Cryoprecipitate

Patterns of Use

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Key Words: Coagulation; Cryoprecipitate; Factor; Fibrinogen; Misuse; Transfusion; Uremia; Warfarin

Abstract

The type of coagulation factors and proteins in cryoprecipitate determine the appropriate indications for its use. To determine the pattern of use at a tertiary care medical center, we performed a retrospective audit of cryoprecipitate utilization. A total of 51 patients received 88 pools of cryoprecipitate. In 39 patients, cryoprecipitate was transfused for appropriate indications: hypofibrinogenemia (n = 19), tissue plasminogen activator reversal (n = 1), management of massive transfusion (n = 7), correction of uremic bleeding (n = 2), and for making fibrin sealant (n = 10). Overall, these patients used approximately 80% of the cryoprecipitate transfused. In 12 other patients, cryoprecipitate was transfused inappropriately to attempt reversal of the anticoagulant effects of warfarin therapy (n = 6), to treat impaired surgical hemostasis in the absence of hypofibrinogenemia (n = 4), and to treat hepatic coagulopathy with multiple factor deficiencies (n = 2). The patterns of misuse, involving 24% of all cryoprecipitate orders, suggest a widespread misunderstanding and need for focused education about the coagulation factors and proteins present in cryoprecipitate and appropriate indications for its use.

Cryoprecipitate is a concentrate of high-molecular-weight plasma proteins that precipitate in the cold. The concentrate contains factor VIII, von Willebrand factor (vWF), fibrinogen, factor XIII, and a few other cryoprecipitable proteins, including fibronectin. Appropriate indications for cryoprecipitate use are limited. The indications for transfusion acceptable at our institution are shown in Table I. These indications have been published in various practice guidelines. At our institution, approximately 1,500 concentrates (bags) of cryoprecipitate were transfused during the year 2000. During this period, the transfusion medicine service encountered several unusual requests for cryoprecipitate use, prompting a retrospective audit of cryoprecipitate use. The results of the audit are presented in this article, and the basis for the excessive use of cryoprecipitate in appropriate clinical settings and the inappropriate use of this blood product are discussed.

Materials and Methods

We reviewed orders for cryoprecipitate at our medical center between October 2000 and February 2001 (19 weeks). For all patients who received cryoprecipitate during this time, we retrospectively reviewed their medical records (including recipient age, sex, clinical diagnosis, and related management) and clinical laboratory data (including the prothrombin time [PT], international normalized ratio [INR], partial thromboplastin time [P TT], platelet count, fibrinogen levels, and serum creatinine values). The number of concentrates of cryoprecipitate and the number of transfusions (pools of concentrates) used were noted, as was the hospital service of the
requesting physician(s) in each case. The indication for cryoprecipitate in each case was evaluated as appropriate or inappropriate. The use of cryoprecipitate was appropriate if it matched identified medical indications (Table 1).

**Results**

Fifty-one patients received a total of 88 cryoprecipitate transfusions (Table 2). These patients were a mean age of 55 years (range, 21-87 years, excluding 2 neonates). A total of 648 concentrates of cryoprecipitate were transfused. The number of concentrates in a pool per transfusion episode ranged from 2 to 10 bags (median, 10 bags), excluding the 2 pediatric cases in which 14 and 29 mL of cryoprecipitate were given.

**Appropriate Use**

In 39 patients (76%), cryoprecipitate was transfused for appropriate indications (Table 2). A total of 518 concentrates (79.9%) of cryoprecipitate were supplied to this group of patients for the reasons given in the following sections.

**Hypofibrinogenemia**

In 19 patients, 323 cryoprecipitate concentrates (49.8% of the total used in the study) were transfused to correct hypofibrinogenemia. Ten of these patients had underlying malignant neoplasms, 4 had serious perioperative bleeding related to orthotopic liver transplantation (OLT), 2 had poor synthetic liver function due to end-stage liver disease, 2 were premature neonates, and 1 had malabsorption. Included in this subset of hypofibrinogenemic patients were 4 with disseminated intravascular coagulation (DIC), 3 of whom had underlying malignant neoplasms; the fourth was a 38-year-old obstetric patient with a fibrinogen level of 63 mg/dL (0.63 g/L) related to placental abruption. The 4 adult patients who underwent OLT received 160 concentrates of cryoprecipitate (24.7% of the total used in the study) and, as a diagnostic group, represented the single largest group of cryoprecipitate consumers in this study.

**Tissue Plasminogen Activator Reversal**

Six concentrates of cryoprecipitate were provided for transfusion to an 83-year-old woman after an acute right parietal hemorrhage with extension into the ventricles developed following tissue plasminogen activator (TPA) therapy for a left middle cerebral artery ischemic infarct. Her laboratory tests immediately after TPA administration revealed a PT of 13.5 seconds (INR, 1.1), a PTT of 25.4 seconds, a platelet count of 182 × 10^3 /µL (182 × 10^9 /L), and a fibrinogen level of 295 mg/dL (2.95 g/L). Following cryoprecipitate infusion, laboratory tests were repeated and

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**Table 1**

**Accepted Indications for the Use of Cryoprecipitate at Beth Israel Deaconess Medical Center, Boston, MA**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Effective Cryoprecipitate Constituent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypofibrinogenemia (fibrinogen ≤100 mg/dL [1.00 g/L])</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>TPA-related life-threatening hemorrhage</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Massive transfusion (&gt;10 RBC units in 24 h with continued bleeding)</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Uremic bleeding</td>
<td>Factor VIII and vWF</td>
</tr>
<tr>
<td>Tissue sealant (fibrin glue)</td>
<td>Factor VIII and vWF</td>
</tr>
<tr>
<td>von Willebrand disease</td>
<td></td>
</tr>
</tbody>
</table>

TPA, tissue plasminogen activator; vWF, von Willebrand factor.

**Table 2**

**Indications for Cryoprecipitate Use at Beth Israel Deaconess Medical Center, Boston, MA**

<table>
<thead>
<tr>
<th>Indication</th>
<th>No. of Patients (n = 51)</th>
<th>No. of Transfusions (n = 88)</th>
<th>No. of Concentrates Used (n = 648)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate indications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypofibrinogenemia</td>
<td>19</td>
<td>46</td>
<td>323</td>
</tr>
<tr>
<td>Fibrin glue</td>
<td>10</td>
<td>14</td>
<td>59</td>
</tr>
<tr>
<td>Massive transfusion</td>
<td>7</td>
<td>12</td>
<td>114</td>
</tr>
<tr>
<td>Uremic bleeding</td>
<td>2</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>TPA-associated bleeding</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Inappropriate indications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin reversal</td>
<td>6</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>Surgical hemostasis</td>
<td>4</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>Hepatic coagulopathy</td>
<td>2</td>
<td>2</td>
<td>20</td>
</tr>
</tbody>
</table>

TPA, tissue plasminogen activator.
showed a PT of 13.9 seconds (INR, 1.3), a PTT of 23.9 seconds, and a fibrinogen level of 463 mg/dL (4.63 g/L). This patient recovered and eventually was discharged from the hospital.

**Massive Transfusion**

Seven patients underwent massive transfusion (6 surgical, 1 obstetric), including cryoprecipitate transfusions. Of the 7 patients, hypofibrinogenemia had developed in 2 (68 mg/dL [0.68 g/L] and 101 mg/dL [1.01 g/L]). The mean fibrinogen concentration for the other 5 patients was 140 mg/dL (1.40 g/L; range, 119-161 mg/dL [1.19-1.61 g/L]). The trauma patient with a fibrinogen level of 68 mg/dL (0.68 g/L) had normal PT and PTT values. In the 6 other patients, prolonged PT (mean, 18 seconds; range, 16.1-26.9 seconds) and PTT (mean, 67.3 seconds; range, 33.3-100.2 seconds) values were noted. Thrombocytopenia was documented in 4 patients, with a mean platelet count of 91 × 10^3 /µL (91 × 10^9 /L).

**Uremic Bleeding**

Two patients received cryoprecipitate transfusions for bleeding related to uremia. The first patient, a 75-year-old man with end-stage renal disease, had initial laboratory tests that revealed a hematocrit value of 37% (0.37), a creatinine level of 7.8 mg/dL (690 µmol/L), a PT of 14.3 seconds (INR, 1.4), a PTT of 31.5 seconds, and a platelet count of 114 × 10^3 /µL (114 × 10^9 /L) before bleeding. He subsequently developed uncontrollable bleeding per rectum due to ischemic colitis. A pool of 6 cryoprecipitate concentrates was transfused, in addition to fresh frozen plasma (FFP), RBCs, and 1-deamino-8-D-arginine vasopressin (DDAVP) therapy, in an attempt to control gastrointestinal bleeding. Despite this therapy, the patient eventually required a right hemicolectomy. The other patient, a 58-year-old man undergoing hemodialysis, developed bleeding from his lower gastrointestinal tract following diagnostic colonoscopy for diarrhea. His laboratory tests revealed a hematocrit of 33% (0.33), a creatinine level of 4.5 mg/dL (398 µmol/L), a PT of 17.3 seconds (INR, 2.0), a PTT of 31.7 seconds, a platelet count of 129 × 10^3 /µL (129 × 10^9 /L) before bleeding. He subsequently developed uncontrollable bleeding per rectum due to ischemic colitis. A pool of 6 cryoprecipitate concentrates was transfused, in addition to fresh frozen plasma (FFP), RBCs, and 1-deamino-8-D-arginine vasopressin (DDAVP) therapy, in an attempt to control gastrointestinal bleeding. Despite this therapy, the patient eventually required a right hemicolectomy. The other patient, a 58-year-old man undergoing hemodialysis, developed bleeding from his lower gastrointestinal tract following diagnostic colonoscopy for diarrhea. His laboratory tests revealed a hematocrit of 33% (0.33), a creatinine level of 4.5 mg/dL (398 µmol/L), a PT of 17.3 seconds (INR, 2.0), a PTT of 31.7 seconds, a platelet count of 129 × 10^3 /µL (129 × 10^9 /L) before bleeding. The bleeding responded to transfusions of RBCs, FFP, and 3 cryoprecipitate transfusions, each containing 10 concentrates. Bleeding times were not available for these 2 patients.

**Fibrin Sealant**

Cryoprecipitate was used to make fibrin sealant for 8 patients undergoing cardiothoracic surgery, in 1 patient to control bleeding from a gastric anastomotic site, and in 1 patient to seal a cerebrospinal fluid leak. A mean of 6 concentrates (range, 2-9) per patient was used to make fibrin sealant.

**Inappropriate Use**

In 12 patients (24%), the use of cryoprecipitate was questioned (Table 2). Multiple services and physicians were associated with these inappropriate transfusions. A total of 130 concentrates (20.0%) of cryoprecipitate were issued to this group of patients.

**Warfarin Reversal**

Six patients (mean age, 62 years; range, 35-82 years) inappropriately received cryoprecipitate to reverse the effects of warfarin. Three patients (INRs of 6.0, 2.7, and 1.2) had life-threatening intracranial hemorrhage, another had an intrapulmonary hemorrhage (INR, 2.9), and another had a substantial retroperitoneal hematoma (INR, 2.5) that developed following femoral artery catheterization. The sixth patient receiving warfarin (INR, 3.6) was admitted with a myocardial infarction and required emergency coronary artery bypass graft (CABG) surgery. Warfarin was discontinued in all cases. Concomitant vitamin K administration and FFP transfusions were used to lower the INR in only 3 of these cases. One of the patients, who also had antiphospholipid syndrome, underwent surgical evacuation of a subdural hematoma. In this case, the neurosurgeons deliberately opted to avoid transfusing large volumes of FFP owing to concern for brain edema. Instead, they transfused a pool of 10 concentrates of cryoprecipitate. In another patient treated with warfarin for prophylaxis in the setting of paroxysmal atrial fibrillation, who had acute hemorrhage into her thalamus at the time of admission, the neurology service elected to not reverse anticoagulation with vitamin K or FFP owing to concern for an embolic stroke in the setting of ongoing atrial fibrillation. This patient died 7 days after extension of hemorrhage into the ventricular system.
Surgical Hemostasis

Four patients (8%) unnecessarily received cryoprecipitate perioperatively to aid surgical hemostasis, although 3 had a normal fibrinogen level and none had excessive bleeding. These patients all were admitted to the thoracic or cardiothoracic service. One was admitted for a CABG (fibrinogen level, 204 mg/dL [2.40 g/L]), another for a repeated CABG and simultaneous aortic valve replacement and removal of a bacterially infected pacemaker (fibrinogen level, 163 mg/dL [1.63 g/L]), a third for repair of a perforated gastric colocolostomy (fibrinogen level, 311 mg/dL [3.11 g/L]), and a fourth for esophagogastrectomy to treat esophageal cancer (fibrinogen concentration not measured).

Hepatic Coagulopathy

Two (4%) elderly women with hepatic malignant neoplasms, both with elevated INRs, received cryoprecipitate, despite a normal fibrinogen level in one patient (180 mg/dL [1.8 g/L]) and no fibrinogen measurement in the other. Neither patient had evidence of bleeding. Dysfibrinogenemia was not considered in either case. An invasive procedure (bronchoscopy) was performed in 1 case. One patient received an additional unit of FFP and the other 3 RBC units.

Discussion

Cryoprecipitate is prepared by slowly thawing FFP at 4°C to 6°C. This results in the formation of an insoluble precipitate (cryoprecipitate) that can be resuspended in about 10 to 15 mL of plasma to be stored (at −18°C or colder) for up to a year. Each concentrate of cryoprecipitate prepared from a single donor unit of plasma contains 80 to 100 U of factor VIII, vWF (with both procoagulant activity and antigen), 150 to 300 mg (4.4-8.8 µmol/L) of fibrinogen, and 40 to 60 U of factor XIII. Approximately 5% of the total protein is represented by factor VIII and vWF. Other proteins in the concentrate include fibronectin (20%-25% total protein), IgG (5%-8%), IgM (1%-2%), and albumin (5%-8%).

Appropriate Use

No people with hemophilia were treated with cryoprecipitate in this study, and cryoprecipitate has not been used at our medical center for this diagnosis in more than 15 years. This is because cryoprecipitate is no longer the product of choice for treatment of hemophilia A. Commercially available factor VIII concentrates have far lower risks of blood-borne viral infection, particularly HIV, and are preferred. However, in many developing countries, cryoprecipitate may be the only available source of factor replacement, and this should be considered in establishing indications for cryoprecipitate use.

Cryoprecipitate also is used for the supplementation of fibrinogen in patients with congenital or acquired hypofibrinogenemia and in patients with normal fibrinogen levels but with dysfibrinogenemia. Fibrinogen levels of more than 100 mg/dL (1.00 g/L) generally are considered adequate for hemostasis. Levels below 100 mg/dL (1.00 g/L) frequently are associated with severe bleeding complications. In our study, half of all the cryoprecipitate provided by the blood bank was used to correct acquired hypofibrinogenemia. In the United States, cryoprecipitate is the only concentrated fibrinogen product available. Although the fibrinogen content of cryoprecipitate may be variable, current standards require that all tested individual units of cryoprecipitate contain a minimum of 150 mg (4.4 µmol) of fibrinogen. Thus, a bag of transfused cryoprecipitate (with 50% recovery in whole blood) can be expected to raise the fibrinogen level by a minimum of 30 mg/dL (0.30 g/L), with a half life of 3 to 6 days.

Clinically, acquired hypofibrinogenemia often is associated with conditions that cause a consumptive coagulopathy, such as DIC. Patients who are receiving transfusions of cryoprecipitate for the correction of hypofibrinogenemia and who are actively bleeding will more than likely also require other blood products to replenish consumed coagulation factors. In patients with acute DIC and worsening laboratory result abnormalities, some authorities believe that the administration of blood products, particularly those containing fibrinogen, may “fuel the fire.” In such patients, these authors consider it important to first interrupt the generation of thrombin by administering heparin before trying to correct the hemostatic deficiencies. None of the 4 patients in the present study received heparin, but all received multiple blood products, including RBCs, platelets, FFP, and cryoprecipitate. All 4 recovered.

In patients receiving thrombolytic therapy, intracranial hemorrhage is the most common form of stroke, occurring in 0.1% to 1.4%. The hematologic management of a TPA-induced hemorrhagic cerebrovascular accident should include the transfusion of cryoprecipitate, the discontinuation of thrombolytic therapy, and, in certain cases, transfusion of FFP and platelets. In our study, cryoprecipitate was used successfully for TPA reversal in 1 patient in whom this therapy was complicated by a life-threatening intracranial hemorrhage.

Bleeding complications and blood product consumption can be major concerns during liver transplantation. Of the cryoprecipitate used during this study period, 24.7% was transfused to 4 OLT recipients to manage perioperative bleeding and hypofibrinogenemia. This mimics published statistics, in which liver transplants have the highest routine blood use of any surgical procedure. This is not surprising, since most patients with end-stage liver disease already have...
diminished synthesis of coagulation factors and thrombocytopenia. In addition, these patients usually develop intraoperative hemostatic derangements, particularly during the anhepatic phase of the operation. For adult liver transplants, the current average intraoperative use of cryoprecipitate in the United States and Europe is 5 concentrates. In our study, liver transplant recipients averaged 40 concentrates of cryoprecipitate in the immediate perioperative period. This high number was due to surgical complications in all cases. Perioperative bleeding during OLT operations can be reduced substantially by avoiding hemodilution during surgery and administering calcium chloride or aprotinin.

Transfusions are considered massive when a volume exceeding the patient’s blood volume is administered within 24 hours. Patients who receive massive transfusions may develop a dilutional coagulopathy and DIC with thrombocytopenia and hypofibrinogenemia. Usually, after 3 or more blood volumes, most often bleeding in such patients is related to thrombocytopenia, but there is evidence to suggest a possible benefit for cryoprecipitate in these cases. In our study, 7 patients received massive blood transfusions. Despite the fact that fibrinogen levels were low in only 2 of our patients, cryoprecipitate was ordered because most of the patients exhibited evidence of coagulopathy (prolonged PT and PTT) and because the dynamic nature of the surgical situation meant that fibrinogen levels could have fallen further.

Formerly, cryoprecipitate was the mainstay of therapy for most types of von Willebrand disease (vWD). The aim of therapy for vWD is to increase vWF and factor VIII levels. Mild cases of vWD (except for type IIb disease) can be treated with the synthetic vasopressin analog desmopressin (DDAVP), which causes the release of endogenous factor VIII and vWF stores. Only severe disease is likely to warrant treatment with FFP or cryoprecipitate. Cryoprecipitate, which contains 40% to 70% of the total amount of original vWF in plasma, has the full range of vWF multimers, with an equal amount of vWF ristocetin cofactor activity and vWF antigen. Therefore, cryoprecipitate provides a much higher concentration of high-molecular-weight vWF than FFP. Nevertheless, the bleeding time in certain cases of severe type III vWD will be corrected only when cryoprecipitate is given together with platelets or DDAVP. A factor VIII concentrate preparation (Humate-P, Aventis Behring, Kankakee, IL) made available in the United States has been shown to contain adequate amounts of vWF for the treatment of vWD and is generally preferred over cryoprecipitate. This may explain why we encountered no cases of vWD in which cryoprecipitate was given.

Cryoprecipitate was used to help control lower gastrointestinal bleeding in 2 uremic patients. Despite numerous transfusions of cryoprecipitate, FFP, and RBCs, as well as DDAVP therapy, bleeding in one of these patients could only be controlled surgically. Bleeding in the other patient responded to transfusions of RBCs, FFP, and cryoprecipitate. Bleeding from the gastrointestinal tract is one of the most important causes of morbidity and mortality in patients with end-stage renal disease. The hemostatic defect in uremia is multifactorial and the underlying mechanism obscure. Nevertheless, cryoprecipitate has been shown to temporarily correct bleeding in patients with uremia. Cryoprecipitate seems to increase circulating vWF, which enhances platelet function. However, multiple doses of cryoprecipitate may be necessary, and the bleeding in as many as 50% of patients may fail to respond. Therefore, the role of cryoprecipitate in the treatment or prevention of bleeding in uremic patients remains controversial.

In addition to using cryoprecipitate, the management of uremic bleeding may include dialysis, correction of anemia, DDAVP, conjugated estrogens, and platelet inhibitory agents. Compared with these other treatment modalities, cryoprecipitate and desmopressin are more useful in acute situations, because of their rapid onset of action.

Finally, 10 cases involved the use of cryoprecipitate to make the biologic topical agent known as fibrin sealant. Fibrin sealant is formed by the coagulation of cryoprecipitate following the addition of bovine thrombin. As evidenced in our study, fibrin sealant has found wide application as a biologic tissue adhesive and hemostatic agent in thoracic and cardiovascular surgery and as a biologic adhesive to help seal anastomotic areas and dural leaks. Although fibrin sealant is well tolerated in general, the use of topical bovine thrombin may result in the development of antibodies against bovine thrombin and factor V in some patients. None of our patients were tested for these antibodies.

Inappropriate Use

Six patients in this study received inappropriate transfusions of cryoprecipitate to reverse the effects of warfarin. Warfarin is the most popular drug for long-term anticoagulant treatment of thromboembolic disease. It induces a hypocoagulable state by blocking the vitamin K–mediated hepatic synthesis of clotting factors II, VII, IX, and X. This is reflected in a prolonged PT and an elevated INR. Bleeding may complicate anticoagulant therapy, particularly since warfarin has a narrow therapeutic window. Although the risk for clinically significant hemorrhage is highest when the INR exceeds 4.5, clinically significant hemorrhage occasionally may still be seen when the INR is in therapeutic or subtherapeutic ranges, often owing to anatomic factors that increase the risk of bleeding. Intracranial hemorrhage, although rare, is the most common cause of death in patients receiving warfarin. Three of the patients in this study had life-threatening intracranial hemorrhage. Two of these patients had therapeutic INRs, a finding reported by others.
Immediate reversal of warfarin-induced anticoagulation is necessary when patients have spontaneous, life-threatening hemorrhage or trauma or require urgent surgery. Therapeutic intervention after intracranial hemorrhage is particularly important since faster normalization of the coagulation status has been shown to improve clinical outcome.35 Cessation of warfarin therapy alone is inadequate in these situations because normalization of the INR may take several days. Moreover, it may be ineffective in patients with liver disease. Therefore, for patients in whom urgent reversal of anticoagulation is necessary or in whom liver dysfunction will prohibit vitamin K–induced recovery, replacement of clotting factors is required.33

Cryoprecipitate is a poor source of vitamin K–dependent factors8 and, therefore, should not be used in this setting. Rather, FFP, which contains all of the coagulation factors, is the optimal product for rapid reversal of warfarin-induced anticoagulation. However, large volumes of FFP may be required to correct a markedly elevated INR. In susceptible people, the amount of FFP needed for the rapid and complete reversal of the anticoagulation effect could precipitate cardiac failure or pulmonary edema. To overcome the limitations of FFP, several clotting factor concentrates have been developed. Products that are rich in vitamin K–dependent factors and of small volume (approximately 20 mL) are known collectively as prothrombin complex concentrates (PCCs).36 Evidence-based studies have shown that PCCs are a better replacement product than FFP for reversing warfarin-induced anticoagulation,37,38 particularly in cases associated with intracranial hemorrhage.39 Clinical studies have documented a more rapid and effective reversal of warfarin in life-threatening emergencies40 and in cases of intracranial hemorrhage with improved neurological status35 compared with FFP. The more rapid reversal of anticoagulation may relate to a higher effective dose given (10 mL of PCC is equivalent to 600 mL of FFP in terms of content of vitamin K–dependent coagulation factors).39 Extreme caution is required when administering PCCs as they may promote thromboembolism and myocardial infarction and incite DIC, and for this reason, PCCs are relatively contraindicated in patients with other active thrombotic processes.33,35,38 The use of other products such as factor VIIa to treat warfarin-induced bleeding has yet to be adequately established.33,37

The value of cryoprecipitate to correct surgical bleeding in the absence of a specific factor VIII, vWF, or fibrinogen deficiency is unclear.10,41 Our audit revealed 4 patients who received unnecessary transfusions of cryoprecipitate to aid in surgical hemostasis, even though none were bleeding excessively or found to have low fibrinogen concentrations and none had vWD. The American Society of Anesthesiologists task force on blood component therapy recommends the perioperative administration of cryoprecipitate in only 3 circumstances3: (1) for prophylaxis in nonbleeding peripartum patients with congenital fibrinogen deficiencies or vWD unresponsive to DDAVP, (2) for bleeding patients with vWD, and (3) for the correction of microvascular bleeding in massively transfused patients with fibrinogen concentrations less than 80 to 100 mg/dL (0.80-1.00 g/L) or when fibrinogen concentrations cannot be measured in a timely manner.

Another common error made in clinical practice is to transfuse cryoprecipitate to correct hepatic-related coagulopathies. Two patients identified in our study, each with metastatic disease involving the liver, were given cryoprecipitate in an attempt to correct their elevated INRs. One of these patients had a normal fibrinogen level, and for the other, no fibrinogen was measured. Patients with liver disease usually have multiple abnormalities contributing to an increased bleeding tendency, including decreased synthesis of coagulation factors (except factor VIII), dysfibrinogenemia, aberrations of the fibrinolytic system, and splenomegaly with secondary thrombocytopenia. FFP, because it contains all the coagulation factors, is considered to be the blood product of choice for treating significant coagulopathies in patients with liver disease and active bleeding.15,42 Even with large amounts of FFP, a prolonged PT may not be corrected in all cases, because consumption, from clotting and fibrinolysis, and losses with bleeding may outstrip replacement speed.15 Volume overload with FFP in these patients may limit the efficacy of this approach, and here cryoprecipitate may be more useful for treating severe coagulopathy with hypofibrinogenemia.42 Antifibrinolytic agents,1 exchange plasmapheresis,42 and also DDAVP43 in combination with plasma therapy may be useful for these patients.

Finally, although not transfused for this purpose in our study, cryoprecipitate has been transfused to provide fibronectin.44,45 Fibronectin is an opsonic glycoprotein thought to help remove blood-borne debris and bacteria.1 Critically ill and septic patients usually have depleted fibronectin levels.44 Previous uncontrolled observations suggested that transfusions of fibronectin-rich cryoprecipitate may benefit patients with sepsis, burns, or trauma.44,45 However, this hypothesis has not been borne out by subsequent studies.44,45

Conclusions

Our review showed that cryoprecipitate was misused in almost one fourth of patients (one fifth of all concentrates issued). Although most of the care at our tertiary
care medical center is directed by residents and fellows in training, they are under the supervision of experienced staff physicians, and, thus, we consider this level of misuse of cryoprecipitate unacceptable. Cryoprecipitate was transfused incorrectly in 3 circumstances: (1) to reverse the anticoagulant effects of warfarin therapy, (2) to correct surgical hemostasis in the absence of a specific coagulation factor or fibrinogen deficiency, and (3) to correct coagulopathies due to liver disease not associated with bleeding. Among these misuses, the transfusion of cryoprecipitate to patients with life-threatening hemorrhage secondary to overanticoagulation with warfarin was particularly dangerous, as adequate correction of the coagulopathy may be delayed if only cryoprecipitate is transfused, with dire consequences, as was seen in one of our patients. We recommend that when the cause of bleeding or coagulopathy is multifactorial, as in the 3 aforementioned circumstances, FFP be transfused instead of cryoprecipitate. The availability of more effective blood products like PCCs and, possibly, factor VIIa is promising. Also, alternative pharmacologic agents such as DDAVP and aprotinin have become more popular treatments for many of these hemostatic disorders.

Adherence to appropriate indications for cryoprecipitate therapy is essential. Cryoprecipitate is not free of risks. In addition to the direct cost of unnecessarily transfused blood products (around $4,500 in this study; calculated using $35 per concentrate of cryoprecipitate), transfusion may be associated with the transmission of infections. The risk of a transfusion-transmitted disease is the same, per cryoprecipitate concentrate, as for a unit of RBCs; because cryoprecipitate is typically transfused as a pool of multiple products, the risk is proportionately higher. Hemolytic anemia from RBC antibodies present in cryoprecipitate concentrates has been reported, as have anaphylaxis and severe pulmonary reactions to proteins in the cryoprecipitate.

The patterns of misuse, especially in overwarfarinized patients, suggest a widespread misunderstanding and need for focused education, especially of internal medicine physicians and surgeons, about the coagulation factors and proteins present in cryoprecipitate and appropriate indications for its use. Prospective intervention by the transfusion medicine service could be effective in curtailing this misuse.

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