The Amount of Fibrinogen in Cryoprecipitate by In-hospital Preparation

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The Amount of Fibrinogen in Cryoprecipitate by In-hospital Preparation

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Background: Cryoprecipitate contains high concentrations of fibrinogen (Fib) that is effective for dilutional coagulopathy in massive blood transfusions. The supply of cryoprecipitate by in-house preparation in our hospital began in July 2013. There is heterogeneity in the Fib content of fresh frozen plasma (FFP) and cryoprecipitates. Here, we measured the Fib content of cryoprecipitates prepared in our hospital.

Methods: We measured the Fib content of 2,715 cryoprecipitate bags prepared in our hospital. Four randomly selected bags were used as the basic order unit, and the amount of Fib per four bags was measured for 579 orders. The number of bags and Fib content of cryoprecipitate administered in all 487 surgical cases were examined.

Results: The average amount of Fib per bag was 516.3 ± 166.8 mg/bag. Per four bags, 551 orders (95.2%) contained >1,500 mg and 28 orders (4.8%) contained <1,500 mg, and 6.1 ± 2.0 bags of cryoprecipitate and 3,115.0 ± 1.0 mg of Fib were administered per surgical case.

Conclusion: The Fib content of cryoprecipitates varied widely, reflecting the heterogeneity of Fib concentrations in FFP. A large amount of cryoprecipitate must be administered to deliver sufficient Fib. Therefore, besides cryoprecipitate, the use of Fib preparations should be considered in treating severe dilutional coagulopathy.

Keywords: massive blood transfusion, cryoprecipitate, fibrinogen, dilutional coagulopathy

Introduction

Massive bleeding amounting to more than 20% of the circulating blood volume requires transfusion of red blood cells. If the amount of blood loss increases further, albumin, fresh frozen plasma (FFP), and platelet concentrates may need to be administered.[1] FFP is required when the amount of blood loss exceeds 100% of the circulating blood volume; however, even if FFP is administered directly, it is difficult to reach an effective fibrinogen (Fib) concentration because it is diluted by the infused fluids and owing to the transfusion of blood components. This phenomenon is called dilutional coagulopathy (DC), and it is necessary to administer high concentrations of Fib to overcome DC.[2,3]

There are two types of high-concentration Fib preparations: cryoprecipitate prepared in the hospital using FFP and Fib preparations as plasma-fractionated preparations. At our hospital, the in-house preparation of cryoprecipitate started in 2013 after discussions with the Department

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of Cardiovascular Surgery and Department of Anesthesiology. The percentage of FFP prepared as cryoprecipitate has been increasing, and approximately 10% of purchased FFP has been supplied as cryoprecipitate. However, the concentration of Fib in FFP is known to be heterogeneous and only small-scale quality control reports have been published.[4] Herein, we provide the results of a large-scale study concerning the measurement of Fib concentration of cryoprecipitates as quality control in our hospital.

Materials and Methods

1. Conditions for preparation of cryoprecipitate

Prior to the supply of cryoprecipitate, we examined the conditions for cryoprecipitate preparation with the maximum Fib recovery rate from 2012 to 2013 using FFP-LR-Ap (450 mL), which was supplied by the Japanese Red Cross Society (JRC) at that period, as a raw material. Since the Japan Society of Transfusion Medicine and Cell Therapy (JSTMCT) had not established a protocol for cryoprecipitate preparation at the time, we examined five different conditions of time of centrifugation (7, 10, 15, and 30 min with brake and 10 min without brake) for maximum Fib recovery. Therefore, we adopted the centrifugation method of 4,500 G for 10 min with brake; this method corresponded to the "high-speed method" of the protocol described below and helped obtain the best result with a recovery rate of 47.2 ± 9.5% (mean ± SD, n= 8) of Fib.

2. Measurement of Fib content in cryoprecipitate

The Fib content of 2,715 cryoprecipitate bags prepared between May 2014 and April 2020 was determined. Since the formulation of FFP supplied by JRC had been changed from FFP-LR-Ap (450 mL) to FFP-LR480 (480 mL) before this period, all raw materials for the cryoprecipitate were FFP-LR480. The preparation method using a blood collection device was the same for FFP-LR-Ap and FFP-LR480, and only the content volume was increased by 30 mL.

The method of preparation of cryoprecipitate is almost the same as the protocol for cryoprecipitate preparation provided by JSTMCT Ver. 1.4,[5] except that the cryoprecipitate was dissolved at 37°C before refreezing to collect sample for the Fib concentration test. The Fib concentration was measured by SRL Co (Tokyo, Japan).

3. Indication criteria for cryoprecipitate

We explained to the cardiovascular surgery and obstetrics and gynecology department staff that cryoprecipitate would be able to improve DC more effectively because it contains a higher concentration of Fib than FFP. The guidelines of JSTMCT recommend that the trigger value for cryoprecipitate administration should be a Fib value of 150 mg/dL for DC associated with massive transfusion, and especially for obstetric critical bleeding, a Fib value of 200 mg/dL should be considered for cryoprecipitate administration.[6] We requested that if possible, rapid measurement of Fib levels in the blood should be performed and that cryoprecipitate should be ordered and administered for ensuring hemostasis by promptly increasing Fib levels, considering the progression rate of DC.

4. Survey of cryoprecipitate bag numbers and Fib doses

Considering the heterogeneity of the amount of Fib in cryoprecipitates, we recommend using four bags as one order and combination of orders for managing DC in our hospital, and we calculated the amount of Fib per four bags of one order used in a surgery. In addition, since there are many cases in which more than two orders of eight bags are administered, we examined the number of cryoprecipitate bags used and the amount of Fib administered in one surgery.

Results

The mean amount of Fib per bag was 516.3 ± 166.8 mg/bag (mean ± standard deviation; minimum: 101.0 mg/bag, maximum: 1,945.5 mg/bag). The total amount of Fib in the 579 combinations of four bags administered to patients was 2,025 ± 918.3 mg/4 bags (mean ± standard deviation), with a minimum of 918.3 mg and a maximum of 3,375.5 mg/4 bags. The total content of Fib per four bags was >2,000 mg in 278 cases (48.0%), between 1,750 and 2,000 mg in 175 cases (30.2%), between 1,500 and 1,750 mg in 98 cases (16.9%), and <1,500 mg in 28

cases (4.8%) (**Table 1**).

The actual number of bags of cryoprecipitate administered in all 487 surgical cases was 4 bags in 185 cases (38.0%), 8 bags in 209 cases (42.9%), and 12 bags in 3 cases (**Figure 1**). The mean number of bags of cryoprecipitate administered per patient was 6.1 ± 2.0 bags, and the mean Fib amount was 3,115.0 ± 1,147.1 mg (mean ± standard deviation) (**Figure 2**).

Discussion

This study is the largest study investigating Fib content, encompassing 2,715 bags of cryoprecipitates, as previous reports comprised a few dozen small cases.[4]

In patients who have difficulty in achieving hemostasis owing to hypofibrinogenemia, a certain amount of Fib must be administered in a short time to rapidly increase the Fib concentration in the blood.[7,8] In the present study, we measured the Fib concentration in cryoprecipitates and found a large variation among preparations, which might be owing to the heterogeneity of the Fib concentration in the original FFP.[8]

Table 1. Amount of fibrinogen by supplying a set of four bags of cryoprecipitate (2014-2020).

Fibrinogen amount (mg)	Set	Percentage (%)
≥1,500	551	95.2
>2,000	278	48.0
1,750-1,999	175	30.2
1,500-1,749	98	16.9
<1,500	28	4.8
Total	579	

The normal range of Fib concentration in serum varies widely from 150 to 400 mg/dL, and the recovery rate of Fib in the cryoprecipitate is poor (in the 30% range) when the Fib concentration in FFP is low.[4] Although the Fib recovery rate was not calculated in this analysis, a low value of 450 mg of Fib per bag of FFP-LR-Ap (450 mL) was determined on examining the preparation conditions; thus, the Fib recovery rate was 30.2% with a total recovery of only 136 mg of Fib. Therefore, cryoprecipitates with very low Fib content are unavoidable, although manufacturing limitations cannot be ruled out. Our analysis revealed a median Fib concentration of 494.5 mg, a 25th quartile of 404.5 mg, and a 75th quartile of 595 mg, but with 75% of the data within the mean ± SD; there was no significant variation.

Therefore, we recommended a single order of four bags of cryoprecipitate for managing DC to offset individual differences in cryoprecipitates and aimed to provide approximately 1,500 mg of Fib in one order. In fact, 95.2% of the four bags of cryoprecipitate contained at least 1,500 mg of Fib, while 48.0% contained 2,000 mg of Fib. However, 4.8% contained < 1,500 mg of Fib.

In addition, 42.9% of patients received eight bags of cryoprecipitate, and those who received more than four bags of cryoprecipitate received an average of 6.1 ± 2.0

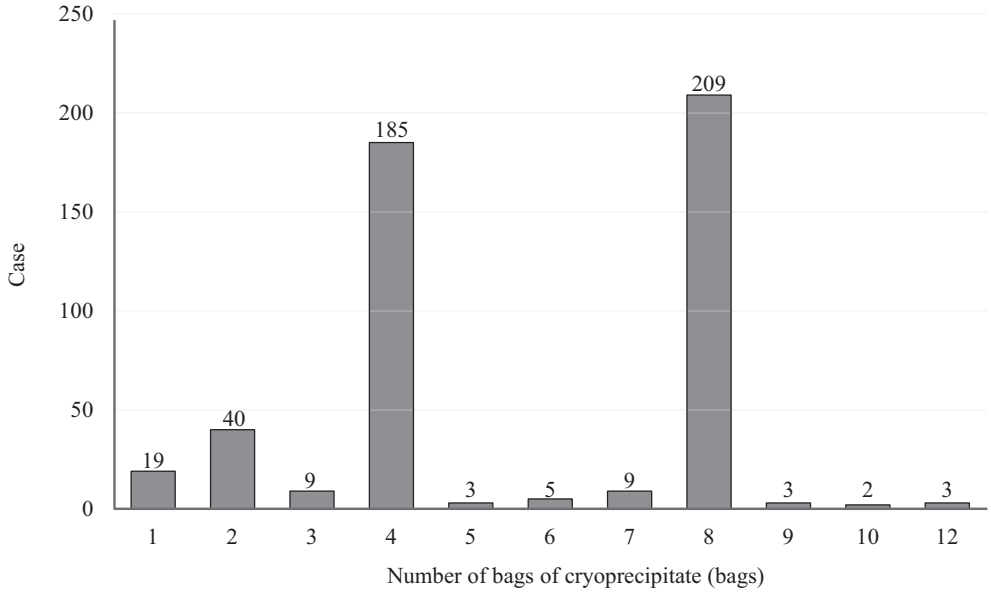

Figure 1. Number of bags of cryoprecipitate administered for each surgical case.

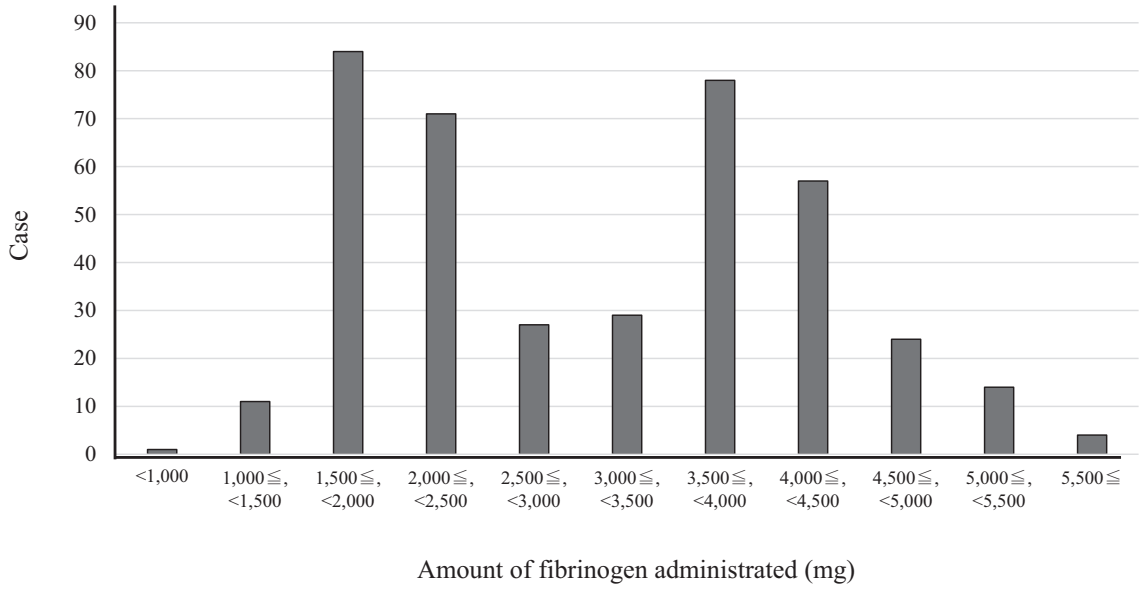

Figure 2. Amount of fibrinogen administrated for each surgical case.

bags of cryoprecipitate and 3,115.0 ± 1,147.1 mg of Fib.

For severe hypofibrinogenemia (< 100-150 mg/dL) caused by massive blood transfusion, it is necessary to raise the blood Fib level by 100 mg/dL to improve hemostasis, and it is considered that 3-4 g of Fib is required for this purpose.[9] The average Fib content of four bags of cryoprecipitate may not be sufficient, and more than six bags—the average dose in this study—may need to be administered to achieve controlled hemostasis.

Although the blood type of the cryoprecipitate should be the same as that of the patient, it may not be possible to simultaneously supply the same blood type cryoprecipitate for several patients. In addition, cryoprecipitates of infrequently used blood types that have passed their expiration date had to be discarded. Although some facilities create and use only AB-type cryoprecipitate to avoid the aforementioned problem, we have discussed and agreed with surgeons and anesthesiologists to supply cryoprecipitates of the same ABO blood type. This is to prevent confusion in the surgical room when the patient authentication system alerts that the cryoprecipitate and patient's blood type are not compatible. In addition, it is not practical for a hospital like ours to use a large amount of cryoprecipitate as it may lead to the depletion of the rare AB-type FFP.

JRC previously manufactured and provided cryoprecipitate to treat hemophilia A. However, the production of cryoprecipitate was discontinued in 1988 owing to the emergence of dried and concentrated factor VIII products in the late 1970s. In recent years, the recognition of the efficacy of cryoprecipitate in managing severe DC has been firmly established,[6, 10-12] and JRC was requested to resume its manufacturing and marketing. New clinical trials and a new marketing approval are required to establish a new indication for DC. However, it is difficult to obtain sufficient clinical evidence for DC owing to the aforementioned heterogeneity of Fib concentrations or the difficulty of conducting double-blinded studies.[13] Therefore, we are forced to use the in-house preparation in our hospital.

The preparation of cryoprecipitate involves 30 h of slow melting at low temperature (4℃) and centrifugation (4,500 G for 10 min), which takes approximately 2 days after obtaining FFP.[5] Another challenge is that owing to the heterogeneity of Fib concentrations, as revealed in our study, sufficient Fib may not be administered in some cases, and the consumption of large quantities of FFP as cryoprecipitate impedes the achievement of proper use of FFP.

JSTMCT conducted a national survey of blood products used in 2020 and found that 132 of 812 (16.3%) facilities in Japan had experienced massive transfusion cases and used Fib products not covered by health insurance. These were more than 44 centers (5.4%) that used FFP and cryoprecipitate.[14]

On September 6, 2021, "fibrinogen replacement in ac-

quired hypofibrinogenemia associated with obstetric critical hemorrhage," was added to the indications for dried human Fib preparation.[15] In the future, it will also be possible to administer the drug for managing hypofibrinogenemia in cardiovascular surgery, but currently, it is only indicated for critical obstetric hemorrhage.

Prior to the expanded indication discussed above, Fib preparations were not covered by health insurance for managing DC. We believe that the introduction of dried human Fib will reduce the use of FFP in many cases and promote the appropriate use of FFP.[16] The Fib preparation has a constant Fib content of 1 g per 50 mL bottle, and the dosage is clear. It can be employed in operating rooms and delivery rooms without the need for blood type compatibility. In addition, it has the advantage of being virus-inactivated and safe, with a long shelf life of more than 2 years. However, it does not contain other coagulation factors contained in FFP and cryoprecipitate and can only be used to replenish Fib. There are concerns that the supply system may become unstable owing to the anticipated rapid increase in use of this product. Therefore, at present, facilities that can prepare cryoprecipitate in their hospitals are urged to use cryoprecipitate as much as possible. Currently, we request obstetricians to administer ABO-matched cryoprecipitate first. However, if bleeding does not reduce or the blood Fib level does not increase sufficiently, additional cryoprecipitate will be administered if the stock of ABO-matched cryoprecipitate is available; if no stock is available, a dried Fib preparation will be administered. We believe that the results of this study will be useful for the rapid and adequate Fib supplementation and contribute to the treatment of DC.

Conclusion

The use of Fib preparations that can deliver sufficient amounts of Fib more reliably should be considered for the treatment of severe DC; however, in the interim, the development of cryoprecipitates should continue. Although the Fib preparation can be administered for critical obstetric hemorrhage as the first choice of highly concentrated Fib preparation, in the future, a new system should be established in which cryoprecipitates of the same blood type as that of the patient are initially administered, even in cardiovascular surgery. In case of stock depletion, Fib preparations can be used for the treatment of DC.

Conflicts of Interest: All authors declare that they have no conflict of interest.

Author Contributions: TU, KY-S, and HK designed the study and analyzed data. YO and KN prepared the cryoprecipitate and analyzed data. TU and HK wrote the manuscript.

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