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STATE OF THE ART REVIEW

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The role of cryoprecipitate in human and canine transfusion medicine

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Abstract

Objective: To evaluate the current role of cryoprecipitate in human and canine transfusion medicine.

Data sources: Human and veterinary scientific reviews and original studies found using PubMed and CAB Abstract search engines were reviewed.

Human data synthesis: In the human critical care setting, cryoprecipitate is predominantly used for fibrinogen replenishment in bleeding patients with acute traumatic coagulopathy. Other coagulopathic patient cohorts for whom cryoprecipitate is recommended include those undergoing cardiovascular or obstetric procedures or patients bleeding from advanced liver disease. Preferential selection of cryoprecipitate versus fibrinogen concentrate (when available) is currently being investigated. Also a matter of ongoing debate is whether to administer this product as part of a fixed-dose massive hemorrhage protocol or to incorporate it into a goal-directed transfusion algorithm applied to the individual bleeding patient.

Veterinary data synthesis: Although there are sporadic reports of the use of cryoprecipitate in dogs with heritable coagulopathies, there are few to no data pertaining to its use in acquired hypofibrinogenemic states. Low fibrinogen in dogs (as in people) has been documented with acute traumatic coagulopathy, advanced liver disease, and disseminated intravascular coagulation. Bleeding secondary to these hypocoagulable states may be amenable to cryoprecipitate therapy. Indications for preferential selection of cryoprecipitate (versus fresh frozen plasma) remain to be determined.

Conclusions: In the United States, cryoprecipitate remains the standard of care for fibrinogen replenishment in the bleeding human trauma patient. Its preferential selection for this purpose is the subject of several ongoing human clinical trials. Timely incorporation of cryoprecipitate into the transfusion protocol of the individual bleeding patient with hypofibrinogenemia may conserve blood products, mitigate adverse transfusion-related events, and improve patient outcomes. Cryoprecipitate is readily available, effective, and safe for use in dogs. The role of this blood product in clinical canine patients with acquired coagulopathy remains unknown.

Abbreviations: aPTT, activated partial thromboplastin time; ATC, acute traumatic coagulopathy; Cryo, cryoprecipitated antihemophilic factor (cryoprecipitate); DIC, disseminated intravascular coagulation; FC, fibrinogen concentrate; FFP, fresh frozen plasma; PRBC, packed red blood cell; PT, prothrombin time; RCT, randomized controlled trial; ROTEM, rotational thromboelastometry; TEG, thromboelastography; TRALI, transfusion-related acute lung injury; VHA, viscoelastic hemostatic assay; vWF, von Willebrand's factor

KEYWORDS
acute traumatic coagulopathy, fibrinogen, hypofibrinogenemia, transfusion medicine, massive hemorrhage protocol

1 | INTRODUCTION

Current human and veterinary transfusion medicine emphasizes goal-directed blood component selection based on individual patient needs. Hemostatic resuscitation following trauma (the use of select blood components to address acute coagulopathies *and* restore effective circulating blood volume in patients with hemorrhagic shock) exemplifies patient-tailored transfusion medicine. Early incorporation of blood products into resuscitation practices, or bundles, may mitigate complications of large-volume isotonic crystalloid resuscitation in these patients, which include the lethal triad of death (ie, acidosis, coagulopathy, and hypothermia), hemodilution, and organ edema and dysfunction. Critically ill human and veterinary patients with severe hemorrhage (or anticipated bleeding) from various other etiologies, including perioperative hepatic or cardiovascular procedures, or obstetric emergencies, may also benefit from tailored selection of blood products. Cryoprecipitate (cryoprecipitated antihemophilic factor [cryo]) is 1 blood component that can be used to address coagulopathies in critically ill patients. The aim of this review is to summarize clinical human medical practices pertaining to cryo therapy, inclusive of product composition, historical and current indications and guidelines, dosing and administration recommendations, and potential complications from component use. Canine cryo is readily available to the veterinary practitioner in certain parts of the United States, and similar clinical indications for cryo in veterinary (vs human) patients are plausible and likely. Therefore, although veterinary data pertaining to use of cryo in clinical canine patients are sparse, these will be incorporated into this review whenever possible.

2 | CRYOPRECIPITATE PREPARATION AND COMPOSITION

Human cryo is derived via a controlled, slow thaw to a temperature of approximately 4°C of either 1 unit of fresh frozen plasma (FFP) or plasma frozen within 24 hours of collection. This product is then centrifuged to remove the supernatant (cryo-poor plasma [CPP]), and the remaining precipitate is resuspended with 10–15 mL of plasma and frozen to less than or equal to −18°C. Shelf life is 1 year from phlebotomy date. Because cryo is resuspended in a small volume, it contains a concentrated (while variable) amount of fibrinogen. Due to donor and manufacturer processing differences, cryo units contain anywhere between 10 and 25 g/L of fibrinogen. Cryoprecipitate also contains clotting factors VIII and XIII (FVIII and FXIII), von Willebrand factor (vWF), fibronectin, platelet microparticles, and small amounts of immunoglobulin. Each cryo unit has approximately 10–15 mL. Prior to administration, human cryo is typically prepared as a pool from 4 to 6 donors; pooling can be performed before freezing or after thaw.[1–3]

Canine cryo is currently available from 2 commercial blood banks, HEMOPET* and Animal Blood Resources International (ABRI).† HEMOPET collects and stores this plasma concentrate from healthy, screened dog donors in a similar fashion to the equivalent human product discussed above. One "unit" of dog cryo (derived from about 250 mL FFP) contains approximately 12.5 mL of concentrated FVIII, vWF, fibrinogen, and fibronectin (and smaller amounts of other clotting factors). It is recommended to store this product frozen at a minimum temperature of −10°C, preferably between −30 and −70°C. Shelf life is 1 year. Cryoprecipitate available from ABRI is lyophilized, or freeze-dried. This product is collected (as previously outlined) from ABRI donor FFP (250–300 mL), and then refrozen and dried under a vacuum. Comprised predominantly of FVIII and fibrinogen, and also containing smaller amounts of vWF and XIII, it is stored without preservative as a sterile powder at 4–6°C until rehydration prior to use. Shelf life is 18 months. Additionally, many specialty veterinary hospitals with blood banking capabilities make and store their own canine cryo. To the author's knowledge, there is currently no species-specific cryo available for clinical use in other nonhuman animals.

3 | HISTORICAL AND CURRENT USAGES OF CRYOPRECIPITATE

The use of cryo in human medicine was first introduced in the 1960s when it was discovered that the slow thaw and subsequent precipitation of FP resulted in a blood product with high concentrations of FVIII and FXIII, vWF, and fibrinogen.[3–5] As such, historically cryo was mainly used for treatment of hemophilia A (associated with FVIII deficiency). In the advent of tailored, or individualized, transfusion medicine, and following the development of a more purified, factor-specific product (FVIII concentrate), use of cryo for treatment of hemophilia has declined.

As cryo is also rich in fibrinogen, today this product is primarily utilized to replenish this clotting factor in bleeding human trauma patients requiring massive transfusion.[1,3,6–8] Other suggested indications in sick people include the following: bleeding from acquired hypofibrinogenemia associated with advanced liver disease, cardiovascular surgery, obstetric procedures, disseminated intravascular coagulation (DIC), or thrombolytic therapy; bleeding associated with renal failure when desmopressin is ineffective; and inherited hypofibrinogenemia (Table 1).[1,3,6,7,9] Use of cryo varies worldwide, depending on the availability and licensure of fibrinogen concentrate (FC) as an alternative

TABLE 1 Indications for cryoprecipitate in people based on current guidelines

Hypofibrinogenemia from massive transfusion (keep fibrinogen > 1.5 g/dL)
Hypofibrinogenemia in major hemorrhage (keep fibrinogen > 1.5 g/dL)
Advanced liver disease with bleeding or as surgical prophylaxis if fibrinogen < 1 g/dL
Prophylaxis for surgery when fibrinogen < 1.5 g/dL
Hepatic or renal failure associated with bleeding when desmopressin is ineffective or contraindicated
Disseminated intravascular coagulation with bleeding and fibrinogen < 1 g/dL
Bleeding from thrombolytic therapy causing hypofibrinogenemia
Inherited hypofibrinogenemia where fibrinogen concentrate is not available

From Wong et al,[3] British Committee for Standards in Haematology Blood Transfusion Task Force,[6] and Spahn et al.[51]

therapy for congenital and acquired hypofibrinogenemia. Cryoprecipitate is currently manufactured for human use in the United States, the United Kingdom, New Zealand, Canada, and Australia. Optimal indications remain to be determined.[3]

In canine patients, cryo is currently recommended for treatment of von Willebrand disease and hemophilia A, as neither vWF nor FVIII concentrates are available to the veterinary practitioner. Cryoprecipitate can be administered either prophylactically prior to invasive procedures or to address clinical bleeding associated with these heritable coagulopathies. This use is an alternative to FFP transfusion, which involves administration of significantly more volume to replenish FVIII or vWF. As dog cryo also concentrates fibrinogen, coagulopathy and resultant bleeding associated with deficiency or depletion of this clotting factor may represent additional scenarios for preferential selection of this blood product.[10,11]

4 | FIBRINOGEN AND COAGULATION

Fibrinogen is a plasma glycoprotein (molecular weight = 340 kDa) that is synthesized in the liver. It functions as a key coagulation protein for hemostasis in both people and dogs and, therefore, hypo- or dysfibrinogenemic states can be associated with bleeding diatheses. Following tissue injury, thrombin is generated during both the initiation phase of coagulation (on tissue factor-bearing cells) and the propagation phase of coagulation (on platelets). Thrombin cleaves fibrinogen into soluble fibrin molecules that then polymerize to form an insoluble fibrin matrix. Subsequent FXIIIa-mediated modification of the polymerized fibrin to cross-linked strands results in a stable fibrin clot that resists fibrinolysis.[12,13] Fibrinogen is also required for platelet aggregation via interaction with an integrin on the membrane of the platelet (glycoprotein IIb/IIIa).[14]

5 | COMMERCIAL SOURCES OF FIBRINOGEN

Fibrinogen supplementation in people can be provided via FFP, cryo, and FC.[16,17] These 3 products contain different amounts of fibrinogen: 2 g/L, 10–25 g/L, and 20 g/L, respectively. One limitation to FFP is the low fibrinogen concentration (requiring a larger infusion volume). Fresh frozen plasma is also associated with increased risk of transfusion-related adverse events such as hypersensitivity, viral transmission, and transfusion-related acute lung injury (TRALI) as compared with cryo and FC. As a more concentrated source of fibrinogen compared with FFP, cryo is associated with reduced risk of volume overload. However, as mentioned previously, units of cryo contain variable amounts of fibrinogen, and transfusion of this product carries a similar risk of pathogen transmission to FFP. Furthermore, due to perceived health risks, cryo production has decreased in several European countries.[3] Fibrinogen concentrate is produced from pooling human plasma. It is stored as a lyophilized product at room temperature. Similar to cryo, FC has a higher fibrinogen concentration compared with plasma, limiting infusion volume.[15] More rapid infusion is also possible, as this product does not require thaw prior to administration.[16] Additional advantages of FC over cryo include a more standardized fibrinogen concentration and lack of pathogen transmission due to viral inactivation. Viral inactivation steps typically involve solvent/detergent exposure or pasteurization.

Past investigations have sought to compare FC with cryo for treatment of acquired hypofibrinogenemia in human patients.[16,18–20] One study in the United Kingdom retrospectively compared the increment in fibrinogen in bleeding adult patients from all major specialties (eg, cardiac surgery, liver failure, and obstetrics) with acquired hypofibrinogenemia after equivalent doses of cryo versus FC. The median fibrinogen increments following transfusion with these blood products were 0.26 and 0.44 g/L, respectively.[16] In a prospective, randomized pilot trial of children after cardiac surgery, administration of FC versus cryo resulted in equivalent increases in fibrinogen concentration and no difference in 48-hour blood loss. This group concluded that FC was as efficient and safe as cryo in this patient population.[18] Several other studies have shown nonsuperiority of cryo as compared with FC for treatment of bleeding associated with low fibrinogen in terms of transfusion effect on fibrinogen concentration, bleeding risk, and outcome.[19,20] A recent systemic review that compared the safety and efficacy of these 2 products in bleeding patients corroborated these findings.[21] Given the lack of superiority of cryo in these studies and the favorable safety profile of FC, preferable selection of the latter product whenever possible in human medicine seems reasonable. However, quality evidence is lacking, and determination of product superiority remains to be determined via prospective, randomized controlled trials (RCTs).

Fibrinogen concentrate is currently not available for use in small animal patients. Provision of fibrinogen in dogs is limited to cryo and FFP. HEMOPET lists fibrinogen deficiency as an indication for canine cryo.

6 | CRYOPRECIPITATE FOR ACQUIRED COAGULOPATHIES FROM FIBRINOGEN DEFICIENCY IN HUMAN CRITICAL CARE

6.1 | Trauma bleeding

Several studies of critically ill people experiencing massive hemorrhage from various etiologies have demonstrated the vital role of fibrinogen (replacement) for hemostasis.[15,22–27] In trauma, coagulopathy often accompanies severe hemorrhage and was historically attributed to hypothermia and acidosis (the lethal triad), hemodilution, and loss of platelets and coagulation factors via bleeding and consumption. More recently, it has been demonstrated that up to one third of severely traumatized patients are hypocoagulable within an hour of injury (at the time of presentation to the emergency department) and prior to any resuscitative efforts.[28,29] Shock and systemic inflammation, severe tissue injury, and endothelial damage are believed to contribute to development of this acute traumatic coagulopathy (ATC).[30] Several pathophysiological mechanisms are purported to explain the combination of systemic hypocoagulability and hyperfibrinolysis that characterize this coagulopathy, including excessive activation and subsequent depletion of the anticoagulant protein Cvia the thrombin–thrombomodulin pathway, catecholamine-mediated endothelial injury, and a hyperfibrinolytic variant of DIC.[30,31]

The major cause of early death in severely traumatized patients (after traumatic brain injury) is bleeding. Early trauma-related mortality rates from these 2 causes are approximately 40–50% and 20–40%, respectively.[32,33] Fibrinogen is the first clotting factor to reach a critically low level in ATC.[24,34] As the primary coagulation substrate, fibrinogen is rapidly consumed. Hyperfibrinolysis, acidosis, hypothermia, and hemodilution likely also contribute to hypofibrinogenemia in trauma.[24] In victims of trauma, hypofibrinogenemia at hospital admission has demonstrated associations with higher base deficit and lower hemoglobin, the presence of shock, higher illness severity score, and larger prehospital fluid volumes.[17,23,35] Rourke et al demonstrated that lower admission fibrinogen was also predictive of 24-hour and 28-day mortality.[23] Furthermore, fibrinogen replacement in this patient population (as part of a massive hemorrhage protocol) has been demonstrated toimprove survival.[17,36,37]

Healthy adults have plasma fibrinogen concentrations between 2 and 4 g/L.[17,38] Although previous investigators have demonstrated increased mortality in trauma patients with fibrinogen concentrations <2.29 g/L, the majority of current guidelines recommend fibrinogen replacement in trauma patients with fibrinogen concentrations <1.5–2 g/L.[17,22,39,40] Fibrinogen replacement (as cryo or FC) is frequently incorporated into massive hemorrhage protocols. Many human trauma centers use massive hemorrhage protocols as a component of damage control resuscitation in exsanguinating trauma patients in an attempt to ameliorate ATC. The optimal transfusion ratio of platelets, plasma-derived products (eg, FFP, cryo, and FC), and packed red blood cells (PRBCs) has been extensively investigated and is a matter of debate.[17,41,42] Two recent trials, the Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMIT) trial and the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial sought to determine optimal blood component ratios in trauma patients.[43,44] Results of both studies support higher plasma/cryo/FC and platelet to PRBC ratios in trauma massive hemorrhage protocols (ie, 1:1:1 plasma:platelets:PRBC). Nine hundred adult trauma patients presenting to 10 Level 1 trauma centers comprised the patient cohort in the PROMMIT trial. In this study, an increased ratio of variable plasma products:RBC was associated with a reduction in 6-hour mortality (patients receiving a ratio of <1:2 were 3–4 times more likely to die). In the PROPPR study (n = 680 patients presenting to a Level 1 or 2 trauma center), a higher ratio did not confer a survival advantage but did reduce deaths from exsanguination.[44] Historical concerns that higher ratios would increase the risk of transfusion-related adverse events were not substantiated in these 2 clinical trials. Zink et al demonstrated that a higher ratio of plasma and platelets to PRBCs improved outcome and reduced 24-hour transfusion requirements in a cohort of massive transfusion trauma patients. The most significant outcome advantage was observed when these components were administered in higher ratios within 6 hours of admission; the authors emphasized early, aggressive hemostatic resuscitation.[45]

The feasibility of early (<90 min) fibrinogen (cryo) replacement in bleeding trauma patients was the subject of investigation in the CRYOSTAT study. In this study, patients assigned to the "standard therapy" arm received blood components as dictated by a hospital-specific massive hemorrhage protocol.[46] Patients assigned to the "intervention" arm (CRYO) received standard therapy and additionally were administered 2 "pools" of cryo within 90 minutes of presentation. A single pool of cryo in the United Kingdom equates to 5 units and contains about 2.0 g of fibrinogen. The primary outcome (administration of cryo in <90 min) was met in 85% of CRYO participants, with a median time to cryo transfusion of 60 minutes. During active hemorrhage, patients assigned to the CRYO versus standard arms achieved higher mean fibrinogen concentrations at 4, 8, and 12 unit time points. Fibrinogen concentration remained >1.8 g/L at all times in the CRYO arm, whereas the standard arm demonstrated a nadir of 0.6 g/L. Transfusion requirements and mortality did not differ between groups.[46] The ability of early administration of cryo (median, 103 min) to maintain higher fibrinogen concentrations in trauma victims (n = 39) has been reported by others. Thirty-nine of 555 trauma patients that received cryo as a source of fibrinogen received this product in a median of 103 minutes and maintained higher fibrinogen concentrations than those that did not receive cryo.[23] However, despite the successful ability to transfuse cryo early and maintain higher fibrinogen concentrations in bleeding trauma patients, an outcome advantage associated with cryo has yet to be determined. Olaussen et al retrospectively evaluated 53 hypofibrinogenemic trauma patients that did or did not receive cryo and found no outcome advantage associated with its administration.[47] A secondary retrospective analysis of the PROMMTT trial focusing on cryo use in trauma patients similarly failed to demonstrate a beneficial impact of this therapy.[48]

The CRYOSTAT study is the only RCT to date reporting on the use of cryo in trauma patients, and there are relatively few retrospective and observational studies evaluating the incorporation of cryo (as fibrinogen replacement) into the hemostatic resuscitation of victims of severe

trauma.[23,47,48] Two RCTs are currently underway to address the following questions: (a) does early high-dose cryo administration as part of a massive hemorrhage protocol improve survival in hemorrhaging trauma patients? (Cryostat2 trial) and (b) what is the optimal method for replacing fibrinogen in these patients, via FC or via cryo? (FEISTY [Fibrinogen Early in Severe Trauma study] trial).[49,50] Current European guidelines designed as part of the international "STOP the Bleeding Campaign" (aimed at morbidity and mortality reduction in bleeding trauma patients) recommend treatment with either FC or cryo if the bleeding patient has a fibrinogen concentration <1.5–2.0 g/L (Grade 1C).[51]

7 | SURGICAL/PROCEDURAL BLEEDING – HEPATIC

Advanced hepatobiliary disease has traditionally been associated with enhanced bleeding risk following invasive diagnostic or therapeutic procedures. More recently, the complex hemostatic profile resulting from this organ dysfunction has been elucidated, with an increased risk of thrombosis also described.[52–54] Thrombocytopenia resulting from reduced thrombopoietin production and splenic platelet sequestration due to portal hypertension can be seen in advanced liver disease. Bleeding risk can be heightened by decreased fibrinogen concentration (seen in 40% of cirrhotic patients), as well as from deficiencies in other clotting factors produced or activated in the liver (FII, FVII, FIX, and FX).[54–57] Hepatic surgery can exacerbate coagulopathy through large-volume crystalloid hemodilution, colloid or PRBC infusion, clotting factor consumption from surgical bleeding, or through the perioperative development of hypocalcemia, acidosis, or hypothermia. Hypofibrinogenemia has been documented in the majority of human liver transplant patients, and administration of fibrinogen (in the form of cryo or FC) has been shown to reduce surgical bleeding.[58] In nonsurgical patients with liver failure and coagulopathy, cryo administration did improve international normalization ratio, activated partial thromboplastin time (aPTT), and fibrinogen concentration.[59] However, an equivalent transfusion of FFP was more efficacious at improving clotting times in these patients and resulted in reduced exposure to other blood products.[59]

As cryo is not a source of all clotting factors, and patients with liver disease often have multiple deficiencies and more global hemostatic defects, exclusive use of cryo in this group is likely not indicated. Furthermore, thrombosis risk may be increased in advanced liver disease secondary to reduced production of the anticoagulants antithrombin (ATIII), protein C, and protein S, and decreased hepatic clearance of vWF.[54,56] Hemostasis may be, in fact, "rebalanced" in patients with liver disease, this despite the fact that routine hemostatic tests might be suggestive of a hypocoagulable state. Fibrinogen administration as cryo in such a circumstance may lead to thrombosis. A single study reported on the administration of cryo for acquired hypofibrinogenemia following massive transfusion in liver transplant patients.[60] In this patient cohort, cryo therapy increased the risk of postoperative biliary complications. Procoagulant microparticles in cryo may increase risk of microthrombosis following liver transplant. Additionally, cryo contains small amounts of immunoglobulins that may increase risk of organ rejection.[60]

8 | SURGICAL/PROCEDURAL BLEEDING – CARDIAC

Fibrinogen deficiency and coagulopathy associated with cardiac surgery is multifactorial. Contributing factors include hemodilution, activation of coagulation from cardiopulmonary bypass, and surgically induced tissue injury. Lower perioperative fibrinogen concentrations in cardiothoracic surgical patients have been shown to predict postoperative bleeding and need for transfusion.[19,61,62] Furthermore, in 1 study, fibrinogen replacement via FC postcardiopulmonary bypass was found to avoid transfusions in more than half (65%) of the patients.[63] Other investigators failed to demonstrate bleeding reduction in postoperative patients after transfusion of either FC or cryo to achieve fibrinogen levels of 1.7 and 2.0 g/L, respectively.[19] Fibrinogen concentrate versus cryo for fibrinogen replacement was recently compared in 63 children undergoing cardiac surgery.[18] This study demonstrated noninferiority of FC with respect to posttransfusion fibrinogen concentration, bleeding, or need for PRBC transfusion. Fibrinogen supplementation in cardiac surgery is an area of ongoing exploration and debate.[61–64] Optimal transfusion threshold (fibrinogen concentration) and product selection (FC vs cryo) remain to be determined and are the main focuses of several ongoing clinical trials.[64]

9 | SURGICAL/PROCEDURAL BLEEDING – OBSTETRICS

Acquired fibrinogen deficiency in obstetric patients was reported as early as 1949.[65] Since this time, fibrinogen replacement for treatment of postpartum hemorrhage in women has been extensively investigated.[20,25,26,61,66,67] In this patient population, a low fibrinogen concentration (<2 g/L) is a risk factor for major obstetric hemorrhage, whereas maintenance of a fibrinogen concentration >4 g/L has a high negative predictive value for postpartum hemorrhage (PPH).[25,26] During late pregnancy, the risk of severe PPH increased 2.63-fold with each 1 g/L decrease in fibrinogen.[25] Both cryo and FC transfusion have demonstrated efficacy in increasing fibrinogen concentration and achieving hemostasis in women suffering from severe PPH.[20] Current guidelines recommend a fibrinogen trigger level of 1–2 g/L for fibrinogen replacement with cryo or FC to avoid major bleeding in this patient population (Grade 1C).[68]

10 | CRYOPRECIPITATE FOR HERITABLE AND ACQUIRED COAGULOPATHIES IN DOGS

A single clinical investigation compared the efficacy of FFP versus cryo for treatment of inherited bleeding disorders in dogs.[69] Dogs

with vWD or hemophilia A received either unpooled FFP (1 plasma bag/15 kg) or cryo (1 unit/15 kg). Efficacy of transfusion in this study was determined via increased vWF:Antigen (Ag) concentrations and correction of prolonged buccal mucosal bleeding time (for vWD) or increased FVIII coagulant (FVIII:C) activity (for hemophilia A). Adverse effects referable to blood component administration were also compared among transfusion groups. In this cohort of dogs, both efficacy and safety data supported the preferential selection of cryo over FFP for treatment of these coagulopathies.[69]

Heritable afibrinogenemia has been rarely documented in dogs.[70–72] Recently, a single case of congenital hypofibrinogenemia was reported in a 1.5-year-old, male German Pointer Dog.[73] The dog presented with swelling thought to be either a retrobulbar hematoma or cellulitis from a previous minor head injury. The patient's hemostatic profile was characterized by prolonged prothrombin time (PT) and aPTT and marked reduction in plasma fibrinogen. Other causes of acquired hypofibrinogenemia (eg, chronic hemorrhage, DIC, and liver failure) were excluded. Although cryo was not administered in this patient, its preferential selection for bleeding associated with fibrinogen deficiency was recommended by the authors.[73]

Despite the vital role of fibrinogen in hemostasis and the availability of cryo for use in dogs, the utility of cryo for treatment of acquired hypofibrinogenemia in this species remains to be determined. To the author's knowledge, there are currently no veterinary studies evaluating cryo for treatment of acquired coagulopathy. Hypocoagulable states associated with acute trauma, severe liver disease, and DIC (among other conditions) are reported in veterinary literature, and fibrinogen replacement (via cryo) may be indicated in these patients as it is recommended in the equivalent sick human.

Acute traumatic coagulopathy has been reviewed in veterinary literature and evaluated in a limited number of small, prospective clinical trials.[31,74-77]Attempts to document ATC in dogs following traumatic injury are complicated by lack of a concise method of confirming a diagnosis. In the available studies, prolongations of traditional clotting times (eg, PT or aPTT > 1.5 times the upper limit of the reference range; activated clotting time [ACT] > 105 s), platelet count below the reference range, reduction in protein C activity, and hypofibrinogenemia were used in various combinations to confirm a diagnosis of ATC.[31,74–77] Given the inherent lack of sensitivity of traditional coagulation assays in assessment of patient bleeding risk following trauma, more global evaluations of these patients' hemostatic profiles have also been evaluated using viscoelastic tests, such as thromboelastography (TEG) or rotational thromboelastometry (ROTEM).[74–76] Several parameters derived from these whole-blood assays measure blood clot time and strength. Additionally, these assays allow for ex vivo assessment of kinetics of clot formation (see further).

In addition to the lack of standardized testing for ATC in dogs, in several of these studies, a variable amount of time elapsed between traumatic injury, initial resuscitative efforts, and study enrollment.[78,79] This delay further complicates identification of ATC. With these limitations in mind, ATC has been reported in 0 of 30,[75] 1 of 18 (6%),[74] and 6 of 40 (15%)[76] dogs in recent clinical investigations.[74–76] These studies also documented correlations between measures of hypocoagulability (eg, prolonged PT or aPTT; decreased TEG-derived maximum amplitude, or MA) and illness severity (as indicated by acute trauma triage or APPLE-fastscore).[74,76] In a prospective, multicenter trial, dogs with ATC were more likely to be hyperlactatemic and hypotensive and had an insignificant increase in mortality compared with dogs without ATC (50% vs 18%, respectively).[76] Prolonged aPTT was the strongest predictor of nonsurvival and this, along with decreased platelet count, MA, or G value, predicted blood product administration.[76] Perhaps most germane to this review, Gottlieb et al showed a significant association between lower fibrinogen concentration and hypocoagulable TEG values (ie, decreased MA and G values).[74] This finding is in agreement with clinical human studies demonstrating increased bleeding risk and transfusion needs in patients with low fibrinogen and supports the notion that fibrinogen replenishment in veterinary trauma patients *may* be beneficial. A single retrospective veterinary study did not demonstrate an outcome benefit from early FFP administration following trauma in dogs.[79] Prospective veterinary studies documenting hypofibrinogenemia in trauma and evaluating the role of cryo for bleeding cessation in trauma patients are needed.

As is seen with the human counterpart, complex coagulation abnormalities are well-documented in dogs with various forms of liver dysfunction.[80–83] Thrombocytopenia is common in dogs with acute liver disease and chronic hepatitis. In both patient populations, hypocoagulable states with prolongation of PT, aPTT, or hypofibrinogenemia are also seen. Bleeding risk in these patients can be exacerbated by hyperfibrinolysis.[80,81] In addition to traditional coagulation assays, viscoelastic tests have been evaluated for assessment of coagulation in dogs with hepatopathies.[83,84] Dogs with acute and chronic hepatopathies exhibited variable coagulation profiles as determined by TEG, with hypocoagulable test parameters in approximately 50% and 25% of these 2 patient cohorts, respectively. Both hyper- and normocoagulable TEG profiles suggest that rebalanced hemostasis exists in veterinary patients, as well. Fry et al documented a strong positive correlation between fibrinogen and the TEG-derived G value in dogs with chronic hepatopathies and suggested that fibrinogen level might be valuable in predicting state of coagulation in this patient cohort.[84] To date, there are no clinical studies demonstrating an effect of cryo on reduction in bleeding, transfusion requirements, or mortality in dogs hemorrhaging from coagulopathy associated with hepatic disease. Cryo transfusion for hypofibrinogenemia-associated liver bleeding (<1 g/L) is, however, cited in the veterinary literature.[80,81]

Other veterinary patient populations with acquired hypofibrinogenemia that may benefit from cryo administration include those with hypocoagulable DIC or those undergoing cardiovascular procedures. As hypercoagulability and thrombosis can be present and complicate all of the previously mentioned clinical scenarios, comprehensive coagulation testing and careful patient selection are advisable prior to consideration of cryo transfusion. There are currently no veterinary data upon which to make evidence-based decisions regarding preferential selection of cryo for acquired coagulopathy in dogs.

11 | FIBRINOGEN MEASUREMENT

The 2 most commonly utilized fibrinogen assays in human hospitals are the Clauss method (considered the gold standard) and PT-derived fibrinogen. The PT-derived fibrinogen provides higher estimates of fibrinogen concentration than the Clauss method and may fail to differentiate between hypo- and dysfibrinogenemia. Fibrinogen concentration can be measured independently or as part of a comprehensive, screening coagulation assay, typically utilizing citrated plasma samples. Whole blood viscoelastic hemostatic assays (VHA) have more recently been developed to evaluate functional blood fibrinogen concentration and are highly correlated with the previously mentioned plasma assays. Platelets and fibrinogen both affect fibrin clot stability in VHA. Platelet function can be separated from the contribution of fibrinogen to clot formation (via platelet inhibition), resulting in a functional fibrinogen assay (functional fibrinogen TEG or FIBTEM ROTEM). In these assays, fibrinogen concentration is proportional to the VHA-derived variable, maximum clot firmness.[40]

There is a point-of-care fibrinogen assay (QuickVet Canine Fibrinogen test[‡]) that has been validated in dogs. This test quantitatively determines plasma fibrinogen concentration in dog blood; the normal reference range is 1.2–3.0 g/L. Plasma fibrinogen level is also provided for clinical canine patients as part of more comprehensive screening coagulation profiles.

12 | CRYOPRECIPITATE DOSING PROTOCOLS: FIXED OR GOAL DIRECTED

Historically, an empiric, fixed dose of cryo for a hypofibrinogenemic, bleeding human patient was 2 units/10 kg bodyweight.[85] Previous guidelines suggest that this dose is likely to increase plasma fibrinogen by approximately 1 g/L (unless bleeding is ongoing in association with trauma or DIC).[85] Due to the more recent recognition of the association of low fibrinogen with ATC, bleeding severity, and mortality in trauma patients, more aggressive replacement protocols are now published. Currently recommended cryo dosages are 15–20 units/70-kg person.[86] Nascimento et al recently reported that 8.7 (± 1.7) units cryo per bleeding trauma patient increased fibrinogen level by 0.55 (± 0.24) g/L, or 0.06 g/L/unit. Another dose recommendation is 0.2 units/kg (the equivalent of 14 units for a 70-kg adult).[87] Alternatively, fibrinogen deficit to be replenished as cryo can be determined using the following equations: (1) Blood volume = weight (kg) × 70 mL/kg; (2) Plasma volume = blood volume × (1-hematocrit); (3) mg of fibrinogen required = (desired fibrinogen − current fibrinogen in mg/dL) × plasma volume divided by 100 mL/dL; and (4) Bags of cryo required = mg of fibrinogen divided by 250.[1]

A relatively recent focus in human critical care is the use of point-of-care coagulation management, specifically TEG or ROTEM, to guide transfusion therapy and predict outcome in the massively hemorrhaging patient.[17,88–100] Cryoprecipitate or FC can be incorporated into an algorithm that includes point-of-care viscoelastic tests.[88] This algorithm is then utilized to guide the massive transfusion needs of both trauma and nontrauma bleeding patients. For example, the TEG values, clot formation time [K] (an indicator of the rapidity of clot formation) and MA (an indicator of final clot strength), are affected by fibrinogen concentration.[91,92] Significant aberrations in either of these values following an initial 1:1:1 transfusion strategy may indicate the need for additional fibrinogen replenishment via cryo, FC, or FFP.

In a cohort of human trauma patients, rapid TEG values, ACT, k-time, and *r*-value were available in <15 minutes, demonstrated strong correlations with PT and aPTT, and were predictive of transfusion requirements. Furthermore, prolongation of ACT predicted the need for MT within 6 hours of presentation.[93] An LY30 (a TEG-derived measure of degree of clot lysis at 30 min) of ≥3% has been associated with increased risk of massive transfusion in trauma patients and may be the critical threshold for initiation of therapy with an anti-fibrinolytic agent (eg, tranexamic acid).[94] Another group demonstrated the ability LY30 to predict 24-hour mortality from trauma.[95] A TEG-guided point-of-care model to guide transfusion therapy in cirrhotic patients requiring invasive procedures reduced blood component exposure from 100% (standard of care group) to 16.7% (TEG group).[96] A single RCT[97] and a recent meta-analysis[98] corroborated the findings that utilizing TEG or ROTEM-guided transfusion strategies in bleeding trauma patients significantly reduced blood component exposure[97,98] or improved patient outcome.[97]

The superiority of goal-directed versus fixed-ratio massive transfusion protocols to guide transfusion therapy in bleeding people remains to be determined, as there currently exists only a body of low-grade evidence.[96,99–101] There is an ongoing multicenter RCT (Implementing Treatment Algorithms for the Correction of Trauma Induced Coagulopathy, iTACTIC Trial) designed to compare use of standard massive hemorrhage protocol with VHA-guided transfusion therapy for treatment of traumatic hemorrhage.[102] The primary outcome of this study is proportion of patients alive and massive transfusion-free at 24 hours. Current transfusion guidelines vary by hospital and country. An active European guideline recommends that FC or cryo be considered to replenish fibrinogen in trauma patients if active bleeding is accompanied by low fibrinogen or a functional fibrinogen deficit is detected by TEG.[51]

In dogs, a standard dosage of cryo has not been established, but cryo manufacturers and (limited) available guidelines suggest an initial dose of 1 unit of cryo (frozen) or 1 vial lyophilized cryo (from a 250 mL bag FFP) per 10–12 kg bodyweight administered intravenously.[11] Stokol et al utilized an empiric dose of cryo (for vWF and FXIII replenishment) of 1 unit/15 kg.[69] There are no clinical data reporting the change in plasma fibrinogen concentration following cryo administration in dogs experiencing massive hemorrhage from acquired coagulopathy. To author's knowledge, optimal timing of prophylactic cryo transfusion (prior to invasive procedures) also remains to be determined. To maintain normal coagulation during longer procedures, the manufacturer recommends repeating cryo doses every 30 minutes.[†]

Should goal-directed protocols based on point-of-care tests be established to guide transfusion decisions in veterinary patients? Use of VHA has been sporadically reported in canine patients with bleeding diatheses (or at risk of bleeding) secondary to coagulopathy.[86,103–106]

These point-of-care tests have been utilized for assessment of patient bleeding risk, determination of hemostatic response to pharmacological interventions, and in outcome prediction. One study demonstrated that hypocoagulable (vs hypercoagulable) DIC determined by tissue factor TEG values was associated with increased fatality in dogs.[103] This was the first veterinary study to suggest that TEG results could be predictive of outcome in sick dogs. Hypocoagulable TEG parameters were subsequently found to be predictive of a worse outcome in dogs with chronic active hepatitis; hyperfibrinolysis (also diagnosed via TEG) was associated with worse disease severity (as determined by transaminase activity) in this patient cohort.[84] Fletcher et al showed that dogs with spontaneous hemoperitoneum were hypocoagulable based on conventional coagulation tests and TEG parameters and also exhibited evidence of hyperfibrinolysis. In a dog suspected of ATC secondary to motor vehicle trauma, modified plasma-based TEG was used to document resolution of hyperfibrinolysis following ε-aminocaproic acid administration.[105] In dogs with naturally occurring infection with *Angiostrongylus vasorum*, ROTEM diagnosed hyperfibrinolysis in 67% and 11% of patients with and without clinical signs of bleeding, respectively.[106] The majority of hyperfibrinolytic dogs (60%) were severely hypofibrinogenemic. In these dogs, administration of FFP normalized fibrinogen function ROTEM maximum clot firmness, and tranexamic acid decreased fibrinolysis detected on ROTEM.

To the author's knowledge, point-of-care VHA and fibrinogen assays have not been applied to the individual bleeding, coagulopathic veterinary patient to guide transfusion of cryo (or other blood products). Potential outcome advantages associated with such an intervention (to be explored in future clinical studies) include reductions in: blood exposure; cost of therapy; length of hospital stay; organ dysfunctions; and mortality (death vs euthanasia).

13 | PRODUCT ADMINISTRATION FOR DOGS

Canine cryo from HEMOPET requires careful thawing (ideally with gentle agitation) to a maximum temperature of 37°C (98.6°F) prior to administration. This can be achieved in a commercial plasma thawer or a warm water bath. The cryo product can be sealed in a plastic bag while thawing to avoid contamination from the water. Excessive warming will denature the plasma proteins. The lyophilized cryo product available through ABRI is reconstituted with 0.9% saline (as per the package insert) and transfused at around 37°C. Concurrent administration of other solutions is ill-advised; co-administration or dilution with normal (0.9%) saline is acceptable. Once ready for administration, a hang-time limited to 4–6 hours is advisable for all blood products to avoid risk of bacterial colonization.

An in-line blood administration filter (170–220 μm) is recommended to capture any debris that may result in embolism. For smaller volume infusions, use of an 18-μm filter attached to IV tubing (ie, a mini-volume extension set) is an acceptable alternative.[107] Blood products may be administered through certain commercial infusion pumps. Contact with pump manufacturers prior to pump use for transfusion purposes is advisable.

14 | TRANSFUSION-RELATED ADVERSE EVENTS

There are only sporadic reports of complications associated with cryo therapy in the human literature. The most concerning transfusion reaction in human patients is viral transmission, as this product is neither pasteurized nor subject to steps to ensure viral inactivation. For this reason, cryo has been replaced with a more purified FC in several European countries.[1,3] Other possible side effects (not specific to cryo) include transfusion-associated circulatory overload and TRALI.[1,3,108] In the United Kingdom, TRALI was recently reported in a single unit of 317,000 units of cryo transfused.[109] Acute anaphylaxis, intravascular hemolysis, and biliary complications have rarely been cited.[60,110] An additional, potential complication associated with fibrinogen transfusion (as cryo or FC) is an increased risk of thrombosis. This has not been reported; the CRYOSTAT trial showed only thrombosis in the standard hemorrhage arm (19% of patients) and not in the cryo arm.[46]

To the author's knowledge, no complications associated with cryo transfusion in veterinary patients have been reported. In the 1 clinical study comparing FFP and cryo for treatment of congenital coagulopathies in dogs, transfusion-related adverse events occurred in 67% and 0% of patients, respectively. Adverse transfusion reactions to FFP included weakness, pallor, and pruritus.[69]

15 | FUTURE DIRECTIONS

The role of cryo in the management of acquired coagulopathies remains to be determined. This plasma-derived product is readily available in the United States, and its administration has been demonstrated to be safe and efficacious in bleeding human and canine patients. The modern day criticalist is honing in, more and more, on therapies directed at the individual sick patient, and transfusion practices are no exception to personalized medicine. With the advent of veterinary blood banking over the last several decades, blood component therapy has become more commonplace. This practice can mitigate transfusion reactions and conserve limited resources. With a greater comprehension of the complex nature of hemostasis and the increased availability of point-of-care coagulation testing, goal-directed transfusion protocols may soon aid in choosing the best transfusion product for each patient. Cryo serves not only as a concentrated source of vWF and FVIII but also, perhaps more importantly, fibrinogen. Its role in cessation of bleeding from fibrinogen-depleted states, including ATC, is the ongoing subject of several prospective RCTs in human medicine. Veterinary trials evaluating the clinical utility of cryo for prevention or cessation of bleeding from acquired coagulopathies and determining indications for preferential selection of cryo (over FFP) are lacking and encouraged forthwith.

CONFLICT OF INTEREST

Prittie is an Assistant Editor of the Journal but only participated in the peer review process as an author. The author declares no other conflict of interest.

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ENDNOTES

* HEMOPET, Garden Grove, CA.
† Animal Blood Resources International, Stockbridge, MI.
‡ Canine Fibrinogen test, QuickVet Specialty Analyzer, Zoetis Denmark Aps, Farum, Denmark.

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