Controversies in the use of fresh frozen plasma in critically ill small animal patients

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Abstract

Objective – To review the literature supporting or discouraging the use of fresh frozen plasma (FFP) transfusion in critically ill patients.

Data Sources – Human and animal publications were searched using PubMed without time limits and the following keywords were used: "fresh frozen plasma," "coagulopathy," "hypocoagulable state," "hypercoagulable states," and "critical illness."

Human Data Synthesis – The commonly used tests of coagulation (eg, prothrombin time, activated partial thromboplastin time, international normalized ratio) are poorly predictive of clinical bleeding. FFP use in critically ill patients is unlikely to result in improved outcomes and may be associated with increased risks.

Veterinary Data Synthesis – There is insufficient evidence to make definitive conclusions regarding the use of FFP in critically ill animals, but clinical studies are underway that may provide further data that clarify the optimal use of FFP in animals.

Conclusions – The use of FFP in critically ill patients remains controversial. In the absence of clinical bleeding or a risk for clinical bleeding associated with a planned procedure, treatment use of FFP is not recommended in human patients. There are insufficient data in critically ill animals to enable formulation of recommendations. Further research is warranted in dogs and cats to establish evidence-based guidelines.

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Introduction

In general, human and veterinary patients are administered fresh frozen plasma (FFP) transfusions for 2 main reasons: prophylactically, to prevent clinical bleeding, and therapeutically, to stop active bleeding (eg, anticoagulant rodenticide toxicity).[1] In human medicine, clinical use of FFP continues to grow: the latest data show that in 2009, 5.7 million units of plasma were produced for transfusion in the United States, representing an increase of 23% compared to 2005.[2] In a large multicenter prospective observational study of critically ill human patients, 30% of patients with prolonged prothrombin time (PT) received FFP transfusions, although there was clinical evidence of bleeding in only 50% of recipients. [3,4] The use of FFP in patients with coagulopathy and no evidence of clinical bleeding is of particular interest in both

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Abbreviations

ALI	acute lung injury
aPTT	activated partial thromboplastin time
DIC	disseminated intravascular coagulation
FFP	fresh frozen plasma
FP	frozen plasma
INR	international normalized ratio
ISI	international sensitivity index
pRBCs	packed red blood cells
PT	prothrombin time
SIRS	systemic inflammatory response syndrome
TACO	transfusion-associated cardiac overload
TF	tissue factor
TFPI	tissue factor pathway Inhibitor
TRALI	transfusion-related acute lung injury
VetALI	veterinary acute lung injury

human and veterinary medicine, since evidence remains scarce to support this practice.

Fresh frozen plasma is plasma that has been separated from whole blood and frozen within 8 hours. It contains coagulation factors, anticoagulation factors

such as antithrombin, fibrinogen, albumin, and alpha-macroglobulins.[5] It can be stored for up to 1 year when frozen from −20 to −30 °C. There is also evidence that thawed FFP can be refrozen within 1 hour of thawing ("freeze-thaw-cycled") and retain its hemostatic protein activity.[6] A recent study found that the use of refrigerated plasma may be feasible with only minor losses in coagulation factor activity.[7] Frozen plasma (FP) is less commonly used in veterinary medicine; it is plasma that is separated from whole blood but not frozen within 8 hours, or that has been frozen quickly but stored between 1 and 4 years. Recent evidence supports the processing of plasma within 24 hours of whole blood collection rather than 8 hours, with suitable retention of coagulation factors.[8] FP contains the stable coagulation factors II, VII, IX, and X as well as albumin.[5]

The effectiveness of an FFP transfusion in abating clinical bleeding or correcting a coagulopathy is important to consider, especially since administration can be costly and is associated with increased risk of morbidity. While reactions have been reported to occur in 8–13% of veterinary patients receiving packed red blood cell (pRBC) transfusions, the incidence of reactions to plasma transfusions is less well characterized in veterinary medicine.[9,10] One retrospective veterinary study reported that the incidence of plasma transfusion-associated reactions was low (affecting 1% of patients) and reactions were characterized by fever, pruritis, and anxiety.[11] Adverse events associated with FFP transfusion can range from mild immunologic or nonimmunologic reactions to life-threatening reactions such as anaphylaxis, transfusion-associated cardiac overload (TACO), and transfusion-related acute lung injury (TRALI).[5,12–14] Less common risks include the transmission of infectious agents, febrile nonhemolytic transfusion reactions, red blood cell alloimmunization, and hemolytic transfusion reactions.[15] TRALI has been reported in critically ill human patients receiving any type of plasma-containing transfusion, although it is still likely underdiagnosed and under-recognized. There are 2 main pathways of TRALI development, one of which is antibody mediated (transfusion of human leukocyte or neutrophil antibodies and subsequent reaction) and the other of which is nonantibody mediated (accumulation of proinflammatory mediators during storage of blood products).[14] In one single-center retrospective human study of 115 patients with coagulopathy (international normalized ratio [INR] > 1.5) but no active bleeding, the administration of FFP was significantly associated with a higher incidence of acute lung injury (ALI) within 48 hours of transfusion (18% versus 4%; $P = 0.021$), leading the authors to conclude that patients receiving plasma transfusions may be more susceptible to TRALI or TACO.[16] There was no difference in severity

of illness between the transfused and nontransfused groups based on acute physiology and chronic health evaluation (APACHE) III scores. A recent prospective study of 54 dogs receiving transfusions of any type reported that 2/54 were suspected to have developed veterinary acute lung injury (VetALI) based on a $PaO_2:FiO_2$ ratio < 300, post transfusion development of radiographic pulmonary infiltrates, or development of respiratory compromise.[17] However, as these 2 patients had underlying diseases that already predisposed them for the development of ALI, the role that transfusion played in the development of ALI is unclear.[17]

Physiology and Coagulation Testing

Before considering the potential benefits of FFP transfusion, it is important to understand the normal coagulation system. The classic model of coagulation is based on the coagulation cascade, which involves a sequence of steps in which enzymes cleave proenzymes to generate the next enzyme in the cascade.[18] Most steps require calcium and occur on phospholipid membrane surfaces. The process is divided into 2 pathways: the extrinsic pathway, which is localized outside of the blood and involves tissue factor (TF) and factor VIIa; and the intrinsic pathway, which is localized within the blood and initiated through contact activation of factor XII on negatively charged surfaces. The intrinsic and extrinsic pathways both lead to the common pathway, in which activation of factor X leads to activation of prothrombin to thrombin, and then fibrinogen to fibrin, resulting in a cross-linked fibrin clot. The cascade model is helpful because it allows for useful interpretation of commonly used laboratory tests. The prothrombin time (PT) test evaluates for abnormalities in the extrinsic and common pathways, and the activated partial thromboplastin time (aPTT) assesses deficiencies in the intrinsic or common pathways. The usefulness of the coagulation cascade is limited by its inability to explain how coagulation works in the body during interactions with the vascular wall or cell surfaces.

The newer model of the coagulation system is the cell-based model, which allows for a more integrated understanding of the mechanisms of coagulation in the dynamic vascular system.[18] It suggests that coagulation occurs in distinct overlapping phases and requires 2 main cell types: the tissue factor (TF)-bearing cell and the platelet. The 3 main phases of coagulation in the cell-based model are initiation, amplification, and propagation. In the first phase, initiation, injury occurs and blood is exposed to a tissue factor-bearing cell, causing factor VII to become activated and eventually resulting in production of a small amount of factor IXa and thrombin that diffuses from the surface of the

TF-bearing cell to the platelet. During amplification, the small amount of thrombin from the initiation phase activates platelets, releasing von Willebrand factor and leading to the generation of activated forms of factors V, VIII, and XI. During the final phase, propagation, enzymes activated during earlier phases assemble on the procoagulant surface of the activated platelet to form intrinsic tenase, which leads to factor Xa generation on the platelet surface and a burst of thrombin generation directly on the platelet that results in fibrin formation.

The main tests of coagulation used for detecting hypocoagulable states include the PT and aPTT, as mentioned earlier. Both of these tests were developed to investigate coagulation factor deficiencies in human patients with a history of bleeding and provide an end-assessment of thrombin generation by fibrin formation. Additionally, in human medicine, the INR is a standardized measurement of coagulation based on the PT test developed to monitor warfarin therapy. It is calculated as INR = (observed PT ratio),[c] where the observed PT ratio is the patient's PT value divided by the mean normal PT, and c is the international sensitivity index (ISI) based on the thromboplastin reagent used.[19] Normal measurements range from 0.8 to 1.2, with values greater than 1.5 times the control generally suggestive of hypocoagulability.[1,19] Thromboelastography (TEG) can also be used to evaluate secondary hemostasis and mild factor deficiencies may be more readily apparent with this test than with the standard PT/aPTT.[20] In one study of human patients, postoperative hemorrhage was predicted by the activated clotting time (ACT) in 30% of cases, by the coagulation profile (PT/aPTT) in 51% of cases, and the TEG in 87% of cases.[21] While there is evidence that TEG/ROTEM (rotational thromboelastometry) may be more helpful than the standard tests of coagulation to predict bleeding, there is thus far insufficient evidence to recommend how hypocoagulability should be defined in companion animals based on these tests.[22,23]

Incidence of Coagulopathy

In critically ill human patients, prolonged global clotting tests (PT, aPTT, INR) are common, affecting 14–28% of ICU patients, and are a strong predictor of mortality.[24] Thrombocytopenia ($<150 \times 10^9$/L) is also common, affecting 35–44% of critically ill people, with severity inversely related to survival.[24] In veterinary medicine, the incidence of hypocoagulability in critically ill patients remains unknown. In a recent study evaluating dogs with and without evidence of systemic inflammatory response syndrome (SIRS) on coagulation, the authors found that ill dogs with and without SIRS were characterized by hypocoagulable states (eg, prolonged

coagulation times, decreased antithrombin and FVIII), although numbers were too small to look at incidence.[25] In human and veterinary medicine, the etiology of coagulopathy in critical illness is likely multifactorial, with inflammation suspected to play a key role.[25–32] In states of severe SIRS, proinflammatory cytokine release leads to activation of mononuclear cells and endothelial cells. These cells produce tissue factor, which initiates coagulation.[25,26] At the same time, downregulation of proteins and endothelial cell disruption causes impairment of anticoagulant mechanisms such as antithrombin, proteins C and S, and tissue factor pathway inhibitor (TFPI).[27,31,32] Concentrations of antithrombin, the primary inhibitor of thrombin and factor Xa, are markedly decreased during severe inflammation, likely due to impaired synthesis, neutrophil-mediated degradation, and consumption due to ongoing thrombin generation.[27,28] Activated protein C, along with protein S, degrades cofactors Va and VIIIa, which are essential to the intrinsic and common pathways. TFPI forms a complex with factors Xa and VIIa to inhibit coagulation induced by tissue factor.[29] These changes cause a tip in the coagulation/anticoagulation balance toward intravascular fibrin formation, which can contribute to impaired microvascular flow and organ dysfunction or failure.[30] A consumptive thrombohemorrhagic disorder can result, in which platelets and hemostatic factors reach critically low concentrations, resulting in prolonged coagulation times and thrombocytopenia with or without clinical bleeding.[27] This disease process may lead clinicians to consider empiric plasma therapy in patients with above mentioned changes in an effort to prevent the progression of a hypercoagulable state to a hypocoagulable one.

Coagulopathy and the Risk of Bleeding

While it is generally agreed upon that coagulopathy and thrombocytopenia are common in critically ill patients, the perception that these abnormalities are indicative of probable hemorrhage or the risk of bleeding is debatable. An evidence-based review of 25 studies looking at coagulopathic human patients that required invasive procedures (eg, angiography, bronchoscopy, liver biopsy, para/thoracentesis) concluded that there was insufficient evidence to indicate that abnormal test results are predictive of bleeding.[33] In another study investigating 580 central vein cannulations in human patients with an INR ≥ 1.5, only one patient experienced major bleeding due to inadvertent arterial puncture; the authors concluded that bleeding complications are rare and experienced physicians could safely perform this procedure in patients with abnormal results of hemostasis tests.[34] In another review of patients with mild to moderate abnormalities in PT/INR, aPTT or platelet count, invasive

bedside procedures (eg, central line placement, biopsies, paracentesis or thoracocentesis, bronchoscopy, lumbar punctures) were performed and PT/INR was similarly poorly predictive of bleeding.[35] No studies exist as of yet in veterinary medicine investigating hypocoagulability and prediction of bleeding.

Several explanations exist for why abnormal coagulation tests are not well correlated with an increased risk of bleeding. First, the relationship between coagulation factors and PT or aPTT is nonlinear, such that there is an exponential relationship between clotting factor concentrations and test results.[35] Next, mildly abnormal test results can occur in patients with biologically normal coagulation.[36] Also, PT and aPTT tests will overestimate deficiencies in the upper limb of the cascade and underestimate deficiencies in the lower limb. For example, the PT test result is dominated by the level of factor VII, so a patient with low factor VII and normal other factors will have a more abnormal PT time than a patient with high factor VII and low other factors.[35] Lastly, in vitro studies have shown that tests overestimate the extent of factor depletion if more than one factor is reduced.[37] In these mixing studies, it was demonstrated that a sample containing 50% activity of a single factor and 100% of all other factors had normal PT and aPTT tests. However, samples with 75% of two factors and 100% of the rest had prolonged PT and aPTT tests, demonstrating that patients with disorders of coagulation affecting multiple factors are more likely to have prolonged clotting times and those changes may represent less of a reduction in factor levels than is generally appreciated.[35,37] It is also important to remember that PT/aPTT were not designed to predict bleeding and their applied clinical validity in wider settings such as the ICU should be questioned. Some of the newer tests of hemostasis (TEG/ROTEM, thrombin generation assays, platelet reactivity based on cytometry) are more reflective of the cell-based model of coagulation and may be more appropriate tests for predicting bleeding, although further research is needed and these tests are not commonly used outside of academic institutions.[38]

The second assumption that is commonly made regarding coagulopathy in critically ill patients is that administration of FFP will reduce the risk of bleeding, although evidence is scarce to support this idea.[39–44] The largest systematic review of this question in human medicine examined 80 randomized controlled trials looking at patients with a number of disease processes including liver disease, cardiac surgery, warfarin reversal, plasmapheresis, DIC, burns, shock, and head injury.[2,39] Meta-analysis of these trials revealed no significant difference in 24-hour postoperative blood loss between transfused and nontransfused patients, and no significant benefit of FFP use across all of the clinical

conditions of these patients. These findings led the authors to conclude that there is no consistent evidence of significant benefit for prophylactic or therapeutic use of FFP in any of the conditions evaluated. In the same study, no differences in coagulation test improvement or survival were noted in patients with DIC and massive transfusion treated with FFP.[2] The results of these studies led the authors of the above mentioned meta-analysis to state that "arguably, [the] use of FFP has over time become so accepted into clinical practice that it has not been subject to the clinical research scrutiny required to demonstrate effectiveness. But transfusion of plasma is not without risk and indeed may carry the highest risk of all blood components."[39] The most recent guidelines regarding the treatment of DIC in human patients recommend that plasma transfusion should be reserved for patients who are bleeding.[45,46] As mentioned earlier, ICU patients with an INR ≥ 1.5 who were not actively bleeding and received FFP had a significantly higher incidence of ALI within 48 hours of transfusion, suggesting that they may be more susceptible to TACO or TRALI.[16] In that same study, there were no significant differences in new bleeding episodes, hospital mortality or length of ICU stay between transfused and nontransfused coagulopathic patients. Additional studies have found associations between FFP transfusion and length of hospital stay and duration of mechanical ventilation.[40–43] A prospective randomized controlled trial is currently ongoing investigating the use of FFP in critically ill coagulopathic human patients.[44]

Veterinary Data Synthesis

In veterinary medicine, the evidence to support or refute either of these key assumptions—that coagulopathy is predictive of bleeding and that FFP corrects coagulopathies—is sparse. In one study examining the indications for FFP use in dogs over a 3-month period in a large urban teaching hospital, the authors found that 42/74 dogs received plasma for provision of coagulation factors, and 22/42 of those patients had evidence of clinical bleeding.[47] Other indications for FFP transfusion included albumin support (45/74 dogs), provision of immunoglobulins (12/74 dogs), and provision of alphamacroglobulins (10/74 dogs). A more recent retrospective study characterizing the use of plasma at another veterinary teaching hospital found that FFP was used primarily for coagulopathies rather than hypoalbuminemia or pancreatitis, but there was no association between volume of FFP given and patient outcome, although the presence or absence of hemorrhage was not investigated.[11] While hypoalbuminemia remains an often-cited reason for administration of FFP, this study found no difference in serum albumin concentrations

pre- and post-transfusion (median FFP dose was 15–18 mL/kg). Given that FFP contains a relatively small amount of albumin and the volumes required to cause a significant change is large, this result is not surprising. The use of FFP for DIC in veterinary patients is often discussed and may hypothetically be helpful due to early activation of coagulation and fibrinolysis. However, there is no current evidence to support its use in these cases, or that it prevents development of hypocoagulability.[48] One additional study investigating the effectiveness of FFP for pancreatitis (used to replenish antiproteases) revealed a higher mortality rate in dogs that received FFP, although illness severity scoring was not performed.[49] Moreover, patients that had received transfusions may have been more critically ill.[49] The preliminary results of a study examining the coagulation response in dogs with and without SIRS found that both groups of ill dogs had evidence of hypocoagulability, leading them to conclude that severe coagulopathies may be present in critically ill dogs without concurrent SIRS.[25]

Conclusion

While guidelines for the use of FFP in human patients suggest that it should be reserved for patients with active bleeding or prior to surgery in coagulopathic patients, no such guidelines exist for veterinary use.[50] The controversy regarding the effectiveness of FFP in nonbleeding critically ill patients is ongoing and further discussion and research in both the human and veterinary medical communities is needed. Given the risks associated with transfusion, the considerable logistics required to harvest blood products, and the associated costs of administration, evidence-based veterinary guidelines are essential. To summarize, in the absence of any data in veterinary medicine regarding the risks and potential benefits of FFP transfusions, appropriate use of FFP should be carefully considered in each and every patient before administration.

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