Original Article

A retrospective review of cryoprecipitate transfusion practice in Kuala Lumpur Hospital

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Abstract:

Background: Cryoprecipitate is generally used to treat bleeding patients with hypofibrinogenemia, and the transfusion decision is guided based on published guidelines. **Aim:** This study aimed to evaluate the practice appropriateness in accordance to cryoprecipitate transfusion guidelines in Hospital Kuala Lumpur. **Methodology:** This cross-sectional study of 117 cryoprecipitates transfused adult patients was conducted in Kuala Lumpur Hospital from January to June 2012. The compliance of the indication of cryoprecipitate was considered as appropriate if indicated for patients who have hypofibrinogenemia (<1.0 g/L) with bleeding, or otherwise inappropriate if pretransfusion fibrinogen level was more than 1.0 g/L, pretransfusion fibrinogen level was not examined and posttransfusion fibrinogen level more than 1.5 g/L. **Results:** Most of the cryoprecipitate prescriptions were found to be inappropriate, which read 81.2% (95% confidence interval = 0.740, 0.880). Patients who underwent neurovascular surgery were the major recipient of cryoprecipitate, but majority of the prescription was found not appropriate. The decision to transfuse cryoprecipitate was found mostly appropriate when was guided by fibrinogen (52.2%), but the percentage dropped to 10.6% when pretransfusion fibrinogen test was not performed. Regrettably, only 19.7% of total cryoprecipitate were given based on pretransfusion fibrinogen level. **Conclusion:** Although this study showed a high rate of inappropriateness, no reduced therapeutic efficacy, and adverse effect were reported. The trigger threshold needs to be revised before enforcing stringent implementation of practice guidelines for ensuring optimal use of cryoprecipitate.

Key words:

Appropriateness, bleeding, cryoprecipitate transfusion, guideline

Introduction

Cryoprecipitate is the cold, concentrated precipitate of blood which contains factor VIII, von Willebrand factor, fibrinogen, fibronectin, factor XIII, and platelet microparticles, with small plasma volume (about 5–15 ml). Each functional cryoprecipitate unit contains a minimum fibrinogen concentration of 150 mg and 80 IU of factor VIIIC for each preparation of 15–20 ml,[1,2] according to the recommendations by the Food and Drug Administration and American Association of Blood Bank.[1,2] The primary indication of cryoprecipitate was for treating congenital factor VIII deficiency[3,4] but the use is expanded to treat von Willebrand disease and hypofibrinogenemia,[5] or as a fibrinogen replacement agent in relieving dysfibrinogenemia and acquired fibrinogen deficiency, the complications which are commonly seen in massive transfusion and disseminated intravascular coagulopathy.[6]

Cryoprecipitate is a pooled, allogeneic blood product produced through vigorous centrifugation of defrosted fresh frozen plasma (FFP, collected within 8 h) at a speed of 5000 × g for 6 min within 1 h at 1–6°C and is then kept frozen at ≤−18°C. This preparation procedure offers the cryoprecipitate a general shelf-life of 12 months.[7] However, the expenses underlying the cryoprecipitate preparation process from donor recruitment, plasmapheresis, quality and safety control to storage are tremendously high. Each functional unit of cryoprecipitate is generally pooled from 4 to 6 donors and the recommended dose for each transfusion in an adult is 1 unit per every 5 kg of body weight which will increase fibrinogen by about 100 mg/dL. This indicates that as high as 8–16 unit of cryoprecipitate are needed for an adult patient. Hence, the yield of cryoprecipitate is low as compared to other blood products from the same group of donors.

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Cryoprecipitate is generally not subjected to pathogen inactivation processing. Although substantial efforts have been put to produce sterile cryoprecipitate by using methylene blue with/without light, riboflavin, amotosalen, solvent detergent filtration, and the functionality of cryoprecipitate in bleeding arrest after the processing remain debatable. Furthermore, several observational studies demonstrated an increase in demand for plasma and cryoprecipitate transfusion when cryoprecipitate derived from pathogen-inactivated plasma was used.[8,9] However, due to a possible decline in therapeutic efficacy of cryoprecipitate after the pathogen inactivation processing, which may subsequently render patients to multiple transfusions, most cryoprecipitates are kept untreated for pathogen inactivation. Thus, the use is often coupled with some risk of transfusion transmittable infections. The rate of an adverse event following cryoprecipitate transfusion is mostly under-reported in hemovigilance report.[7] The use of cryoprecipitate should be carefully indicated to suitable patients only, and the prescription should be strictly based on recommended guidelines to balance between risk and benefit in recipient patients.

Many countries have withdrawn cryoprecipitate from use in clinics due to safety reason, but it is still available in countries like Malaysia due to the absence of alternatives to cryoprecipitate. Several practice guidelines have been published to facilitate and guide clinicians on cryoprecipitate transfusion to ensure judicious use of the blood product (Ayob 2008; Droubatchevskaia *et al*. 2007; Lundberg 1994;[10] O'Shaughnessy *et al*. 2004; Nuttall *et al*. 2006). However, most prescriptions remain empirical despite clear institution guidelines. Several other audit reports also revealed a high rate of inappropriate cryoprecipitate usage in developed countries (Schofield *et al*., 2003, Corkery *et al*.,[11] 2005, Alport *et al*.,[12] 2008, Anderson *et al*., 2008). Considering the adverse reactions and the cost associated with cryoprecipitate transfusion, this study was conducted to examine the current usage and practice of cryoprecipitate transfusion in Kuala Lumpur Hospital.

Methodology

This was a retrospective, cross-sectional study conducted at Kuala Lumpur Hospital, a government-funded tertiary hospital in the capital city of Malaysia, in collaboration with National Blood Centre (NBC). All data collection and analysis were reviewed and approved by Medical Research and Ethics Committee, Malaysian Ministry of Health (ID: 11826). All the data were retrieved from medical records of cryoprecipitate recipient patients, cryoprecipitate order (Group Crossmatch Form [GXM]) forms, and laboratory data. A total of 117 adult patients (18 years and above) were identified based on the receipt of grouping and cross-match requests by the Transfusion Medicine Unit, Malaysian NBC, who were treated with cryoprecipitate between 1st January and 30th June 2012 at Kuala Lumpur Hospital, were recruited in this study. Patients younger than 18 years old or with inherited bleeding disorders, or cases of which data was incomplete or missing were excluded from the study. All data retrieved from medical record, cryoprecipitate order form, laboratory group, and cross-match data and proforma were made anonymous to investigators. The appropriateness of cryoprecipitate transfusion is herein referred to the compliance of medical practitioners in the hospital to cryoprecipitate transfusion guidelines, with defined criteria as shown in Table 1. Categorical results were presented as a percentage, and numerical data were presented as a median and interquartile range. Statistical analysis was performed using SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.), and the observed differences were tested using Chi-square test and $P < 0.05$ was considered significant.

Results

A total of 117 adult patients aged from 18 to 85 (56% male and 44% female, mean body weight = 63.8 ± 9.2 kg) were recruited in this study [Table 2]. These patients were transfused with cryoprecipitate between 1st January and 30th June 2012 at Kuala Lumpur Hospital, which involved 676 units of cryoprecipitate in total. The use of cryoprecipitate in Kuala Lumpur General Hospital (HKL) showed the inconsistent pattern from 2007 to 2012 [Figure 1]. The total cryoprecipitate usage in HKL decreased dramatically from 5533 units in 2007 to 4169 units in 2009. Although the usage was found to increase slightly to 4389 in 2010, it dropped 34.5% to 2891 units in 2012 as compared to 4413 units in 2011. These inconsistencies raised questions whether the use of cryoprecipitate in the hospital was compliant to published guidelines.

Level of practice appropriateness in cryoprecipitate transfusion practice guideline

Of 117 recruited patients, as high as 95 cases (81.2%) of the cryoprecipitate prescription were found to be inappropriate [Figure 2a]. Of those, about 81% were transfused with cryoprecipitate without prior determination of patient blood fibrinogen level. Furthermore, 11 (11.6%) of the cases showed cryoprecipitate were transfused to patients with pretransfusion fibrinogen level more than the 1 g/L, and in 7 cases, posttransfusion fibrinogen levels were found more than 1.5 g/L [Figure 2b]. Among all cases of which cryoprecipitate was transfused without pretransfusion fibrinogen check, almost 90% of them were found to be inappropriate. Notably, pre-transfusion fibrinogen testing

Table 1: Definition of practice appropriateness in cryoprecipitate transfusion

	Definitions
Appropriate	The transfusion was compliant to the following: Patients with hypofibrinogenemia (fibrinogen level ≤1g/L) with bleeding (Note: In case of emergency when the fibrinogen level was not tested prior to cryoprecipitate transfusion, it is considered as appropriate if the fibrinogen level was tested and did not exceed 1.5 g/L after transfusion)
Inappropriate	The transfusion was based on empirical decision, or matches any one of the following: a. No fibrinogen testing was performed pre- and post-transfusion b. No evidence of hypofibrinogenemia (fibrinogen level more than 1 g/L) c. No pre-transfusion fibrinogen reading and post transfusion fibrinogen level exceeded 1.5 g/L

Table 2: Demographic characteristics of cryoprecipitate-transfused patients

Age	47.8±19.1
Weight	63.8±9.2
Gender	
Male	66 (56.4%)
Female	51 (43.6%)

Data are mean±standard deviation and *n* (%)

increased the level of practice appropriateness from 10.6% to 52.2% [Figure 3].

Diagnostic category of patients transfused with cryoprecipitate

As shown in Figure 4, the percentage of cryoprecipitate transfused to patients who underwent neurovascular surgery was 34.1%, followed by gastrointestinal bleeding which accounted for 16.2% cases. Both trauma and postpartum hemorrhage or obstetric bleeding constituted 15 cases each, and about 11.1% were from cases related to bleeding and nonbleeding intravascular coagulation. Overwarfarinization, bleeding in malignant patients, burns and traumatic chest tube insertion accounted for 7.7% of cryoprecipitate recipient patients. Renal and uremic bleeding were the least common among all clinical conditions of which cryoprecipitate was used as hemostatic treatment.

Location and timing of cryoprecipitate transfusion

To investigate whether the inappropriateness of cryoprecipitate transfusion was due to a critical emergency, the number of cryoprecipitate transfusion was analyzed according to the location where the procedure was performed. Our data showed that most of the cryoprecipitate were transfused in Intensive Care Unit (ICU) or high dependency ward (HDW), with 30% transfused in operating theater, about 23% in wards and only a few were transfused in resuscitation room at Emergency Department (5.1%). However at a glance, only 16.3% of the transfusions were found compliant to the practice guidelines. Of 49 cryoprecipitate transfusions that were given in ICU or HDW, about 84% of the cases were considered inappropriate, and only eight (16.3%) transfusions were considered appropriate [Figure 5]. Likewise, about 74% of the cryoprecipitate transfusions in operating theater/recovery room were found to be inappropriate based on the practice guideline. Furthermore, cryoprecipitate transfusion in resuscitation rooms at Emergency Department showed 83.3% cases to be inappropriate, albeit with only a total of six cryoprecipitate transfusion cases reported. Surprisingly, fibrinogen testing was neglected in 65.8% of the cases [Table 3]. Only 9.4% initiated cryoprecipitate transfusion based on patients' fibrinogen level, and 14.5% performed fibrinogen check after the transfusion. This also suggests that more than half of the decisions made to transfuse cryoprecipitate were empirical and independent of fibrinogen reading.

Cryoprecipitate transfusion and its effectiveness in handling bleeding

To examine whether the cryoprecipitate transfusion was effective in treating bleeding, a total number of 108 cryoprecipitate transfusion cases were analyzed, excluding those indicated for nonbleeding cases (n = 9). As expected, more than half of the cases (68.5%) showed successful bleeding cessation, although 28.7% of them had no effect on hemostasis. Only three patients of whom the bleeding status was unable

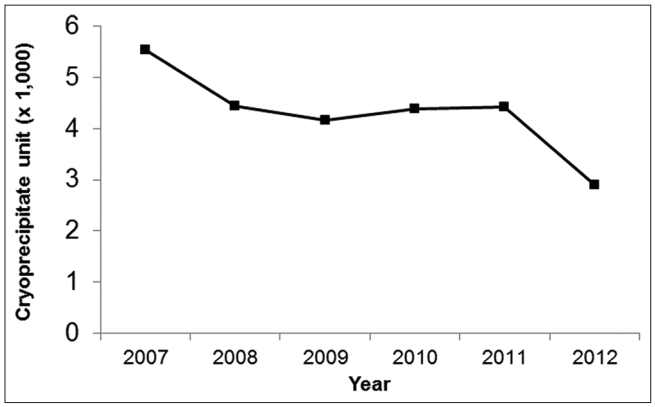

Figure 1: Pattern of cryoprecipitate transfusion in Kuala Lumpur Hospital from the year 2007 to 2012

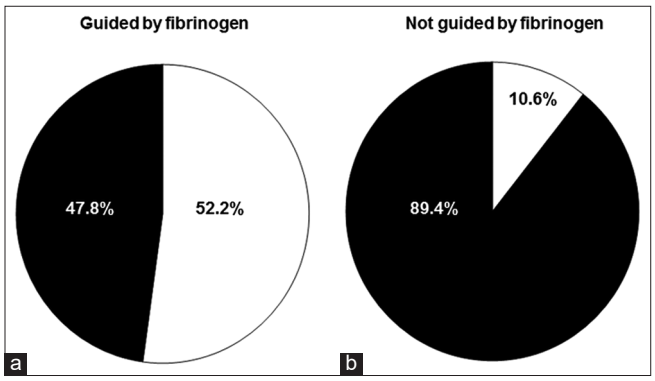

Figure 3: Cryoprecipitate prescription guided with pretransfusion fibrinogen check (a) was found to have substantially higher level of compliance (52.2%) to the transfusion guideline than (b) cases without the fibrinogen check before transfusion (10.6%)

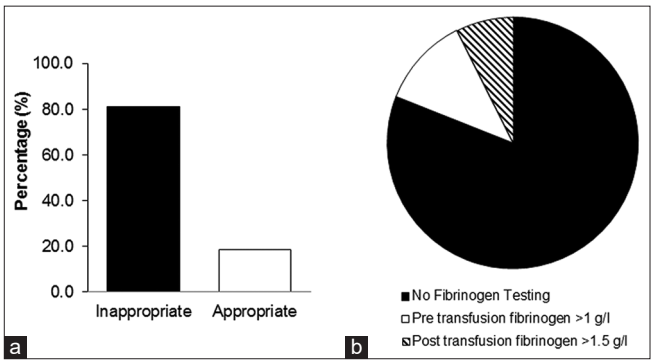

Figure 2: The appropriateness of cryoprecipitate transfusion in Kuala Lumpur Hospital. (a) More than 80% of total prescribed cryoprecipitate transfusion in 2012 were found not compliant to the given guidelines. (b) About 81% of the cryoprecipitate prescription was not based on fibrinogen reading from the laboratory

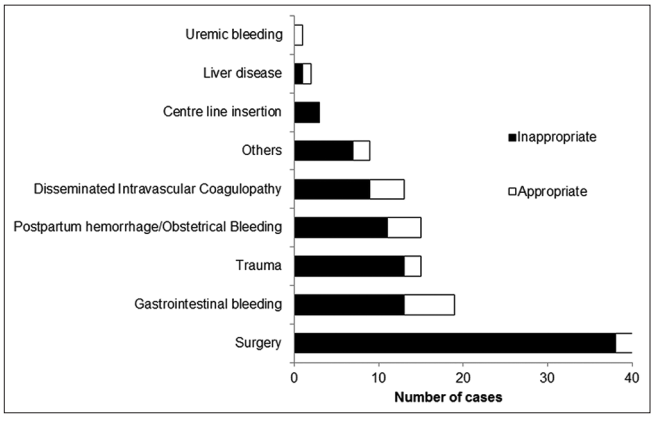

Figure 4: Practice appropriateness in cryoprecipitate transfusion in Kuala Lumpur Hospital according to diagnostic category

to be determined. This was due to incomplete clinical record and laboratory data. No statistical significance was found to support the association between the appropriateness of cryoprecipitate usage and effectiveness of the treatment, using Pearson Chi-square test [Table 4]. Notably, transfusion with cryoprecipitate alone comprised only 1.7%. Others were co-transfused FFP and/or platelet, which accounted for 88.9% and 9.4%, respectively [Figure 6].

Discussions

Cryoprecipitate is a pooled allogeneic blood product not subjected to any pathogen reduction treatment. Thus, administration of cryoprecipitate couples with risks to high donor exposure and transfusion-transmitted infection. Due to this safety reason, cryoprecipitate has been withdrawn from many European countries,[13] but it remains available in countries where the supply of substitute is limited. Several recommendations for cryoprecipitate transfusion have been made by different organizations, which have also been adopted by many hospitals as the core guideline to assist clinical decision to achieve the desired therapeutic outcome and minimize any risk associated with the therapy.[6] Although the use of cryoprecipitate in Kuala Lumpur Hospital dropped in 2012, the inconsistency in the use pattern prompts concerns about safety and inappropriate usage of the product. This study revealed 81.2% of total cryoprecipitate transfusions were not compliant to any of the published guidelines, an alarmingly high percentage for a tertiary hospital in the federal territory of Malaysia with a population of approximately 1.7 million residents.[14] Similar transfusion audits conducted in other countries also suggested that cryoprecipitate is often found not aligned to published guideline.[6,15-17] Nonetheless, this study outlined the main contributor for the practice inappropriateness is the absence of pretransfusion fibrinogen level estimation.

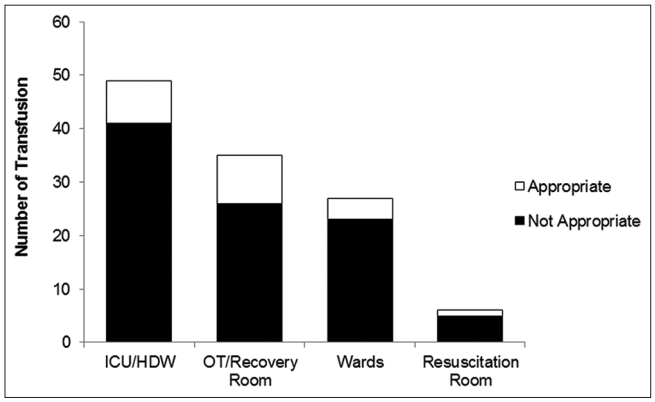

Figure 5: Practice appropriateness in cryoprecipitate transfusion in Kuala Lumpur Hospital according to designated location

Fibrinogen is an important, 340 kDa glycoprotein in hemostasis. Consumptive coagulopathy, lack of synthesis, placental abruption, amniotic fluid embolus, treatment with asparaginase, dilution (due to massive transfusion) or inherited deficiency, can cause hypofibrinogenemia. Cryoprecipitate is recommended for treating hypofibrinogenemia in the in-house Malaysian National Blood Service Transfusion guidelines, and it is currently the only option for the disorder especially when fibrinogen concentrate is not commonly available in Malaysia. Patient fibrinogen level is not only a crucial guide to its diagnosis but can also be used to determine the reliability of prothrombin time and activated partial thromboplastin time,[18] and predict the aggravation of postpartum hemorrhage.[19] However, most transfusion decisions made (81%) in this study were found empirical without fibrinogen reading.

According to our in-house transfusion guideline, cryoprecipitate transfusion is administered if plasma fibrinogen level is <1 g/L in the presence of massive bleeding and disseminated intravascular coagulation,[20] a similar trigger for cryoprecipitate transfusion as recommended in the most published guidelines.[6,21-23] The latest European guideline suggests the trigger for cryoprecipitate treatment is when the fibrinogen concentration falls below 1.5–2 g/L,[24] a more liberal trigger value compared to others, including British recommendation.[22] An audit conducted in Victorian Department of Health and Australian Red Cross Blood Service in 2008 showed only 26% of total cryoprecipitate transfusions were compliant to the national guideline. When the fibrinogen-based transfusion trigger was increased to 1.5 g/L, the rate of appropriateness improved to 61%.[17] In postpartum bleeding cases, studies showed that fibrinogen level <2 g/L were strongly associated with high risk of severe bleeding, with a predictive value of 100%.[25]

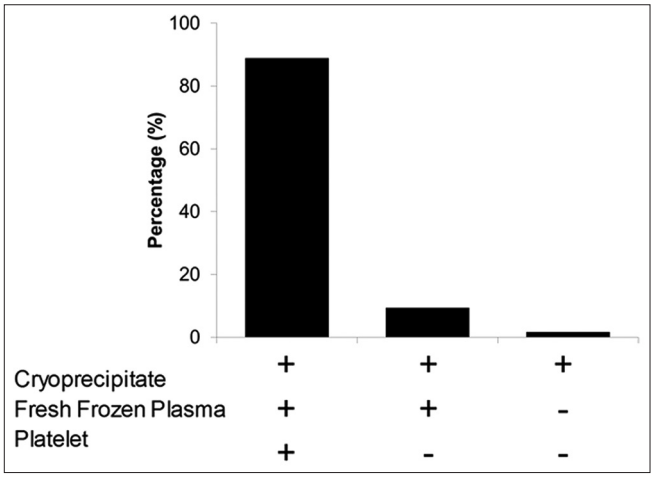

Figure 6: Majority of the cryoprecipitate was co-transfused with fresh frozen plasma and platelets which were 88.9% (104 cases). Only 1.7% (1.2 cases) was transfused with cryoprecipitate alone

Table 3: Pre fibrinogen level testing according to venue of transfusion

Location	Pre-transfusion fibrinogen testing	Post-transfusion fibrinogen testing	Pre and Post transfusion fibrinogen testing	No fibrinogen testing	Total transfusion
ICU/HDW	5	9	4	31	49
OT/Recovery rooms	2	7	5	21	35
Wards	4	0	3	20	27
Resuscitation Room	0	1	0	5	6
Total	11 (9.4%)	17 (14.5%)	12 (10.3%)	77 (65.8%)	117 (100%)

ICU: Intensive care unit, HDW: High dependency unit, OT: Operation theatre

Table 4: Correlation between appropriateness of cryoprecipitate transfusion with effectiveness of the episodes of transfusion

Effectiveness	Compliance *n* (%)		χ^2 (df)	*P* value*
	Yes	No		
Effective	15 (20.3)	59 (79.7)	0.243 (1)	0.622
Not effective	5 (16.1)	26 (83.9)		

*Pearson Chi-Square (*P* value=0.05)

Conclusion

This study showed significantly poor compliance to standard transfusion guidelines among clinicians with a high level of inappropriate prescription of cryoprecipitate in Kuala Lumpur Hospital. However, no known adverse effect was reported, and the effectiveness in handling bleeding remained acceptable. Hence, more evidence is needed to re-define the trigger for cryoprecipitate use to ensure the practicality and optimal use of the blood product. Consistent hemovigilance and compliance monitoring should be in place to achieve this.

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Conflicts of interest

There are no conflicts of interest.

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