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Comparison of albumin, colloid osmotic pressure, von Willebrand factor, and coagulation factors in canine cryopoor plasma, cryoprecipitate, and fresh frozen plasma

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Abstract

Objective – To compare albumin concentrations, coagulation factors activity, and colloid osmotic pressure (COP) of cryoprecipitate (CRYO) and cryopoor plasma (CPP) to that of source fresh frozen plasma (FFP).
Design – Prospective in vitro study.
Setting – University teaching hospital.
Animals – Ten healthy, non-Greyhound dogs enrolled in an academic teaching hospital blood donor program.
Interventions – Fresh blood was obtained from canine blood donors and separated into FFP and packed red blood cells. The source FFP was further separated into CRYO and CPP. Albumin and fibrinogen concentrations, COP, activities of coagulation factors II, V, VII, VIII, IX, X, and von Willebrand factor (vWf) were assessed for each FFP, CRYO, and CPP.
Measurements and Main Results – The mean albumin concentration and COP in CPP were significantly higher compared with those found in FFP, with 31.7 g/L (±6) in CPP compared to 28.9 g/L (±0.5) in FFP ($P < 0.001$) and 14.5 mm Hg (±0.7) in CPP compared to 12.7 mm Hg (±0.3) in FFP ($P = 0.03$), respectively. CRYO had significantly higher concentrations of fibrinogen (median 3.46 g/L, 95% CI 2.65–4.27), and higher activities of factor VIII (mean activity 427.0%, ±95.4) and vWf (mean activity 504.7%, ±41.39) as compared to the other products. The activities of vitamin K dependent factors II, VII, and X were similar in CPP compared to FFP, although factor IX activity was lower in CPP. There was no significant difference in factor II or VII activities between the 3 products.
Conclusions – The mean albumin concentration and COP were highest in CPP, suggesting that CPP may be a potential alternative to FFP for oncotic support and albumin replacement. CRYO contained higher activities of vWf and factor VIII than other products and could be used to treat vWf deficiency and hemophilia A. As vitamin K dependent coagulation factors II, VII, and X in CPP were similar to FFP, CPP may be an option for replacement of most of vitamin K dependent factors.

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Keywords: blood products, dogs, natural colloids, transfusion medicine

Abbreviations

COP	colloid osmotic pressure
CPP	cryopoor plasma
CRYO	Cryoprecipitate plasma
FFP	fresh frozen plasma
vWf	von Willebrand factor

Introduction

Blood banks commonly separate whole blood donations into packed red blood cells and fresh frozen plasma (FFP)

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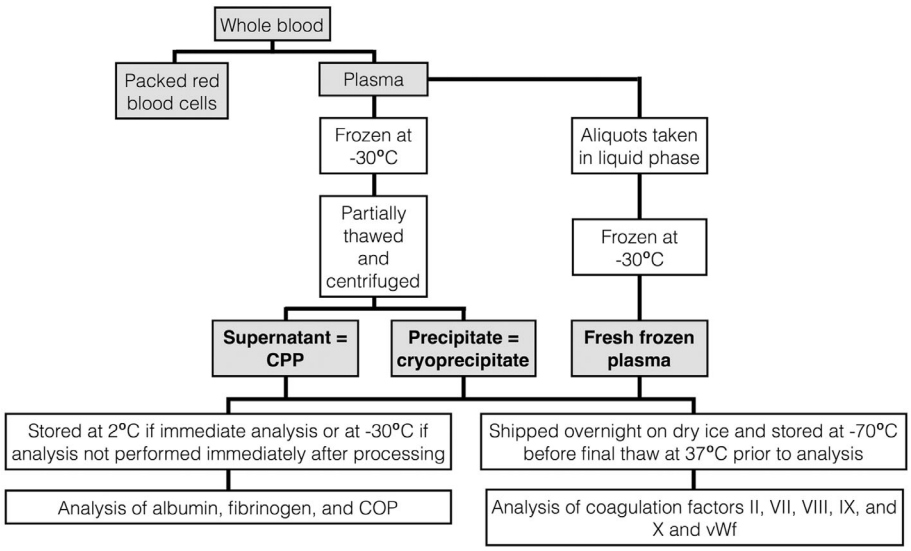

Figure 1: Stages of processing whole blood into the studied products and the corresponding testing. CPP, cryopoor plasma; COP, colloid osmotic pressure; vWf, von Willebrand factor.

in order to maximize the use of each donation.[1] Further division of FFP into cryoprecipitate (CRYO) and cryopoor plasma (CPP) can be made.[1] Cryoprecipitate is made by partially thawing FFP and removing the supernatant, which leaves the precipitate CRYO, theoretically containing factor VIII, fibrinogen, and von Willebrand factor (vWf).[2] The supernatant is referred to as CPP, and also known as cryosupernatant or cryodepleted plasma, presumably containing the remaining contents of FFP.[2] Cryopoor plasma is often considered a less useful by-product from the production of CRYO and is not readily available through commercial veterinary blood banks. Although CPP is sometimes listed for use in vitamin K antagonist rodenticide toxicities, hypoalbuminemia, and for immunoglobulin administration, to the authors' knowledge, there are no published data on the analytical characterization of CPP in veterinary medicine.[3] When available, CPP is approximately half the cost of FFP; therefore, evaluation of this product for its potential uses may reveal a more cost-effective alternative to FFP for certain conditions and may encourage better blood product stewardship.

The objectives of this study were to measure colloid osmotic pressure (COP), determine albumin concentration, and measure the activities of vWf and coagulation factors found in CRYO and CPP as compared to parent FFP. We hypothesized that CRYO would have a higher concentration of fibrinogen (factor I) and higher activities of vWf and factor VIII than its source FFP, and that CPP would be deficient in these factors. Additionally, we hypothesized that CPP would have COP, albumin concentrations, and activities of vitamin K dependent factors that were similar to its source FFP.

Materials and Methods

Animals

Ten non-Greyhound dogs that were part of a community-based blood donor program were used in this study. Each dog was deemed healthy based on physical examination performed by a veterinarian and normal baseline blood work (complete blood count, biochemistry profile, *Dirofilaria immitis* antigen, *Anaplasma phagocytophilum* antibody, *Anaplasma platys* antibody, *Borrelia burgdorferi* antibody, *Ehrlichia canis* antibody, and *Ehrlichia ewingii* antibody). All dogs were required to be ≥1 year of age, ≥22.7 kg, current on vaccines, and be on no medications that affect coagulation. The study protocol was approved by the Ohio State University's Institutional Animal Care and Use Committee.

Blood collection and processing

Whole blood from 10 healthy blood donor dogs was collected according to standard operating procedures of the Ohio State University's Canine Blood Donor Program. For donation, the dogs were placed in lateral recumbency without sedation and the jugular vein aseptically prepared.[a] A 16-Ga needle that was part of a quadruple collection set[b] was inserted into the jugular vein. Approximately 450 mL of whole blood was collected from each dog. The collection sets of whole blood were centrifuged[c] for 15 minutes at 4,657 × *g* to separate the plasma from the packed red blood cells (Figure 1).

For the purpose of the study, the fresh plasma was transferred into 3 plasma bags containing volumes of 9–30 mL of fresh plasma using a sterile tubing welder.[d] The transfusion lines were sterilely removed from these bags

and transferred into 4 Eppendorf tubes[e] each containing 1–2 mL of fresh plasma for evaluation of the source plasma content. These aliquots and the remaining fresh plasma (~200 mL) were then frozen[f] at –30°C to make FFP.

Within 2 days of being frozen at –30°C, the FFP was placed in a refrigerator at 2–5°C to thaw for 15–20 hours, until it reached a semiliquid ("slushy") consistency. The FFP was then centrifuged[c] at 1–6°C at 4,657 × *g* for 5 minutes. The precipitate obtained from this process yielded the CRYO while the supernatant yielded the CPP. As per standard protocol, the liquid CPP was then transferred into a satellite bag,[g] with the remaining liquid referred to as CRYO.[4]

The CPP was equally divided into 3 plasma bags containing 36–80 mL. Four aliquots of 1–2 mL of CPP were obtained from the lines and transferred to Eppendorf tubes[e] using the same procedure as with FFP. The CRYO was similarly processed, with satellite bag volumes of 9–30 mL. One aliquot each of CRYO and CPP were submitted for same day testing of COP and for concentrations of albumin and fibrinogen. All remaining samples were then frozen[f] at −30°C until testing.

Laboratory testing

Albumin[h] and fibrinogen[i] concentrations and measurement of COP[j] were performed at The Ohio State University Veterinary Medical Center, which participates in the annual Veterinary Laboratory Association Quality Assurance Program (Figure 1). The albumin was measured using a colorimetric assay in which cationic albumin binds with anionic dye bromocresol green to form a blue-green complex. The color intensity produced is directly proportional to the concentration of albumin and is measured photometrically using the analyzer.[h] The fibrinogen assay is based on the Clauss methodology, in which plasma is allowed to clot in the presence of high concentrations of thrombin. The analyzer recognizes that the fibrin clot has formed when the optical density of the sample mixture has exceeded a specific threshold.[i] The COP assay is based on water and diffusible solute particle movement through a synthetic semipermeable membrane from a reference chamber to the sample chamber. When equilibrium is reached between the 2 chambers, the pressure is measured by an electrical pressure transducer.[j] Quality control is performed each time a sample is requested for COP and daily for albumin and fibrinogen assays.

Additional aliquots were shipped overnight on dry ice to the Comparative Coagulation Laboratory at Cornell University according to the laboratory recommendations for measurement of coagulation factors II, V, VII, VIII, IX, and X as previously reported (Figure 1).[5] An ELISA with monoclonal anticanine vWF antibodies was used to measure the concentration of vWf.[6] The laboratory is accredited by the American Association of Veterinary Laboratory Diagnosticians and regularly undergoes proficiency testing.

Statistical analysis

All analyses were performed by a statistical software package.[k] Data were assessed for normality via the D'Agostino–Pearson test. Descriptive statistics are presented as mean (±standard deviation) or median (95% confidence interval). The outliers were identified as defined by Tukey's method (a value lower than the lowest interquartile minus three times the interquartile or greater than the upper interquartile plus three times interquartile) and removed. Analysis of variance for repeated measures with Bonferroni correction was then performed, with a statistical significance set at $P < 0.05$.

Results

Animals

All dogs used for this study were non-Greyhounds and deemed healthy on routine predonation screening. The dogs included 5 (50%) mixed breed dogs, 2 (20%) German Shepherd Dog, 1 (10%) Belgian Malinois, 1 (10%) American Bulldog, and 1 (10%) Pit Bull. There were 5 (50%) female spayed dogs and 5 (50%) male castrated dogs. The mean age of the dogs was 3.4 years (±1.7).

Albumin and colloid osmotic pressure

The mean albumin concentrations were 28.9 g/L (±0.5) in FFP, 31.7 g/L (±0.7) in CPP, and 23.1 g/L (±1.3) in CRYO (Table 1, Figure 2). The albumin concentrations were higher in CPP compared to FFP ($P = 0.0001$), higher in CPP compared to CRYO ($P = 0.002$), and higher in FFP compared to CRYO ($P = 0.006$). The mean COP in FFP was 12.73 mm Hg (±0.31), in CPP 14.5 mm Hg (±0.649), and in CRYO 9.8 mm Hg (±0.74) (Table 1). The COP was higher in CPP than in FFP ($P = 0.0326$), higher in CPP than in CRYO ($P = 0.0068$), and higher in FFP than in CRYO ($P = 0.0098$).

Coagulation factors

After exclusion of 3 outliers, the median (95% confidence interval) value for fibrinogen concentration in FFP was 1.19 g/L (0.98–1.40) and in CRYO was 3.46 g/L (2.65–4.27) (Table 1, Figure 2). The mean fibrinogen concentration for CPP was 0.53 g/L (±0.05) (Table 1, Figure 2). Fibrinogen concentrations were higher in CRYO than in FFP ($P = 0.0004$), higher in CRYO than in CPP ($P = 0.0002$), and higher in FFP than in CPP ($P = 0.0002$). After removal of 1 outlier, the median (95% confidence interval) value for the activity of factor II in FFP was 120.33% (109.07–131.60), with a mean activity level for CPP of 123.22% (±8.29) and CRYO 110.56% (±8.38) (Table 1). There was no significant difference in factor II

Table 1: Mean levels and standard error or median and 95% confidence interval *median and 95% confidence interval* for each plasma product

	FFP	CPP	CRYO	Reference range
Fibrinogen (g/L)	*1.19* (*0.98–1.40*)*,†	0.53 (0.05)‡	*3.46* (*2.65–4.27*)	1.00–3.84
Factor II (%)	*120.33* (*109.1–131.6*)	123.22 (8.29)	110.56 (8.38)	50–150%
Factor V (%)	113.63 (3.83)	118.00 (5.08)	88.3 (4.57)†,‡	50–150%
Factor VII (%)	118.8 (6.51)	101.75 (11.57)	116.2 (8.29)	50–150%
Factor VIII (%)	86 (7.98)*,†	22.2 (2.37)‡	427 (95.4)	50–150%
Factor IX (%)	84.7 (5.92)	67.9 (2.96)*,‡	131.9 (21.87)	50–150%
Factor X (%)	145 (13.4)	121.8 (10.9)	125 (11.5)	80–175%
vWf (%)	130.7 (6.12)*,†	22.5 (1.88)‡	504.7 (41.39)	70–180%
COP (mm Hg)	12.73 (0.31)*,†	14.5 (0.65)‡	9.8 (0.74)	20–25
Albumin (g/L)	28.9 (0.5)*,†	31.7 (0.6)‡	23.1 (1.3)	31–43

*FFP and CPP are significantly different ($P < 0.05$).
†FFP and CRYO are significantly different ($P < 0.05$).
‡CPP and CRYO are significantly different ($P < 0.05$).
FFP, fresh frozen plasma; CPP, cryopoor plasma; CRYO, cryoprecipitate; vWf, von Willebrand factor; COP, colloid osmotic pressure.

activity between any of the products. The mean value for the level of activity for factor V in FFP was 113% (±3.83), in CPP 118% (±5.08), and in CRYO 88.3% (±4.56) (Table 1). The factor V activity levels were lower in CRYO than in FFP ($P = 0.018$), lower in CRYO than in CPP ($P = 0.004$), and not significantly different between FFP and CPP ($P = 1.0$). The mean values for factor VII activity levels were 118.8% (±6.51) in FFP, 107.5% (±11.57) in CPP, and 116.2% (±8.29) in CRYO (Table 1). There was no significant difference in factor VII activity levels between any of the products. The mean value for factor VIII activity level in FFP was 86.0% (±7.98), in CPP 22.2% (±2.37) and in CRYO 427.0% (±95.4) (Table 1, Figure 2). Factor VIII activity levels were higher in CRYO compared to FFP ($P = 0.012$), higher in CRYO compared to CPP ($P = 0.006$), and higher in FFP compared to CPP ($P < 0.0001$). The mean value for factor IX activity level in FFP was 84.7% (±5.92), in CPP 67.9% (±2.95), and in CRYO 131.9% (±21.87) (Table 1). The factor IX activity levels were lower in CPP than in FFP ($P = 0.036$), lower in CPP than in CRYO ($P = 0.037$), and not significantly different in FFP than in CRYO ($P = 0.071$). The mean value for factor X activity level in FFP was 145.0% (±13.4), in CPP 121.8% (±10.9), and in CRYO 125.0% (±11.5). There were no significant differences in factor X activity levels between any of the products. The mean value for vWf activity level in FFP was 130.7% (6.12), in CPP 22.5% (1.88), and in CRYO 504.7% (41.39) (Figure 2). The vWf activity levels were significantly different between all 3 products ($P < 0.001$ for all 3).

Discussion

To the author's knowledge, this study is the first to report the albumin concentration, COP, and coagulation factor activity levels in the canine plasma fractionation by-products CPP and CRYO, compared to their source plasma. FFP is partially thawed in order to separate out factors based on their different freezing points, which should in theory separate fibrinogen, factor VIII, and vWf in CRYO, leaving the remaining coagulation factors at higher concentrations in CPP.[1] Our findings confirmed that our method used to process FFP into CRYO does successfully produce the expected product.

Deficits of one or multiple coagulation factors are common in dogs, with diseases such as disseminated intravascular coagulopathy, hemophilia A (deficiency of factor VIII), hemophilia B (deficiency of factor IX), von Willebrand's disease, hepatic disease, or anticoagulant rodenticide toxicity.[7–9] A goal of this study was to determine the vWf and coagulation factor content of various plasma products that may be used to treat some of these conditions.

In our study, CRYO contains higher activity levels of factor VIII, vWf, and fibrinogen as compared to FFP and CPP. These factor activity levels were also higher in FFP as compared to CPP. There are limited data on the use of CRYO in veterinary medicine. One study found that greater increases in vWF activity levels were achieved with cryoprecipitate than FFP in dogs with von Willebrand's disease.[9] That study also documented similar increases in factor VIII activity with infusions of FFP and CRYO in dogs with hemophilia A. Another study documented shortened mean buccal mucosal bleeding time and increases in vWf activity levels in Doberman Pinschers with von Willebrand's disease that were treated with CRYO.[10] In that study, administration of FFP increased the plasma vWf but did not shorten the buccal mucosal bleeding time. Neither of these studies, however, investigated activity levels of vWf and factor VIII in the blood products themselves.

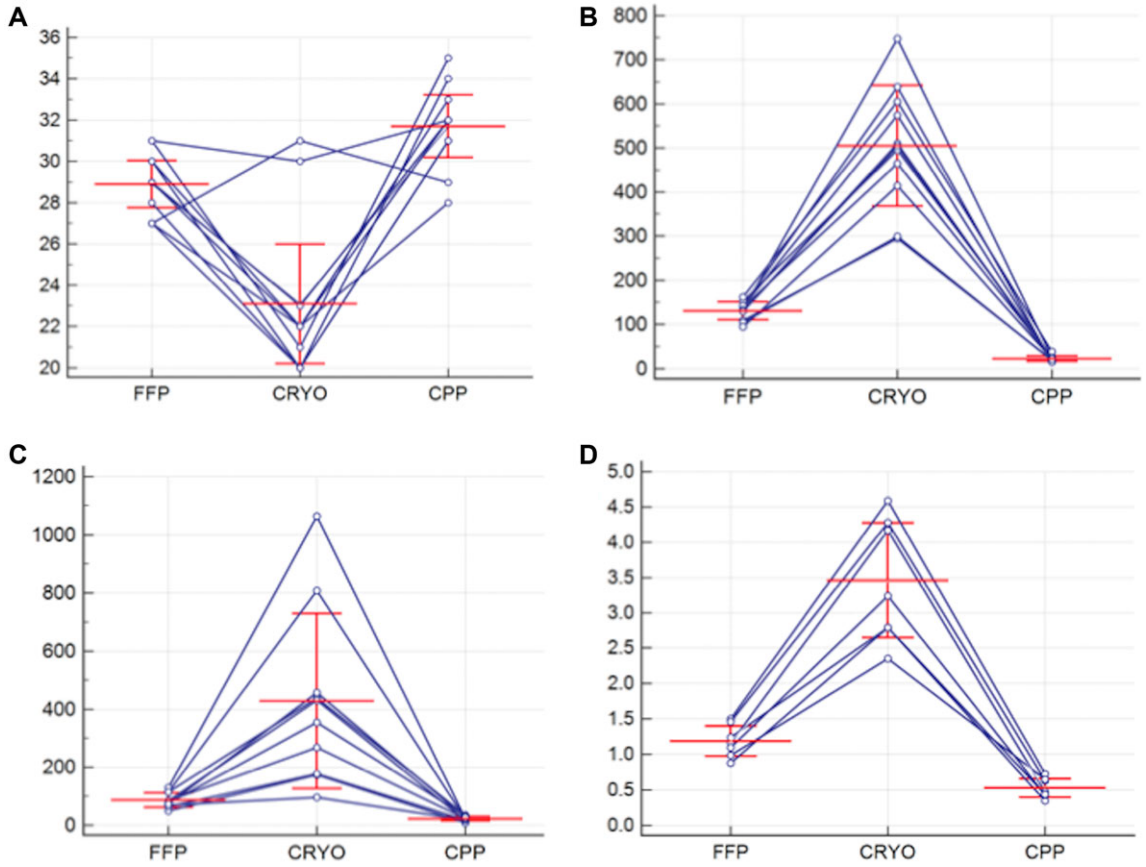

Figure 2: Activity levels measured for each unit of fresh frozen plasma (FFP), cryoprecipitate (CRYO), and cryopoor plasma (CPP). (A) Albumin concentrations. *Y*-axis represents g/L. (B) von Willebrand factor activtity levels. *Y*-axis represents %. (C) Factor VIII activity levels. *Y*-axis represents %. (D) Fibrinogen concentrations. *Y*-axis represents mg/dL. Mean activity levels and standard deviation are reported for (A)–(C). Mean and 95% confidence interval are reported for (D).

Our study also found a higher fibrinogen concentration in CRYO than in FFP. In people, CRYO is recommended for fibrinogen replacement.[11] A recent human clinical trial evaluated the feasibility of treating patients with significant hemorrhage secondary to trauma with CRYO shortly after presentation to provide early fibrinogen support.[12] This study found that the use of fibrinogen supplementation with CRYO is feasible in trauma patients; however, no 28-day mortality difference was observed and further investigation on outcome is warranted. Another study retrospectively investigated the administration of CRYO on human trauma patients and found that it was uncommonly administered (3.6% of patients) and no mortality difference was observed in patients with hypofibrinogenemia who were treated with CRYO versus those who did not receive CRYO.[13] In contrast, the MATTERs II Study found that concurrent use of CRYO may independently improve the survival benefit of tranexamic acid in trauma patients requiring red blood cell transfusions.[14] No clinical study has investigated the impact of CRYO on fibrinogen concentrations in canine patients. However, our study suggests that CRYO can be used if blood products containing high concentrations of fibrinogen are needed in canine patients.

There are no previously published data on CPP in veterinary medicine. In people, CPP is reported to have reduced activity levels of vWf, fibrinogen, and factor VIII.[2,15] Due to high levels of a disintegrin and metalloproteinase thrombospondin type 1 motif, member 13 (ADAMTS13) in CPP, its use in human medicine is primarily for treatment of thrombotic thrombocytopenia purpura, a condition not reported in veterinary medicine, in lieu of FFP for plasma exchange.[11,16,17] Cryopoor plasma has been also reported for use in lieu of FFP for the treatment of disseminated intravascular coagulation associated with pancreonecrosis and generalized peritonitis in people.[18,19] In veterinary medicine, CPP is listed for use in treatment of vitamin K antagonist rodenticide toxicity, although there are no published data to support its use for this condition.[3] Our study found that CPP contains statistically similar activity levels of vitamin K dependent factors II, VII, and X compared to FFP

and CRYO. These data also support the use of CPP as a treatment for anticoagulant rodenticides, although in vivo studies comparing the efficacy of CPP to FFP to treat anticoagulant rodenticide toxicity are warranted. However, it contains significantly less factor IX activity than FFP and CRYO, suggesting that CRYO or FFP should be preferred over CPP for treatment of hemophilia B. Reports of factor IX activity levels in various plasma products are scarce in human medicine and not available in veterinary medicine. One study reported significantly higher activity levels of factor IX in FFP than CPP; however, factor IX levels were not measured in CRYO.[20] Another study also found lower factor IX activity levels in CPP than FPP and higher levels of factor IX in CRYO than FFP, consistent with our findings.[21] The division of factors in plasma fractionation products is due to the difference in freezing points of the various factors. To the authors' knowledge, the freezing points of canine coagulation factors have not been published.

Decreased albumin concentration and COP are common findings in critically ill dogs with conditions such as septic peritonitis, hemorrhage, and renal or intestinal losses.[22–26] Hypoalbuminemia is associated with a variety of negative effects, including decreased survival, poor healing, and changes in drug binding capacity in both human and veterinary studies.[22,23,26,27] Additionally, albumin is responsible for 70–80% of COP, thus hypoalbuminemia is often associated with a decreased COP and increased risk of edema.[28] In people, albumin replacement has been shown to be beneficial in septic patients.[29,30] The human SAFE study compared the use of a 4% albumin solution with normal saline for fluid resuscitation in patients in the intensive care unit.[29] Analysis of the septic subgroup of the SAFE study showed improvement of survival in the group treated with 4% albumin. It is of note that the percentage of albumin found in the CPP in our study was similar to the 4% used in the SAFE study. The ALBIOS study found improved survival in septic shock patients treated with 20% albumin and crystalloids as compared to patients treated with crystalloids alone.[30] Species-specific albumin replacement is the most logical replacement product for hypoalbuminemia, but accomplishing this goal in veterinary medicine is difficult due to the lack of readily available, canine-specific albumin concentrate.[31] As such, veterinary clinicians may have to rely on the administration of FFP, 25% human serum albumin or synthetic colloids such as hydroxyethyl starches (HES). All 3 may be used to increase COP; however, synthetic colloids do not contain albumin. However, use of 25% human serum albumin and HES is associated with various risks, many of which have only recently been recognized and investigated in veterinary medicine.[31,32] Because of the large volume of FFP needed to treat hypoalbuminemia (up to 45 mL/kg to raise the albumin by 10 g/L depending the formula used), there is increased concern for volume overload.[33,34] Additionally, the cost of FFP transfusions for oncotic or albumin support is often too high to be a feasible treatment option for this condition for most pet owners. Some veterinary references suggest the use of CPP for albumin replacement, although there are no published supporting data for this claim.[3] Our study found that albumin concentrations and COP measurement were significantly higher in CPP compared to FFP and CRYO. It appears that the process of separating CRYO and CPP from FPP also separates albumin, probably due to its freezing point temperature, that allows its concentration with CPP. Additionally, the removal of the volume of albumin-deficient CRYO from FFP to make CPP results in a more concentrated albumin product. This suggests that CPP may be a less expensive to produce and may provide more effective canine-specific albumin replacement than FFP. The use of CPP for albumin replacement warrants further investigation.

There were some limitations to this study. Although Greyhounds are frequently used for blood donation, we elected to use non-Greyhounds to evaluate a more diverse breed population that may be more representative of a community-based blood bank. Use of Greyhound donors may have revealed different results. It has been documented that albumin concentrations in Greyhound are similar to non-Greyhound dogs.[35] It has also been documented that Greyhounds have lower globulin concentrations, a lower total protein, and lower fibrinogen concentrations than non-Greyhound dogs.[35] Although some standard protocols for processing of veterinary plasma products exist, it is unclear if those results can be extrapolated to a different blood bank that may use a different protocol, and therefore only represent the standards in our blood bank. Individual variation in levels of measured values in each product was seen, although these differences were not statistically significant. Lastly, our study does not provide any information about the long-term storage of CPP, although our blood bank recommends a shelf life for up to 6 years at standard storage conditions.

The data in this study support the use of cryoprecipitate for treatment of deficiencies in vWf, fibrinogen, factor VIII, and factor IX, as well as the use of CPP for treatment of hypoalbuminemia and low COP and vitamin-K dependent factor deficiency. Further investigation of the clinical use of CPP in these situations is warranted.

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Footnotes

[a] Zephiran Chloride, Lab Stores, Columbus, Ohio and Dermachlor Solution (2% chlorhexidine gluconate), Henry Schein, Dublin, OH.
[b] Anticoagulant citrate phosphate dextrose solution, USP (CPD) BLOOD-PACK unit; transfer-pack container with ADSOL red cell preservation solution, quadruple set, Fenwal, Lake Zurich, IL.
[c] Sorvall RC3B plus centrifuge, Thermo Fisher Scientific, Waltham, MA.
[d] Terumo SCD 312 sterile tubing welder, Terumo BCT, Lakewood, CO.
[e] Microcentrifuge tubes, Fisherbrand, Waltham, MA.
[f] Freezer model UPF3030A18, Kendro Laboratory Products, Asheville, NC.
[g] Satellite bags without anticoagulant, sterilely removed from the quadruple set[ii], Fenwal, Lake Zurich, IL.
[h] Roche Cobas c501, Roche Diagnostics, Basel, Switzerland.
[i] Diagnostica Stago, Parsippany, NJ.
[j] 4420 Colloid Osmometer, Wescor, Logan, UT.
[k] MedCalc Statistical Software version 15.4 (MedCalc Software bvba, Ostend, Belgium; 2015).

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