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When do we transfuse cryoprecipitate?

M. A. Anderson,[1] B. Glazebrook,[2] B. Cutts,[1] L. Stevenson,[2] L. Bielby[1,2] and M. Borosak[1]

[1]Transfusion Medicine, Australian Red Cross Blood Service, and [2]Department of Health, Melbourne, Victoria, Australia

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Correspondence
Linley Bielby, Department of Health Victoria, GPO Box 4541, Melbourne, Vic. 3001, Australia.
Email: linley.bielby@health.vic.gov.au

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Abstract

Background: The 2001 National Health and Medical Research Council/Australasian Society of Blood Transfusion Clinical Practice Guidelines for cryoprecipitate are being updated, and cryoprecipitate has been incorporated into new Patient Blood Management modules.

Aims: This clinical audit sought to clarify current cryoprecipitate use in Victoria, Tasmania and the Australian Capital Territory; assess adherence to guidelines; and gain insights into deviations from recommended practice. This information can be utilised in updating guidelines to make them more relevant, to identify areas for clinician education and to form a baseline of practice prior to release of the 2011 guidelines.

Methods: Participating institutions were invited to audit up to 30 consecutive episodes of cryoprecipitate transfusion over an 11-month period in 2008. The audits were conducted using a standardised *pro forma* and involved review of patient records. These were collated electronically using algorithms to determine alignment versus non-alignment with guidelines.

Results: Cryoprecipitate is used in a variety of situations with surgery accounting for the highest volume. Twenty-six per cent (26%) of transfusions were aligned with 2001 guidelines rising to 61% with a modified fibrinogen trigger. Fibrinogen levels did not appear to dictate all clinical decisions regarding cryoprecipitate use perhaps owing to the acuity of many cases. Additional bleeding risk together with low fibrinogen levels (e.g. thrombocytopenic patients) may contribute to empiric cryoprecipitate use.

Conclusions: These results highlight discrepancies between guidelines and practice, providing rationale for the update of the guidelines that is currently underway. Cryoprecipitate has attendant risks, and it is appropriate that transfusion be restricted to situations with good evidence or sound principles to underpin use.

Introduction

Blood Matters is a collaborative between the Department of Health Victoria and the Australian Red Cross Blood Service (the Blood Service). Its purpose is to improve outcomes in patients requiring blood transfusion by enhancing safety and appropriateness. It undertakes regular audits of clinical practice, policy and procedures, administration, and blood storage. The aim of this audit was to clarify current cryoprecipitate use in three Australian jurisdictions (Victoria, Tasmania and the Australian Capital Territory (ACT)), assess adherence and gain insights into deviations from recommended practice.

Fibrinogen is an important component in clot formation and provides substrate for fibrin formation and clot stability.[1] Deficiency or dysfunction (e.g. dysfibrinogenaemia) predisposes to bleeding. Cryoprecipitate is a blood component containing high concentration of fibrinogen and is indicated for fibrinogen deficiency in the setting of bleeding or invasive procedures as per the 2001 National Health and Medical Research Council (NHMRC)/Australasian Society of Blood Transfusion (ASBT) Clinical Practice Guidelines.[2] Previous audits of cryoprecipitate use show that clinical practice varies considerably.[3,4]

Understanding patterns of clinical use and alignment with guidelines assists in improving safety and appropriateness of cryoprecipitate use. Audits may identify possible reasons for deviation from guidelines so that strategies to improve alignment between clinical practice and guidelines can be developed. It may be appropriate to update guidelines to reflect more accurately clinical practice and in other circumstances identify areas for improved clinician education. This study was conducted before the national guidelines were updated. The results will provide a valuable baseline to monitor change in practice following the release of the Patient Blood Management Guidelines.[5]

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The evidence base underlying many areas of transfusion is limited by difficulties performing randomised studies in this field. Hence, much of the basis for guidelines relies on expert opinion, and recommendations vary internationally.[6,7] Transfusion of cryoprecipitate can be important in fibrinogen replacement, for instance in critical bleeding including when associated with disseminated intravascular coagulation (DIC).[8,9] However, cryoprecipitate also carries transfusion-associated risks including allergic reaction, haemolytic transfusion reaction, transfusion-related acute lung injury and blood-borne infection. The decision to transfuse can be complex and challenging, particularly in emergency scenarios. This highlights the importance of relevant, contemporary and scenario-based clinical guidelines.

The 2001 national guidelines for cryoprecipitate use are consensus recommendations and restrict use to indications where fibrinogen deficiency is associated with bleeding, invasive procedure, trauma or DIC. The guidelines recommend against treatment of haemophilia, von Willebrand disease or fibronectin deficiency, unless other more appropriate therapies are unavailable.

Methods

Thirty public and private hospitals from Victoria, Tasmania and ACT with cryoprecipitate usage (determined by 2007 issue data from the Blood Service, range 48–3161 units, mean 668 units) were invited to participate. The Transfusion Committee, or equivalent, designated staff to collect data using a standardised *pro forma* gathering demographic data, laboratory parameters, clinical information and blood components, as assessed by review of patient records. The auditors were provided detailed written instructions and access to Blood Matters staff if questions arose. Active bleeding included any bleeding up to 24 h before transfusion. Types of invasive procedures included insertion of central lines and endoscopy. Data were collected between January and November 2008, and involved up to 30 transfusion events within a hospital with a maximum of two events per patient. In smaller centres, all cryoprecipitate transfusions over the 11-month period were captured, while in larger centres, every third cryoprecipitate transfusion was audited. A transfusion event was defined as blood bank issuing one or more doses of cryoprecipitate. One bag of cryoprecipitate was defined as a unit and included either a single donor whole blood cryoprecipitate (30–40 mL) with an average fibrinogen content of 378 mg/unit, or a single donor apheresis cryoprecipitate (60 mL ± 10%), with an average fibrinogen content of 856 mg/unit (J. Wong, pers. comm., 2012).

Using a Microsoft ACCESS 2003 database (Microsoft, Redmond, WA, USA), an algorithm was run for each transfusion event to determine alignment with guidelines. Based on answers to the *pro forma*, alignment was defined as a pre-transfusion fibrinogen of <1.0 g/L with active bleeding, surgery or invasive procedure within 24 h or DIC (with bleeding or high risk of bleeding).

Data were also evaluated in the setting of active bleeding or trauma using a modified fibrinogen pre-transfusion trigger of ≤1.5 g/L, and results compared with the 2001 guideline based fibrinogen of <1.0 g/L. This modification was based on the likelihood of test results lagging behind the clinical situation because of turn-around times in testing. To ensure consistency, all data were assessed by a primary medical reviewer with 10% randomly reviewed by a second medical reviewer. Where no pre-transfusion fibrinogen was available, a case was designatedly aligned if the post-transfusion fibrinogen was <2.0 g/L in an appropriate setting.

Transfusion episodes were identified as aligned or non-aligned, and categorised into clinical groups. This enabled analysis based on clinical category and identification of groups where the guidelines may require revision.

Statistical analysis was carried out using SPSS 19 (SPSS, Inc., Chicago, IL, USA). Data were expressed as percentages for categorical variables and mean for continuous variables. When reporting on comparisons between categorical variables using Pearson's chi-squared test, a P - value less than 0.05 was considered significant.

Results

Twenty-three hospitals (87% return rate) reported on 460 episodes of cryoprecipitate transfusion during the 11 months of the audit (range 1–30, mean 20). Issue data for Victoria suggest that Victorian hospitals participating represented 91% of the cryoprecipitate use across that state. Surgery accounted for 51% of all clinical indications with cardiac surgery accounting for 22% (Fig. 1). Cryoprecipitate use in trauma accounted for 9% of indications, which may rise as new critical bleeding guidelines are implemented.[10] Among the most common medical diagnoses were gastrointestinal bleeding, liver disease and haematological malignancy. The designation of 'other' includes small numbers of miscellaneous conditions, including solid organ malignancy, ischaemic encephalopathy, foetal hydrops and thrombolysis.

Twenty-six per cent (26%, 95% confidence interval (CI) 22–30) of transfusions were aligned with national guidelines (<1.0 g/L), rising to 61% (95% CI 57–65%) if a modified trigger was applied (fibrinogen ≤ 1.5 g/L). There was a significantly (P = 0.001) higher rate of alignment when modifying the fibrinogen trigger. The

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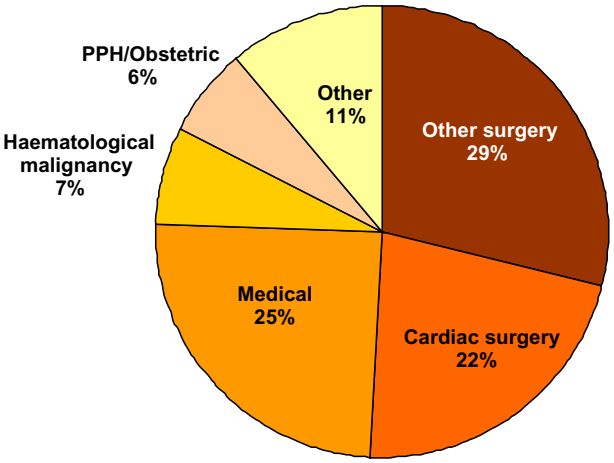

Figure 1 Indications for and frequency of indication for cryoprecipitate. PPH, post-partum haemorrhage.

category with the greatest non-alignment was all forms of surgery regardless of fibrinogen trigger (Table 1).

Pre-transfusion fibrinogen was recorded in 87% of patients; 73% had a post-transfusion fibrinogen (within 6 h), and 66% had both. There were 143 (35%) transfusions with pre-transfusion fibrinogen 1.0–1.5 g/L. A further 33% of transfusions had a fibrinogen >1.5 g/L (Fig. 2).

Among non-aligned (based on 2001 national guidelines) cryoprecipitate transfusions, the majority occurred with a pre-transfusion fibrinogen 1.0–1.5 g/L, suggesting discomfort among prescribers with fibrinogen ≤1.5 g/L. When the modified trigger is applied, the number of non-aligned cryoprecipitate transfusions at fibrinogen levels 1.0–1.5 g/L drops from 143 to 5. Further analysis of the 143 cases where fibrinogen 1.0–1.5 g/L revealed that 62% were related to critical bleeding (Fig. 3). Of the critical bleeding cases, 35% were cardiac surgery followed by aortic aneurysm repair (16%), gastrointestinal bleeding (14%), trauma (13%) and post-partum haemorrhage (7%), and the remaining miscellaneous cases were related to a variety of surgical procedures. Among cases not associated with critical bleeding in this category, eight cases were DIC and 47 miscellaneous medical cases including four cases of leukaemia.

There were few cases ($n = 6$) where cryoprecipitate was non-aligned in patients whose fibrinogen was <1.0 g/L. The majority were haematology patients, and in all instances, cryoprecipitate was used to rectify low fibrinogen. The majority of haematology patients receiving cryoprecipitate had pre-transfusion fibrinogen levels around 1.0 g/L. Among 32 episodes in haematology patients, 24 were prophylactic (i.e. absence of bleeding or invasive procedure). Hypofibrinogenaemia is common in these patients (L-asparaginase therapy or DIC) along with risk factors for bleeding (e.g. thrombocytopenia, sepsis and coagulation factor depletion). Other groups with increased risk of bleeding and prophylactic transfusions included four patients post-liver transplant and 21 neonates with low fibrinogen.

The medical reviewer identified and categorised 17% of episodes as massive transfusion. The majority of patients were surgical (42%), many cardiac. The pre-transfusion fibrinogen levels were mostly higher among the non-aligned group (Table 2). Only 34% of massive transfusion episodes were considered aligned against national guidelines, rising to 65% with a modified fibrinogen trigger. Cardiac surgery accounted for 28% of non-aligned transfusions with little change using the modified trigger (25%).

In 29 transfusions, recombinant activated factor VII (rFVIIa) was given in conjunction with cryoprecipitate, with 17 cases considered aligned. Non-aligned cases were either because testing results were unavailable or fibrinogen was >1.5 g/L; however, in all cases, there was active bleeding.

Discussion

The NHMRC/ASBT 2001 clinical guidelines are being updated; however, a strong evidence base is lacking.

Table 1 Indications for cryoprecipitate transfusion and alignment by clinical groups against national guidelines and modified fibrinogen ≤1.5 g/L trigger

Indication for transfusion	National guidelines		Modified fibrinogen trigger		Total
	Aligned	Not aligned	Aligned	Not aligned	
Cardiac surgery	6 (6%)	95 (94%)	38 (38%)	63 (62%)	101
Other surgery	33 (25%)	101 (75%)	89 (66%)	45 (34%)	134
Medical	45 (40%)	67 (60%)	83 (74%)	29 (26%)	112
Haematological malignancy	8 (25%)	24 (75%)	20 (63%)	12 (38%)	32
PPH/obstetric	11 (37%)	19 (63%)	21 (70%)	9 (30%)	30
Other	17 (33%)	34 (67%)	30 (59%)	21 (41%)	51
All transfusions	120 (26%)	340 (74%)	281 (61%)	179 (39%)	460

Percentages have been rounded and may not total to 100%. PPH, post-partum haemorrhage.

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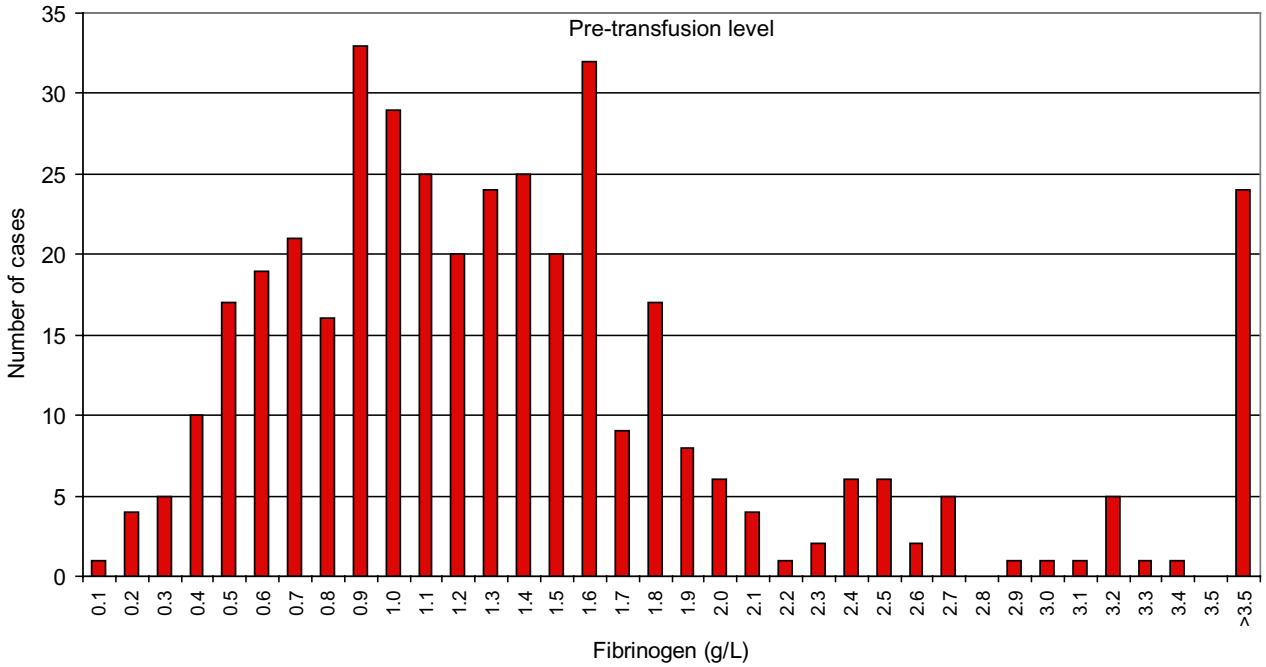

Figure 2 Spread of pre-transfusion fibrinogen level. (■), Pre-transfusion level.

Randomised, clinical trials are needed. In the interim, understanding current practice and assessing alignment to guidelines is important to bring guidelines and day-to-day transfusion medicine closer. Despite being conducted in 2008, this audit provides the most contemporary summary of cryoprecipitate use across three jurisdictions of Australia and is reflective of the altered patterns of cryoprecipitate use with the availability of new massive transfusion literature.[10–12]

Subjectivity was minimised using a computerised algorithm when considering alignment against guidelines. Two independent haematologists further reviewed data for alignment to a modified trigger. There was a 100% agreement with the reviewers' decision of appropriateness. Auditors were not trained in the data collection method and may have led to inconsistency in data; however, it enabled a broader group of hospitals to participate. Hospitals with any cryoprecipitate use were

Figure 3 Critical bleeding in patients transfused cryoprecipitate with fibrinogen 1.0–1.5 g/L. GIT, gastrointestinal tract; PPH, post-partum haemorrhage.

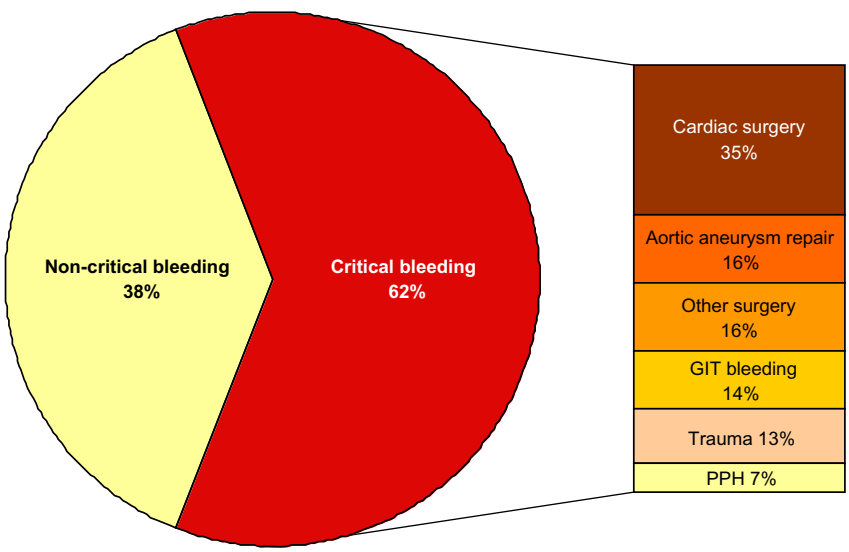

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Table 2 Cryoprecipitate use in massive transfusion with alignment categorised by bleeding type and pre-transfusion fibrinogen

Category	Pre-fibrinogen level (g/L)	Aligned	Non-aligned	Total
All Surgery	≤1.5	24	0	24
	>1.5	0	6	6
	Not performed	3	6	9
Obstetric	≤1.5	11	0	11
	>1.5	0	6	6
	Not performed	2	2	4
Gastrointestinal tract	≤1.5	6	0	6
	>1.5	0	1	1
	Not performed	0	1	1
Carcinoma	≤1.5	1	0	1
	>1.5	0	4	4
	Not performed	0	0	0
Other	≤1.5	3	0	3
	>1.5	1	2	3
	Not performed	0	0	0

invited to participate with a participation rate of 87%. There was a wide variation in audits submitted by individual hospitals (1–30, mean 20). Low audit return by individual hospitals was not investigated but likely due to low cryoprecipitate use, difficulties with access to an auditor or other organisational priorities.

Only 26% of transfusions were aligned with guidelines, increasing to 61% when a modified fibrinogen trigger was applied. Although the modified trigger is somewhat arbitrary, it more accurately reflects limitations of test turn around. Our data suggest that a fibrinogen trigger of 1.5 g/L is commonly utilised. The majority of non-aligned transfusions occurred in surgical patients, in particular cardiac surgery, and may relate to the acuity of clinical decision-making in this setting. Another significant non-aligned category was massive transfusion where clinical concern regarding adequacy of haemostasis is likely to be high. In the absence of strong evidence, it is important to consider the dynamic nature of the bleeding scenario, availability of testing and empiric-based transfusion. Other subgroups in which non-aligned use was prevalent included neonates, haematology and post-liver transplant. These patients have multiple bleeding risk factors that may impact clinical decision-making to transfuse cryoprecipitate prophylactically at higher fibrinogen levels.

Our findings are comparable with other national and international studies. A retrospective study[3] of 1147 patients in NSW public hospitals in 2000 found that 62% of cryoprecipitate transfusions were inappropriate using a definition of appropriate transfusion as a pre-transfusion fibrinogen level of <1.0 g/L. When criteria were relaxed to a fibrinogen <1.5 g/L, 52% of transfusions were inappropriate. In a 2003 US study of 51 patients receiving 88 pools of cryoprecipitate,[7] 24% were deemed inappropriate. This is despite a broader range of indications accepted as appropriate, including tissue plasminogen activator reversal and uraemic bleeding. In a 2008 Canadian study of 25 hospitals, in which the most common indication for cryoprecipitate was cardiac surgery,[4] only 24% of transfusion events were considered appropriate with 19% having a pre-transfusion fibrinogen <1.0 g/L. When considering trauma only, a single Canadian institution in a retrospective audit from 1998–2008 using a fibrinogen of <1.0 g/L within 6 h of transfusion as a marker of appropriateness found that 66% of transfusions were appropriate.[6]

Management of critical bleeding has changed since the 2001 national guidelines were released,[10] with consensus that fresh frozen plasma (FFP), platelets and cryoprecipitate should be utilised proactively with red cells.[13] As a result, many centres have adopted massive transfusion guidelines and rapid access blood packs, which drive early and aggressive transfusion. In massive transfusion, fibrinogen levels can be difficult to obtain in a timely fashion (with prolonged laboratory turnaround and lack of point of care testing in most centres), and some have suggested moving away from the use of fibrinogen levels to guide management.[8] Thromboelastography can prove useful in critical bleeding particularly related to cardiac surgery as it provides real-time data[12] and the ability to detect hyperfibrinolysis.

In this study, 13% of cases had no pre-transfusion fibrinogen available indicating some empirical use of cryoprecipitate. The data suggest that clinicians may transfuse cryoprecipitate in the context of falling fibrinogen rather than awaiting a level <1.0 g/L. Given the frequency of either a pre-transfusion fibrinogen that was

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not available or when transfusion was undertaken despite a high fibrinogen level, the role of the fibrinogen trigger in isolation must be reviewed. Our data showed that 24 transfusions (5%) occurred with a fibrinogen level greater than 3.5 g/L. Data collected found that 13 cases had active bleeding, and six were cardiac surgical cases. Anticipated falling fibrinogen in critical bleeding prior to coagulation test availability may have had a role in these decisions.

Although a fibrinogen level <1.0 g/L is the traditional trigger for cryoprecipitate, there is little evidence underpinning this value with studies suggesting that optimal clot formation may occur at higher levels.[14] In future studies, it would be of value to collect trend measurements to explore this observation further. Use of cryoprecipitate in cases of active bleeding or invasive procedures may be appropriate at higher levels and would reflect more accurately current management.[15] Despite the limitations of the fibrinogen level, it remains, along with the clinical scenario, an important guide when evaluating the bleeding patient.

Cryoprecipitate transfusion rarely occurs in isolation from other transfusion decisions. Although this study did not capture information regarding concurrent transfusion, this needs to be considered, particularly with respect to newer agents such as rFVIIa. Evidence for rFVIIa continues to be controversial, and its role in critical bleeding is still being defined. The concurrent use of cryoprecipitate and rFVIIa is an area requiring further research with *in vitro* reports suggesting that the combination of the rFVIIa and fibrinogen improves clot formation.[16,17] The rate of rFVIIa use was high in this study and may be partly explained by the high levels of critical bleeding, but further interpretation is not possible with the limited data obtained. The authors are aware that some of the participating hospitals included use of rFVIIa in bleeding protocols during this period. These results suggest that more data regarding concurrent transfusion of cryoprecipitate and other products such as rFVIIa are needed.

Fibrinogen concentrates have been licensed in Europe for management of bleeding with the important potential advantages of being virally inactivated[18] and amenable to storage at room temperature.[19] One of the main advantages of fibrinogen concentrates is their portability enabling use in the field, with early evidence suggesting that patients with acquired fibrinogen deficiency have improved survival with these products.[20] *In vitro* studies demonstrate that fibrinogen concentrates have similar pharmacokinetic properties to cryoprecipitate[21] and in a porcine model fibrinogen and prothrombin complex concentrates (PCC) reverse dilutional coagulopathy.[22] However, it should be noted that the study was using a four-factor PCC, whereas Australia and New Zealand use a three-factor PCC, and therefore, results may not be comparable.

Rahe-Meyer *et al*.[23] used a fibrinogen concentrate aiming for a high normal fibrinogen as guided by thromboelastography during cardiac surgery. The study suggested that fibrinogen concentrates enabled higher fibrinogen levels intraoperatively and reduced red cell requirements and postoperative bleeding. This has been supported in a retrospective audit of massive transfusion where fibrinogen concentrates were substituted for cryoprecipitate.[16] There is also evidence to support use of this product in diverse settings including cystectomy,[24] congenital fibrinogen deficiency[25] and DIC.[9]

Conclusion

Cryoprecipitate use varies significantly reflecting the absence of a strong evidence base. The high frequency of inappropriate transfusion in this 2008 study (using 2001 guidelines) suggests a need for new guidelines updated with current evidence while also reflecting the acute and dynamic nature of the clinical scenarios. Examples include massive transfusion and prophylaxis with other risk factors for bleeding. Ongoing research and potentially novel approaches to managing coagulation testing such as thromboelastograpy are needed to answer key questions such as the additional benefit of cryoprecipitate when added to FFP and the clinical efficacy of cryoprecipitate in cessation of bleeding and overall patient outcomes.

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