission, systolic blood pressure on admission, respiratory rate on admission, AIS diagnostic codes, Revised Trauma Score (RTS), Injury Severity Score (ISS), probability of survival calculated using the Trauma and ISS (TRISS), laboratory results obtained at admission and within 24 h after admission, type and number of transfused units given in the hospital, time from patient arrival at the hospital to plasma component (FFP or cryoprecipitate) transfusion, administration

of tranexamic acid, acute adverse events related to cryoprecipitate transfusion, and information on discharge from the hospital.

The RTS is a scoring system based on the physiological severity of trauma that incorporates the GCS score, systolic blood pressure, and respiratory rate. The values range from 0 to 7.84, and low scores indicate a high severity of injury. The ISS is a scoring system based on the anatomical severity of trauma that positively correlates with mortality. The TRISS comprises the RTS and the ISS, and indicates the probability of survival after trauma.[16]

The primary outcome was in-hospital mortality. The secondary outcomes were the incidence of acute transfusion-related adverse events and the development of coagulopathy in the first 24 h after admission. Coagulopathy was defined on the basis of a previous study[2] as an activated partial thromboplastin time of ≥35 s, a prothrombin time international normalized ratio of ≥1.3, and/or platelet count of $\leq 10 \times 10^9$/L.

Statistical analysis

For descriptive statistics, numeric variables are presented as medians with interquartile ranges (IQRs), while categorical variables are presented as counts and percentages. We tested for differences in baseline characteristics between patients in the observation period (control group) and those in the intervention period (intervention group) using the Chi-square or Fisher's exact test for categorical data and the Mann–Whitney *U*-test for continuous data. We used a multivariate logistic regression model to determine whether the cryoprecipitate transfusion protocol was independently associated with in-hospital mortality.

Explanatory variables, such as age and probability of survival estimated using the TRISS, were chosen *a priori* based on previously available evidence. Variance inflation factors were used to check for multicollinearity. The adjusted odds ratios and 95% CIs were calculated. All statistical tests were two-tailed, and a *P*-value of <0.05 was considered significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[17]

Ethical approval

The study was approved by the Institutional Review Board of the Tokyo Metropolitan Bokutoh Hospital (approval number: 29-117). The need for informed consent was waived as the data were collected from existing patient records, and the de-identification standard was followed to protect the confidentiality of personal information.

Results

We identified 33 patients who were transfused with cryoprecipitate under the cryoprecipitate transfusion strategy between March 2013 and December 2016 (intervention group) (Fig. 1). No acute adverse events related to the cryoprecipitate transfusion were reported during the study period. For analysis, 46 patients treated between January 2011 and February 2013 were considered eligible to be included in the control group.

Table 1 shows the demographic and clinical features of patients in these two groups. The median ages in the control and intervention groups were 69 (IQR, 61–77) and 72 (IQR, 62–79) years, respectively. Most patients in both the groups were men. There were five patients with pre-existing liver disease (four and one in the control and intervention groups, respectively). There were five patients who were on anticoagulant medication (three and two in the control and intervention groups, respectively).

The GCS score on arrival and RTS tended to be lower in the intervention group than in the control group [GCS score: 3 (IQR, 3–6) vs. 5 (IQR, 3–6), $P = 0.063$; RTS: 5 (IQR, 4–6) vs. 4 (IQR, 4–6), $P = 0.041$]. As evaluated using TRISS, the predicted probability of survival was significantly lower in the intervention group [43% (IQR, 27–63%)] than in the control group [60% (IQR, 45–66%), $P = 0.029$].

The levels of fibrinogen degradation product and D-dimer were elevated in all patients. The

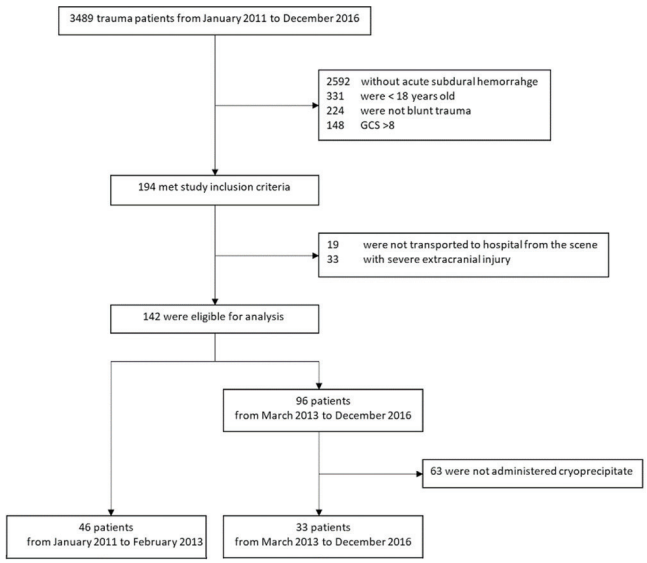

Fig. 1 Flowchart of patient enrolment. GCS: Glasgow Coma Scale.

Table 1 Patient characteristics and outcomes

Variables	Control period	Intervention period	*P*-value
No. of patients	46	33	
Age (years)	69 [61–77]	72 [62–79]	0.39
Men	30 (65)	18 (55)	0.36
Pre-existing liver disease	4 (9)	1 (3)	0.39
Use of anticoagulants	3 (6)	2 (6)	0.99
Mechanism of trauma			0.60
Fall at ground level	14 (30)	10 (30)	
Traffic accident	11 (24)	12 (37)	
Fall on stairs	11 (24)	8 (24)	
Others	5 (11)	2 (6)	
Unknown	5 (11)	1 (3)	
Glasgow Coma Scale score	5 [3–6]	3 [3–6]	0.063
Eye response	1 [1–1]	1 [1–1]	
Verbal response	1 [1–1]	1 [1–1]	
Motor response	3 [1–4]	1 [1–4]	
Revised Trauma Score	5 [4–6]	4 [4–6]	0.041
Maximum AIS in the head region			0.30
4	7 (15)	2 (6)	
5	39 (85)	31 (94)	
Injury Severity Score	25 [25–25]	25 [25–25]	0.086
Injury Severity Score >25	2 (4)	4 (13)	
Probability of survival (TRISS model)	60 [45–66]	43 [27–63]	0.029
Coagulopathy on admission	10 (22)	9 (27)	0.60
aPTT ≥35 s	6 (13)	7 (21)	
PT-INR ≥1.3	4 (9)	4 (12)	
Platelet $\leq 10 \times 10^9$/L	5 (11)	3 (9)	
FDP on admission (μg/mL)	91 [37–241]	158 [65–410]	0.085
D-dimer on admission (μg/mL)	43 [21–145]	82 [31–208]	0.17
Fibrinogen on admission (μg/mL)	251 [146–546]	216 [95–574]	0.10
Time from arrival to plasma component transfusion (min)	222 [170–274]	72 [53–123]	<0.001
Cryoprecipitate transfusion (pack)	0 [0–0]	3 [1–6]	
Fresh frozen plasma transfusion (unit)	6 [0–10]	6 [0–14]	0.74
Red blood cell transfusion (unit)	4 [0–8]	4 [0–18]	0.98
Platelet transfusion (unit)	0 [0–20]	0 [0–20]	0.92
Tranexamic acid administration	19 (41)	33 (100)	<0.001
Neurosurgical interventions			0.084
ICP sensor placement and/or drainage	2 (4)	5 (15)	
Craniotomy or craniectomy	40 (87)	28 (85)	
None	4 (9)	0	
Blood loss during craniotomy or craniectomy (mL)	496 [179–898]	495 [260–923]	0.58
Coagulopathy development in 24 h	16 (49)	7 (23)	0.066
In-hospital mortality	24 (52)	12 (36)	0.18

Data are presented as number (%) or median [interquartile range, Q1–Q3]. AIS: Abbreviated Injury Score, aPTT: activated partial thromboplastin time, FDP: fibrinogen degradation product, ICP: intracranial pressure, PT-INR: prothrombin time international normalized ratio, TRISS: Trauma and Injury Severity Score.

fibrinogen levels on arrival were not significantly different between the two groups. There were four patients (two patients each in the control and intervention groups) with severe hypofibrinogenemia (<100 mg/dL), and 32 patients (16 patients each in the control and intervention groups) with moderate hypofibrinogenemia (<200 mg/dL) on admission. All four patients with severe hypofibrinogenemia died; among those with moderate hypofibrinogenemia, 19 patients (59%) died, including 12 and seven patients in the control and intervention groups, respectively.

The time from patient arrival at the hospital to plasma component transfusion was significantly shorter in the intervention group than in the control group [72 (IQR, 53–123) vs. 222 (IQR, 170–274) min, respectively (P <0.001)]. For each type of transfusion, the number of transfused units was not significantly different between the two groups. The rate of tranexamic acid administration was significantly higher in the intervention group than in the control group (41% vs. 100%, P <0.001).

The two groups did not differ significantly in terms of the rate of neurosurgical interventions, or in terms of blood loss during craniotomy or craniectomy. Although the differences were not statistically significant, the in-hospital mortality rate (36% vs. 52%, P = 0.18) and the rate of coagulopathy development in 24 h after admission (23% vs. 49%, P = 0.062) tended to be lower in the intervention group than in the control group. In the intervention and control groups, the cause of death was refractory increased intracranial pressure in nine (75%) and 19 (79%) patients, acute circulatory failure in one (8%) and three (13%) patients, sepsis in two (17%) and one (4%) patients, and pulmonary embolism in zero (0%) and one (4%) patients.

Table 2 shows the results of the multivariate logistic regression analysis. Among the predetermined explanatory variables, the variance inflation factors for multicollinearity were lower than 1.64, indicating a lack of collinearity in the model. After adjusting for possible confounders, logistic regression analysis revealed that in-hospital mortality was significantly lower in the intervention group, with an adjusted odds ratio of 0.25 (95% CI: 0.08–0.78, P = 0.017).

Table 2 Results of the multivariate logistic regression analysis with in-hospital mortality as the outcome variable

	Odds ratio (95% CI)	*P*-value
Age (years)	0.97 (0.93–1.01)	0.13
Probability of survival (TRISS model)	0.94 (0.91–0.97)	<0.001*
Control group	1.0 (Reference)	
Intervention group	0.25 (0.08-0.78)	0.017*

*Statistically significant. TRISS: Trauma and Injury Severity Score.

Discussion

In this study, we have reported initial results for a cryoprecipitate transfusion strategy, including data on the efficacy and safety of its early administration in the treatment of patients with severe TBI. No acute transfusion-related adverse event was observed in the study cohort. Additionally, we found that the rates of coagulopathy and in-hospital mortality was lower in the patients treated with our cryoprecipitate transfusion protocol, although some of the reductions were not statistically significant. To the best of our knowledge, this is the first study to have reported the efficacy of early intervention in acute coagulopathy after TBI using transfusions of in-house-produced cryoprecipitate.

Coagulopathy is known to develop after severe TBI, and its key initiator is a high amount of tissue factor contained in the cortical parenchyma of the brain.[2] After brain injury, an extensive release of tissue factor from the cortex triggers the extrinsic coagulation pathway, resulting in disseminated intravascular coagulation that causes consumption of coagulation factors,[18,19] progression of bleeding, cerebral ischemia, and brain edema.

The incidence of acute coagulopathy after TBI increases up to 60–90% according to the severity of ASDH,[5] while it is approximately <1% in mild TBI.[20] Worsening coagulopathy during the early phase after injury is common, and one study reported that coagulopathy developed in the first 24 h after injury in more than 50% of patients with isolated TBI, even if the coagulopathy was not evident on admission.[21] Considering the high prevalence of acute coagulopathy after severe TBI with ASDH, the criteria for our cryoprecipitate transfusion protocol were reasonable. However, it should be noted that the reported prevalence of coagulopathy was significantly different between patients with a GCS score of 7 or 8 and those with a GCS score of ≤6 (0% vs. 81%);[22] the GCS scores of 75% of the patients in the current study were ≤6. The severity of injuries in these patients may have been key to the therapeutic benefit derived from early cryoprecipitate transfusion.

Plasma components are often used to treat such coagulopathy. In addition to the replenishment of clotting factors, it is indicated for the initiation of the repair of endothelial injury through re-establishment of the blood–brain barrier, mitigation of excitotoxicity, and subsequent limitation of edema and secondary brain injury.[23,24] Considering

these numerous effects of plasma components, it is plausible that the benefits of early cryoprecipitate transfusion were demonstrated in this study in cases of isolated TBI, which is rarely accompanied with substantial bleeding.

Cryoprecipitate has several reported advantages over FFP. Assuming that early transfusion of plasma component is important, the rapid thawing process (<9 min) in our protocol, which is possible owing to the concentrated small volume of cryoprecipitate (approximately 50 mL/pack), is an advantage. Combined with the empirical decision to provide transfusion, the cryoprecipitate transfusion protocol significantly reduced the time from admission to transfusion of plasma component in the present study to a median of 72 min in the intervention group, as compared with 222 min in the control group. The high concentrations of some clotting factors, particularly fibrinogen that decreases due to hyperfibrinolysis, is another advantage of cryoprecipitate over FFP. According to a mathematical simulation model, a fibrinogen target level of >180 mg/dL would be difficult or impossible to achieve using FFP in some circumstances because the number of required units increases exponentially as the target value approaches the fibrinogen level of the hemostatic agent.[8] Furthermore, clotting factor XIII, which is also concentrated in our in-house cryoprecipitate, has been reported to bind with endogenous anti-plasmin and exert an anti-fibrinolytic action in addition to fibrin polymerization.[25] Fibrinogen levels decrease after TBI and the outcome is worse in patients with low fibrinogen; this was reflected in our results. It is therefore plausible that the inhibitory effect of cryoprecipitate on hyperfibrinolysis in patients with severe TBI contributed to the better outcome.

Cryoprecipitate also has potential advantages over other blood concentrates, such as fibrinogen and factor XIII concentrate. Fibronectin, which has a binding activity with fibrinogen and induces hemostatic action,[26] is condensed in cryoprecipitate, but not in fibrinogen and factor XIII concentrate.[15] In severe TBI, cellular fibronectin increased in plasma after injury, and it correlated with the severity of TBI.[27] It has been reported that TBI worsened in plasma fibrinogen knock-out mice, and fibronectin administration improved the outcome after TBI.[28] Based on this evidence, we speculate that cryoprecipitate might be superior to fibrinogen and factor XIII concentrate in relation to fibronectin. Currently, comparative evidence of the TBI effects of cryoprecipitate and other blood concentrates is lacking, and further studies are therefore warranted. However, our results highlight the possibility that cryoprecipitate could be a beneficial intervention in severe TBI, and may contribute to the approval of cryoprecipitate production in Japan.

Cryoprecipitate is costly, and the direct cost of unnecessarily transfused blood products in the current study was approximately $222 per pack of cryoprecipitate, $215 for 480 mL FFP, and $7 for consumable supplies. Moreover, cryoprecipitate transfusion carries substantial risks of thromboembolic disease, transfusion-transmitted disease, hemolytic anemia, anaphylaxis, and severe pulmonary reactions to proteins in the cryoprecipitate. However, according to a hemovigilance report, the rate of adverse events for cryoprecipitate is relatively low (6/10,000 use of cryoprecipitate).[29]

Although the decision to transfuse is preferably guided by clinical and laboratory data, clinicians are in a dilemma because conventional coagulation tests are time-consuming and waiting for the results of coagulation studies prior to initiating treatment introduces an inherent delay that may allow worsening of the coagulation disturbance and negatively influence the outcome. Viscoelastic point-of-care testing is one of the promising breakthroughs in this problem. However, its application in clinical care is currently limited to a few high-resource trauma centers. Therefore, we believe that empirical intervention for acute coagulopathy after TBI is justified in judiciously selected patients unless such point-of-care evaluation tools for coagulopathy become a standard in clinical practice.

Limitations

We recognize several limitations in this study. First, this study was a retrospective cohort study and was therefore prone to the bias associated with this research method. We sought to address this bias by adjusting for confounding factors in the statistical analysis. The TRISS, which was incorporated into our statistical model, is an established scoring system that reflects the anatomical and physiological severity of trauma. We included age in the model because the TRISS considers age as categorical data (<55 or ≥55 years), whereas the patients in our cohort were older (median age, 71 years). However, it is possible that factors that were not considered may have biased our results (e.g., guideline update during the study period, and the decision of transfusion was left to the discretion of different attending physicians). In particular, since administration of the anti-fibrinolytic agent tranexamic acid has demonstrated improved mortality and an excellent safety profile in trauma patients with severe bleeding,[30] it has been considered as a possible treatment option to decrease mortality

in patients with isolated TBI. Consequently, the rate of tranexamic acid administration was significantly higher in the intervention period. Although the benefit of tranexamic acid administration in patients with isolated TBI is uncertain, tranexamic acid may limit fibrinolysis and the effects of tissue plasminogen activator, thereby potentially impeding peri-lesional edema progression. Under the assumption that tranexamic acid has these effects, the administration of tranexamic acid would result in reduced coagulopathy and mortality after TBI; thus, it would be a confounder. Second, the cryoprecipitate was empirically transfused only in those cases in which the physician was certain of the benefit of the transfusion. This selection bias was inherent in our strategy, and could not be adjusted for in the analyses. Third, based on our results, we speculated that early cryoprecipitate transfusion reduced the mortality rates of patients with isolated TBI and ASDH by preventing coagulopathy development; however, it was not possible to definitively comment on the mechanisms behind our findings. Fourth, only acute transfusion-related adverse events were assessed in this study. Although a low rate of adverse events for cryoprecipitate has been reported,[29] it should be noted that the incidence of long-term adverse events remains unclear, and transfusion has inherent risks such as unknown-virus infection. Fifth, the sample size of this study was small, and statistical power was low. Observed differences did not reach significance in some analyses. Further research with larger sample size is therefore warranted. Finally, the patients in this study were older than those included in a previous study. Our results therefore warrant validation in other cohorts.

Conclusion

We report the initial results of early cryoprecipitate use in severe TBI. In our cohort of patients with severe isolated TBI and ASDH, no acute transfusion-related adverse event was observed, and early transfusion of the in-house-produced cryoprecipitate may have decreased the rates of coagulopathy development and in-hospital mortality. These results highlight the possibility that early cryoprecipitate transfusion would be a beneficial intervention in severe TBI, warranting further studies.

Acknowledgments

The authors would like to thank the staff of the transfusion department for their cooperation and effort toward the cryoprecipitate transfusion protocol.

Funding and Resources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

KSh conceived and designed the study and drafted the manuscript. SN, KSu, HH, YH, and HF supervised the conduct of the trial and data collection. All authors contributed substantially to its revision, have read and approved the final manuscript, believe that the paper represents honest work, and are able to verify the validity of the results reported. KSh takes responsibility for the paper as a whole.

Conflicts of Interest Disclosure

The authors declare no conflict of interest.

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