Cryoprecipitate transfusion in bleeding patients

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CLINICIAN'S CAPSULE

What is known about the topic?
Cryoprecipitate is frequently administered for the treatment of hypofibrinogenemia induced by massive hemorrhage.
What did this study ask?
The latest evidence on cryoprecipitate therapy for hypofibrinogenemia following major surgery, postpartum hemorrhage or trauma was reviewed.
What did this study find?
Cryoprecipitate administration has demonstrated efficacy in raising plasma fibrinogen levels, although further large-scale clinical trials in bleeding settings are required.
Why does this study matter to clinicians?
This review supports the current guidelines regarding cryoprecipitate and demonstrates the utility of cryoprecipitate administration for treating acquired hypofibrinogenemia.

ABSTRACT

Objectives: The management of acquired coagulopathy in multiple clinical settings frequently involves fibrinogen supplementation. Cryoprecipitate, a multidonor product, is widely used for the treatment of acquired hypofibrinogenemia following massive bleeding, but it has been associated with adverse events. We aimed to review the latest evidence on cryoprecipitate for treatment of bleeding.
Methods: We conducted a narrative review of current literature on cryoprecipitate therapy, describing its history, formulations and preparation, and recommended dosing. We also reviewed guideline recommendations on the use of cryoprecipitate in bleeding situations and recent studies on its efficacy and safety.
Results: Cryoprecipitate has a relatively high fibrinogen content; however, as it is produced by pooling fresh frozen donor plasma, the fibrinogen content per unit can vary considerably. Current guidelines suggest that cryoprecipitate use should be limited to treating hypofibrinogenemia in patients with clinical bleeding. Until recently, cryoprecipitate was deemed unsuitable for pathogen reduction, and potential safety concerns and lack of standardized fibrinogen content have led to some professional bodies recommending that cryoprecipitate is only indicated for the treatment of bleeding and hypofibrinogenemia in perioperative settings where fibrinogen concentrate is not available. While cryoprecipitate is effective in increasing plasma fibrinogen levels, data on its clinical efficacy are limited.
Conclusions: There is a lack of robust evidence to support the use of cryoprecipitate in bleeding patients, with few prospective, randomized clinical trials performed to date. Clinical trials in bleeding settings are needed to investigate the safety and efficacy of cryoprecipitate and to determine its optimal use and administration.

RÉSUMÉ

Objectif: La prise en charge des coagulopathies acquises dans différents contextes cliniques nécessite souvent un apport supplémentaire de fibrinogène. Les cryoprécipités, produits à base de sang de plusieurs donneurs, sont utilisés très souvent dans le traitement de l'hypofibrinogénémie acquise par suite d'une hémorragie massive, mais leur administration est associée à des effets indésirables. L'étude visait donc à examiner les données les plus récentes sur le traitement des hémorragies par les cryoprécipités.
Méthode: Il s'agit d'un examen descriptif de la documentation actuelle sur le traitement par les cryoprécipités, qui fait état de l'historique, de la préparation du produit ainsi que des doses recommandées. L'équipe a aussi passé en revue les recommandations contenues dans les lignes directrices sur l'utilisation des cryoprécipités dans les cas d'hémorragie, ainsi que les études récentes sur leur efficacité et leur innocuité.
Résultats: Les cryoprécipités ont une teneur relativement élevée en fibrinogène, mais celle-ci peut varier considérablement d'un sac à l'autre, car le produit est obtenu par la mise en commun de plasma frais congelé provenant de plusieurs donneurs. D'après les lignes directrices actuelles, les cryoprécipités ne devraient être utilisés que dans le traitement de l'hypofibrinogénémie chez les patients en état d'hémorragie clinique. Jusqu'à tout récemment, on considérait que les cryoprécipités ne se prêtaient pas à la réduction des micro-organismes pathogènes; de plus, des préoccupations relatives à

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l'innocuité et l'absence de normalisation de la teneur en fibrinogène ont incité certaines organisations professionnelles à recommander que les cryoprécipités ne soient indiqués que dans le traitement des hémorragies et de l'hypofibrinogénémie en contexte périopératoire, en cas de manque de concentrés de fibrinogène. Si les cryoprécipités sont efficaces dans l'augmentation des taux de fibrinogène plasmatique, les données sur leur efficacité clinique, elles, sont peu nombreuses.
Conclusion: L'équipe n'a pu que constater le manque de données probantes robustes sur l'utilisation des cryoprécipités dans les cas d'hémorragie, et le peu d'essais cliniques prospectifs, à répartition aléatoire, réalisés jusqu'à maintenant. Pourtant, des essais cliniques s'imposent en contexte d'hémorragie afin que soient déterminées l'innocuité et l'efficacité des cryoprécipités ainsi que leur utilisation optimale.

Keywords: Hemostasis, plasma derivatives, transfusion, trauma

INTRODUCTION

Acquired coagulopathy can occur in multiple clinical settings, including cardiac surgery, liver transplantation, trauma, and obstetrics. In the trauma setting, uncontrolled hemorrhage is responsible for approximately 40% of early deaths.[1] Fibrinogen is the first coagulation factor to fall to critical levels during hemorrhage,[2] and evidence suggests that fibrinogen supplementation in the bleeding patient can restore hemostasis.[3] Three therapeutic options are available for fibrinogen supplementation: donor plasma, fibrinogen concentrate, and cryoprecipitate.

Fresh frozen plasma (plasma frozen within 8 hours after collection) is widely used and recommended in the European Trauma Guidelines for initial administration to patients with massive bleeding.[4] However, it has a lower fibrinogen content than cryoprecipitate or fibrinogen concentrate,[3] and is associated with several risks and adverse events, including allergic and anaphylactic reactions, multiorgan failure, acute respiratory distress syndrome, transfusion-related acute lung injury, and potential transmission of infections.[5–8] Fresh frozen plasma is typically stored at −30°C and must be thawed before use, meaning that it may not be immediately available.[4,9] Two recent randomized controlled trials on 1:1 ratios of plasma to red blood cells (RBCs) failed to demonstrate survival benefits of higher volume plasma transfusion[10,11]; however, one of these studies was a feasibility trial, and was not powered for clinical endpoints.[10]

Of the three available therapeutic options, fibrinogen concentrate has the highest fibrinogen content (~2000 mg/dL), can be stored at room temperature and can be reconstituted within 15 minutes. It is also possible to infuse 1 g in under 20 seconds in an emergency situation.[3,12] Studies investigating the safety and efficacy of fibrinogen concentrate have been conducted in major surgery (including cardiovascular, abdominal, and orthopedic spine), trauma, and postpartum hemorrhage settings.[13–17] A recent Cochrane review assessed available evidence and identified six randomized controlled trials investigating the use of fibrinogen concentrate in bleeding patients.[18] The authors concluded that evidence supporting the use of fibrinogen concentrate is weak, and that its use should be limited to a controlled clinical setting or trial until further data are available. However, no alternative to fibrinogen concentrate for use in bleeding patients was recommended, and it should be noted that fibrinogen concentrate has become standard-of-care in some countries,[19] and is recommended in the European Trauma Guidelines for the continued management of significant bleeding accompanied by hypofibrinogenemia.[4]

The third option, cryoprecipitate, contains around 32% of the fibrinogen from plasma.[20] However, owing to the small plasma volume used for cryoprecipitate resuspension, it has a higher fibrinogen concentration than fresh frozen plasma.[4,21] Cryoprecipitate was previously used as a treatment for hemophilia A before factor concentrates were available; however, its main use today is to replenish fibrinogen in acquired bleeding and coagulopathy.[3,21] Due to its relatively high fibrinogen content (~300–3,000 mg/dL), cryoprecipitate has been used to replenish fibrinogen levels in various clinical settings, including trauma,[22] gastrointestinal hemorrhage,[23] cardiac surgery,[24] vascular surgery,[23] and liver transplantation.[25] However, its use has been associated with several adverse events, including infectious disease transmission, transfusion-related acute lung injury, and transfusion-associated circulatory overload.[21,26]

The routine and widespread use of cryoprecipitate as an alternative therapeutic option for fibrinogen supplementation occurs irrespective of the known adverse events associated with its transfusion. Here, we review the evidence supporting its use as a therapeutic agent to treat acquired bleeding.

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The development of cryoprecipitate

In the 1940s, concentrated antihemophilic factor, created by means of the fractionation of plasma with ethanol, was developed by Edwin J. Cohn and used for treatment of hemophilia.[27,28] Cryoprecipitate arrived in the 1960s, when investigations to create an improved, concentrated form of factor VIII (FVIII) revealed that thawing frozen plasma slowly at 1–10°C provided a product rich in FVIII, FXIII, and fibrinogen.[21,29]

Preparation and components of cryoprecipitate

Cryoprecipitate is prepared from fresh frozen plasma.[30] One unit of fresh frozen plasma from a single donor is thawed at 1–6°C and centrifuged to remove the supernatant. The remaining insoluble precipitate is resuspended in a small amount of plasma and refrozen at −18°C to form a single unit of cryoprecipitate.[21] Typically, five single units from multiple donors are pooled into one bag before use.[21] Cryoprecipitate may be prepooled, with pooling of units occurring at the central blood bank before freezing.[21] Alternatively, units may be pooled by licensed centers upon thawing, either by the blood bank or at the patient's bedside, potentially leading to delayed treatment that may be unacceptable in an emergency setting.[31] The best method of pooling (laboratory v. bedside) remains to be determined, and the reliability of the pooling process regarding the content of each pool and ensuring the full dose is administered have not been established.[21,31]

In accordance with AABB (American Association of Blood Banks) guidance, cryoprecipitate should be thawed in a protective plastic overwrap in a water bath at 30–37°C.[32] Once thawed, cryoprecipitate can be stored between 20 and 24°C, but must be administered within 6 hours (or within 4 hours if pooled after thawing).[32] Although fibrinogen levels and von Willebrand factor (vWF) activity do not appear to be significantly affected by extended storage of thawed cryoprecipitate (up to 120 hours at ambient temperature), the levels of FVIII activity were significantly decreased.[33,34] Moreover, although some studies have not identified any bacterial contamination following extended storage, a recent report showed that, while bacterial growth was not observed in spiked, thawed cryoprecipitate samples after 4 hours, considerable proliferation was seen after 24 hours.[33–35]

Fibrinogen content per cryoprecipitate unit has been shown to vary, ranging from 183 to 611 mg/unit, potentially due to between-donor variability, and preparation and storage methods at different institutions.[24] Cryoprecipitate also contains several other clotting factors, including FXIII (20–30% of levels found in plasma), FVIII, vWF (40–70%), fibronectin (20–25%), as well as albumin (5–8%), immunoglobulins G (5–8%), and M (1–2%), and platelet microparticles.[31]

Cryoprecipitate dosing

As cryoprecipitate contains variable amounts of fibrinogen, dosing may provide variable amounts of fibrinogen repletion. The European Trauma Guidelines recommend an initial cryoprecipitate dose of 50 mg/kg (15–20 units for a 70 kg individual) in patients with significant bleeding following major trauma[4]; the AABB recommends 1 unit per 7–10 kg bodyweight to raise plasma fibrinogen by 50–75 mg/dL in patients with fibrinogen deficiency-associated bleeding[32]; and the Australian National Blood Authority suggests a dose of 3–4 g in patients with critical bleeding.[36] The British Committee for Standards in Haematology (BCSH) suggests using 10 units with the aim of raising plasma fibrinogen by 100 mg/dL for management of disseminated intravascular coagulation.[37] A common adult dose is a pool of 10 single-unit bags or two pools of 5 units each, i.e., 10 units of cryoprecipitate.[9,38]

Appropriate use of cryoprecipitate

Current guidelines for appropriate use of cryoprecipitate generally agree that it should be limited to hypofibrinogenemia treatment in clinical bleeding events; however, specific recommendations vary between guidelines. The European Trauma Guidelines recommend fibrinogen supplementation if plasma fibrinogen concentrations fall below 150–200 mg/dL, and suggest that cryoprecipitate may be used for treatment of bleeding accompanied by thromboelastometric signs of a functional fibrinogen deficit or a plasma fibrinogen level below the specified threshold.[4]

The Association of Anaesthetists of Great Britain and Ireland and the European Society of Anaesthesiology recommend cryoprecipitate for fibrinogen replacement in massive hemorrhage only in the absence of fibrinogen concentrate.[39,40] Similarly, the Australian National Blood Authority guidelines indicate that cryoprecipitate may be used in critical bleeding requiring massive transfusion, if fibrinogen levels are not maintained above 100 mg/dL

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by fresh frozen plasma.[36] However, these guidelines also indicate that early cryoprecipitate administration may be warranted in major obstetric hemorrhage.[36]

The BCSH guidelines for use of fresh frozen plasma, cryoprecipitate, and cryosupernatant note that cryoprecipitate is commonly used to enhance fibrinogen levels in dysfibrinogenemia and acquired hypofibrinogenemia in massive transfusion and disseminated intravascular coagulation, where plasma fibrinogen is below 100 mg/dL.[6] The related BCSH guidelines on management of massive blood loss recommend that cryoprecipitate should be given if fibrinogen cannot be maintained above this 100 mg/dL threshold using fresh frozen plasma, further noting that cryoprecipitate is rarely needed except in disseminated intravascular coagulation.[41] Considering the treatment of disseminated intravascular coagulation, the BCSH recommend that severe hypofibrinogenemia (plasma fibrinogen below 100 mg/dL) that persists despite fresh frozen plasma replacement may be treated with fibrinogen concentrate or cryoprecipitate.[37]

In the United States, the AABB, American Red Cross, America's Blood Centers, and Armed Services Blood Program advise that cryoprecipitate is indicated for the control of bleeding associated with fibrinogen deficiency, FVIII, or FXIII deficiency only if recombinant or virus-inactivated FVIII or FXIII are unavailable, and for the control of uremic bleeding if all other modalities have failed.[32] The American Society of Anesthesiologists Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies note that cryoprecipitate is rarely required for fibrinogen levels above 150 mg/dL, but is indicated when fibrinogen levels are below 80–100 mg/dL and accompanied by excessive microvascular bleeding, or in a massively transfused patient with excessive microvascular bleeding in whom fibrinogen levels cannot be rapidly assessed.[42] Several of these guidelines are currently undergoing revision.

Efficacy of cryoprecipitate

Impact on fibrinogen and clotting factors

Galas et al. evaluated the hemostatic effects of fibrinogen concentrate compared with cryoprecipitate in 63 children following cardiac surgery with cardiopulmonary bypass. Compared with baseline values, patients in the fibrinogen group exhibited higher levels of FVII and FIX 1 hour after treatment, whereas patients from the cryoprecipitate group exhibited higher levels of FII, FVII, FIX, and FX.[43] At this time point, patients in the cryoprecipitate group had higher levels of FII, FVII, and FX compared with patients in the fibrinogen group (no between-group difference was observed at baseline). This is perhaps due to a multitude of variable factors that exist in cryoprecipitate during isolation. Treatment with both fibrinogen concentrate and cryoprecipitate increased FIBTEM maximum clot firmness (MCF). Posttreatment plasma fibrinogen concentration increased and was similar in both groups at all time points.[43]

Curry et al. assessed the feasibility of administering cryoprecipitate within 90 minutes of hospital admission in 43 adult trauma patients.[44] Patients received either the standard major hemorrhage therapy or the standard hemorrhage therapy plus two early pools of cryoprecipitate (five single units per pool, in a volume of 150–200 mL with a mean fibrinogen content of 2 g per pool). The primary outcome was the feasibility of early cryoprecipitate administration. Mean plasma fibrinogen concentration was the same in both treatment arms at admission; during active hemorrhage, fibrinogen concentration was higher in the cryoprecipitate arm compared with the standard therapy arm following the infusion of 4, 8, and 12 units of RBCs.[44] Fibrinogen concentration increased in both groups after 24 hours and up to 72 hours, but was not significantly different between the treatment arms.

A trend toward lower fibrinogen concentration was observed from day 7 to study end (day 28) in the cryoprecipitate arm. ROTEM FIBTEM CA5 (clot amplitude at 5 minutes) and MCF values followed the same pattern as fibrinogen concentration at 24 and 72 hours. ROTEM EXTEM values rose significantly in both groups at 24 hours and 72 hours, with a larger increase seen in the cryoprecipitate arm. As this study assessed the feasibility of administering cryoprecipitate within 90 minutes of hospital admission, these results should be treated with caution as the study was not powered for evaluating these clinical outcomes.[44]

An increase in, or maintenance of, plasma fibrinogen levels following cryoprecipitate administration has been observed in both prospective and retrospective studies,[22,24,45,46] although two studies noted that fibrinogen concentrate dosage had a stronger correlation with plasma fibrinogen levels than cryoprecipitate.[17,47]

Impact on bleeding

In the randomized study conducted by Galas et al., there was no significant difference between fibrinogen

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concentrate and cryoprecipitate groups in the primary outcome of postoperative blood loss during 48 hours after surgery (320 v. 410 mL, respectively; $p = 0.672$).[43] The posttreatment incidence of allogeneic blood transfusion was also similar between fibrinogen and cryoprecipitate groups (RBCs, 83.3% v. 97.0%, $p = 0.094$; platelets, 0% v. 9.1%, $p = 0.240$; FFP, 10.0% v. 24.2%, $p = 0.137$; cryoprecipitate, 43.3% v. 42.4%, $p = 0.942$).[43] No deaths occurred during the study (up to postoperative day 7 or hospital discharge) in either treatment arm.

By comparison, Curry et al. found a nonsignificant difference in all-cause 28-day mortality between treatment groups: 10.0% (2/20 patients) in the cryoprecipitate arm and 28.6% (6/21 patients) in the standard therapy arm ($p = 0.14$).[44] Causes of death in the cryoprecipitate arm were severe head injury (n = 1) and sepsis (n = 1), while in the standard therapy arm they were uncontrolled hemorrhage (n = 1), severe head injuries (n = 4), and hypoxic ischemic encephalopathy (n = 1). The patient who died from uncontrolled hemorrhage received tranexamic acid, but no cryoprecipitate. Transfusion requirements were not significantly different between cryoprecipitate and standard therapy treatment arms at 6 hours, 24 hours, or 28 days, except for the number of cryoprecipitate pools at 6 hours, which was significantly greater in the cryoprecipitate group (median 2 [interquartile range 2–4] v. 2 [0–2] pools; $p = 0.03$).[44] Again, this study was not powered for evaluation of clinical outcomes, so results should be interpreted cautiously.

Among women with major obstetric hemorrhage, cryoprecipitate administration was associated with a greater, but nonsignificant, increase in blood loss (5.2 v. 3.3 L; $p = 0.10$), red cell concentrate (7.2 v. 5.9 units; $p = 0.40$), and FFP (4.1 v. 3.2 units; $p = 0.36$) transfusions, compared with FCH.[17]

A retrospective observational study compared tranexamic acid, cryoprecipitate, tranexamic acid plus cryoprecipitate, and no tranexamic acid or cryoprecipitate in 1332 patients in a wartime injury setting. An independent beneficial effect on mortality associated with cryoprecipitate administration (odds ratio, 0.61; $p = 0.02$) additional to that of tranexamic acid was observed.[48] Similarly, early cryoprecipitate administration in trauma patients was associated with improved survival in a UK-based, prospective cohort study; risk of death during the first 28 days decreased with increasing cryoprecipitate dose (conditional on initial 12-hour survival).[22] However, Watson et al. and Holcomb et al. have observed no significant effect of cryoprecipitate on mortality rates in trauma patients.[8,49]

Risks of cryoprecipitate use

Although the adverse-event rate with cryoprecipitate is difficult to quantify precisely, one hemovigilance study of adverse transfusion events reported a rate of 6.57 events per 10,000 units administered.[50] This is considerably lower than rates reported for all other blood components evaluated, including for fresh frozen plasma (28.84 events per 10,000 units).[50] In a UK retrospective observational study of 89 patients between October 2010 and September 2011, there were no reports of acute adverse transfusion reactions following cryoprecipitate infusion,[51] and the Serious Hazards of Transfusion report published in 2011 reported only one serious acute transfusion reaction (urticaria and a sudden drop in cardiac output) in the United Kingdom.[52] Furthermore, the specific risk of transfusion-related acute lung injury has been estimated at 1 in 317,000 units of cryoprecipitate administered, compared with 1 in 81,000 units for fresh frozen plasma/cryosupernatant.[26]

In a small, randomized controlled pilot study in children after cardiac surgery, Galas et al. found no significant differences between fibrinogen concentrate and cryoprecipitate arms in percentage of patients experiencing clinical complications (acute myocardial infarction, stroke, acute kidney injury requiring dialysis, septic shock, reoperation, peripheral artery occlusion, deep venous thrombosis) up to 7 days after surgery or hospital discharge.[43] No adverse events were observed in either group. In a randomized, controlled feasibility trial in adult trauma patients, Curry et al. observed no increase in thrombotic events in the cryoprecipitate arm, and no acute or nonacute transfusion reactions were attributed to cryoprecipitate.[44] Seven serious adverse events were recorded in the cryoprecipitate arm (three incidents of sepsis, one multiorgan failure, and three events classified as "other"), v. 11 events in the standard therapy arm. No severe bleeding events were described in the Galas et al. and Curry et al. studies.[43,44]

In a large, prospective cohort study of patients with blunt trauma (N = 1,175), cryoprecipitate administration was independently associated with a 4.4% lower risk of developing multiorgan failure (hazard ratio, 0.956; $p = 0.01$ [95% confidence interval, 0.923–0.989]) per unit transfused.[8] In contrast, fresh frozen plasma was associated with a 2.1% increased risk of multiorgan failure for each transfused unit. In addition, no significant dose–response relationship was observed for

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cryoprecipitate transfusion and the increased risk of multiorgan failure or acute respiratory distress syndrome.[8]

Intraoperative cryoprecipitate transfusion was independently associated with biliary complications following liver transplantation (relative risk, 3.46; $p < 0.001$) in a retrospective analysis.[25] Randomized controlled studies are needed to determine the safety and role of cryoprecipitate in liver transplantation.

Until recently, cryoprecipitate has been considered unsuitable for pathogen reduction, so there is a small risk of viral transmission associated with this product. Cryoprecipitate can be produced from plasma subjected to viral reduction or inactivation (e.g., by means of methylene blue treatment); however, this can reduce fibrinogen content by up to 40%.[53] As 1 unit of cryoprecipitate is produced from 1 unit of fresh frozen plasma, the risk of adverse events per unit is assumed to be similar for both products. However, as cryoprecipitate is usually administered as a pooled dose of approximately 10 units from multiple donors, the risk of viral transmission per dose is actually higher compared with fresh frozen plasma.[31] In 2017, the manufacture of a pathogen-reduced cryoprecipitate was announced; this product should reduce the risks of viral transmission previously associated with cryoprecipitate.[54]

Galas et al. observed no significant difference between fibrinogen concentrate and cryoprecipitate groups regarding the median length of mechanical ventilation, length of intensive care unit (ICU) stay and vasopressor requirement.[43] Curry et al. noted that patients in the standard therapy arm remained in the ICU for 7 days longer on average, but no difference was observed in total hospital stay between the treatment arms.[44]

CONCLUSION

Despite its widespread use, there is limited evidence supporting use of cryoprecipitate in bleeding patients. Perhaps unsurprisingly, several recent publications have highlighted the lack of robust evidence to support the use of cryoprecipitate.[21,55–57] This highlights a clear need for large-scale clinical trials, in bleeding settings, to investigate the safety and efficacy of cryoprecipitate, and assess whether its ongoing use in bleeding patients is justified. CRYOSTAT-2, which builds on the study by Curry et al., is currently investigating the effect on 28-day mortality of early administration (within 90 minutes) of high-dose cryoprecipitate in trauma patients in the hospital setting,[58] while the FIBRES study is investigating administration of fibrinogen concentrate v. cryoprecipitate in patients with cardiac surgery-induced hypofibrinogenemia.[59] Furthermore, a phase 2 randomized control trial comparing fibrinogen concentrate with cryoprecipitate in traumatic hemorrhage has recently completed and results are awaited with interest.[60,61]

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