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Cryopreserved platelet concentrate transfusions in 43 dogs: a retrospective study (2007–2013)

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Abstract

Objective – To clinically characterize a group of thrombocytopenic dogs that received cryopreserved platelet concentrate (cPC) transfusion, assess efficacy of cPC treatment in improving patient outcome, and compare treated dogs to a control population of thrombocytopenic dogs that did not receive cPC transfusions.
Design – Retrospective study.
Setting – University teaching hospital.
Animals – Eighty-six client-owned dogs (43 in treatment group, 43 in control group).
Interventions – None.
Measurements and Main Results – Medical records of thrombocytopenic dogs that received cPC transfusions and those of thrombocytopenic dogs that did not receive cPC (control population) from January 2007 through March 2013 were reviewed. Dogs receiving cPC were statistically more likely than controls to have a platelet trigger for cPC transfusion ($P = 0.01$), lower platelet count ($P = 0.009$) and hematocrit at presentation ($P = 0.001$), and lower hematocrit after cPC ($P = 0.02$). Although there was a statistically significant increase in platelet count from pre- to post-cPC transfusion ($P = 0.002$), cPC was not found to be effective in improving clinical bleeding or increasing survival compared to the control group. No other characteristics were statistically different between groups. No dogs receiving cPC had an acute transfusion reaction during hospitalization.
Conclusions – In the population described in this study, cPC was not found to increase survival, but was well tolerated. Controlled, prospective studies are necessary to determine indications for and efficacy of cPC transfusions.

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Keywords: canine, immune-mediated disease, threshold, thrombocytopenia, trigger

Abbreviations

cPC	cryopreserved platelet concentrate
DMSO	dimethyl sulfoxide
IMT	immune-mediated thrombocytopenia
PC	platelet concentrate

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Introduction

Thrombocytopenia is the most common hematological abnormality seen in dogs presenting to veterinary emergency clinics.[1,2] Many presentations of severe thrombocytopenia in dogs are classified as primary (idiopathic) immune-mediated thrombocytopenia (IMT).[3–6] Moderate to marked thrombocytopenia can increase the risk of spontaneous hemorrhage, particularly in anemic patients,[7] varying in severity from mild superficial bleeding to severe hemorrhaging into vital organs or body cavities.[8] When bleeding is severe enough to result in anemia and hypovolemia, rapid therapeutic intervention, including administration of fluid therapy and red blood cell products, is required.[8] Additionally, platelet transfusions can be used specifically to treat

thrombocytopenia. In human medicine, specific triggers, or indications, for platelet transfusions due to thrombocytopenia include severe hemorrhage and intracranial bleeding, ocular bleeding that impairs vision, as well as prophylaxis to prevent major clinical bleeding, particularly before surgery or invasive procedures.[9,10] Similar indications for platelet transfusion have been described in thrombocytopenic dogs.[11,12]

Despite these indications, platelet transfusions present challenges and are not without controversy in veterinary medicine. Limitations to providing platelet transfusions to veterinary patients include the need of donors for fresh whole blood, the high cost of platelet concentrate (PC), limited storage time of fresh PC, and the large amount of platelets generally required to meet a patient's needs.[6,8,12] Uncertainty over ideal use of platelet transfusions is due to the paucity of evidence showing efficacy; lack of an evidence-based dosing protocol; and disagreement over what should be considered appropriate platelet threshold triggers.[11–13] In addition, each type of platelet product presents its own advantages and disadvantages, which further complicates the decision-making process of when to transfuse a platelet product.[6,8]

Currently available veterinary blood products that can provide functional platelets for platelet transfusion in dogs include fresh whole blood, platelet-rich plasma, fresh PC, and cryopreserved platelet concentrate (cPC). These products have been reviewed in detail elsewhere.[6,8] Although the most commonly available product for platelet transfusion is fresh whole blood,[8] fresh PC is the product of choice for control of bleeding in thrombocytopenic people.[6] However, fresh PC is costly to produce and difficult to maintain in clinical practice because it can be stored for only 5–7 days.[6,12,14] Lyophilized PC and cPC are promising alternatives to fresh PC because they can be stored long-term, and have increased concentrations of platelets per unit of volume compared to fresh PC.[6,8] While transfusion with lyophilized PC has been found to be feasible and safe in dogs with mild to severe hemorrhage in the research setting, it has been used infrequently in clinical cases and is not currently commercially available.[8,12,15–17] Although cPC is commercially available, it is still less readily available than other canine blood products and is used infrequently to manage clinical bleeding from thrombocytopenia.[11,16,18]

Cryopreserved PC consists of platelets cryopreserved in either 6% dimethyl sulfoxide (DMSO) alone or 2% DMSO plus ThromboSol.[a,14] Cryopreservation in DMSO allows canine platelets to have a storage time of at least 6 months[19] to 1 year[18] when stored at −80°C. ThromboSol is a solution consisting of select second messenger effectors, such as amiloride, sodium nitroprusside, and adenosine, which inhibit premature platelet activation.[14,20,21] In one study, there was no significant difference in platelet survival between dogs given cPC stored in 6% DMSO versus cPC stored in 2% DMSO with ThromboSol.[14]

Table 1: Classification of bleeding severity

Classification	Characteristics
None	No gross evidence of bleeding
Minor	Ecchymosis, epistaxis (not requiring red cell transfusion), hematochezia, petechiation, scleral bleeding
Major	Bleeding requiring red cell transfusion (such as severe epistaxis), gross hematuria, hematemesis, hemoptysis, hyphema, melena, retinal bleeding, unexplained neurologic signs

Although currently accepted dosages for PC transfusions do not significantly increase platelet counts in research dogs with normal platelet counts,[6] evidence exists that platelet transfusion may provide short-term hemostasis despite negligible increases in platelet count post-transfusion.[17,19] Despite data confirming efficacy of cPC when tested in vitro and when transfused in research dogs with normal platelet counts,[6,14,18] little evidence exists about its use in thrombocytopenic dogs in a clinical setting. Appropriate triggers for, optimal dosage, efficacy of, and frequency of transfusion reactions are unknown.

Because scant information exists in the veterinary literature regarding the use of cPC and clinical outcome of dogs receiving it, there is a lack of evidence to support or negate its use.[11,12] Accordingly, the main objective of this study was to describe the clinical characteristics of a group of thrombocytopenic dogs receiving cPC within a veterinary teaching hospital. Additional objectives were to evaluate clinical efficacy of cPC, by assessment of clinical bleeding and platelet count post-cPC transfusion and recording survival, and to compare clinical characteristics and outcomes to a control population. We hypothesized that thrombocytopenic dogs receiving cPC would have improved clinical bleeding, higher platelet counts post transfusion, and increased survival rates compared to thrombocytopenic dogs that did not receive cPC.

Materials and Methods

The University of Tennessee's John and Ann Tickle Small Animal Hospital's medical record database was searched to identify thrombocytopenic dogs that received cPC between January 1, 2007, and March 29, 2013. The following information was obtained from each dog's medical record: signalment, body weight, character of bleeding (Table 1) at presentation, presence of

Table 2: Indications for platelet transfusion

Trigger	Platelet count	Indications
Prophylactic	$<10 \times 10^9$/L ($<10 \times 10^3/\mu$L)	In absence of other risk factors for bleeding
	$<20 \times 10^9$/L ($<20 \times 10^3/\mu$L)	If other risk factors for bleeding present, such as disseminated intravascular coagulopathy, sepsis, elevated clotting times
Therapeutic	$<50 \times 10^9$/L ($<50 \times 10^3/\mu$L)	Prior to surgery
	$<60 \times 10^9$/L ($<60 \times 10^3/\mu$L)	Major bleeding requiring red cell transfusion, such as severe epistaxis, gross hematuria, hematemesis, hemoptysis, hyphema, melena, retinal bleeding, unexplained neurologic signs

trigger and indication for cPC at presentation (Table 2), platelet count and hematocrit (HCT) at presentation and approximately 24 hours posttransfusion, improvement in bleeding approximately 24 hours posttransfusion, cause of thrombocytopenia (IMT or other), final diagnoses, dosage and number of cPC transfusions, number of transfusions of non-cPC blood products, length of hospitalization from presentation to discharge (or death), short-term survival (to discharge), and occurrence of acute transfusion reactions.

Evidence of major bleeding (Table 1)[11,22] was needed to determine if a trigger for cPC transfusion was present for each patient (Table 2).[11] Major bleeding was defined the same as it is in people,[22] with the exception that in the current study, hyphema or retinal hemorrhage of any severity were considered major. In people, only retinal hemorrhage severe enough to cause impairment of vision is considered a trigger for cPC transfusion.[11]

Improvement in bleeding was defined as a cessation or decrease of active bleeding (such as epistaxis or gross hematuria) or decrease in size or number of petechial or ecchymotic hemorrhages. Dogs were diagnosed with idiopathic IMT if no cause for thrombocytopenia could be found, including but not limited to infection, neoplasia, or drug reaction; otherwise, the cause of thrombocytopenia was characterized as "other." Each final diagnosis described herein was recorded by the attending clinician on the case and extracted from each patient's medical record; final diagnosis constituted the patient's main problem list or diagnosis at time of discharge or death. A "day" was defined as a 24-hour period, and dogs that died or were discharged <24 hours after presentation were listed as being hospitalized for 0 days. Nonsurvivors included dogs that died or were euthanized.

Similarly, the medical record database was searched for thrombocytopenic dogs not receiving cPC. The control population was matched to the treatment population by age and cause of thrombocytopenia (idiopathic IMT or other). Identical data were collected for the control dogs, with the exception of platelet count, HCT, and improvement in clinical bleeding approximately 24 hours after presentation.

The treatment population was administered leukoreduced cPC[b] collected through platelet apheresis. Product specifications stated that each 100 mL unit of cPC contained a minimum of 500×10^9L (average 600–800 $\times 10^9$/L) platelets in 6% DMSO; the product was not washed prior to administration. The product was stored at −20°C for no more than 6 months and thawed at room temperature per the manufacturer's instructions.

The cPC was administered at approximately 10 mL/hour for the first 15 minutes, then the remainder of each unit was administered within 4 hours of thaw. Dogs were monitored in the intensive care unit during the entire procedure. Temperature, heart rate, and respiratory rate were recorded at these approximate time points: immediately prior to administration; at 15, 30, 60, and 120 minutes after initiation of transfusion; and at completion. Development of a change in body temperature greater than 1.1°C (2°F) or any new abnormality, such as vomiting, diarrhea, wheals, facial swelling, or pruritus, was considered a transfusion reaction.

Platelet counts were measured with an Advia 120 hematology system.[c] According to manufacturer specifications, within a platelet count range of 5–208 $\times 10^9$/L (5–208 $\times 10^3/\mu$L), standard deviation in platelet count was within 10×10^9/L ($10 \times 10^3/\mu$L). Additionally, a blood smear was evaluated to assess for platelet clumping.

Statistical methods

Categorical data (breed and sex) were expressed as frequencies and percentages. Continuous data were expressed as mean, median, and range. Comparisons between control and treated dogs were analyzed by use of χ^2 tests. The association between each variable and clinical outcome as defined by survival to discharge was analyzed by use of the χ^2 statistic. Due to nonnormal distribution, platelet counts in dogs receiving PC transfusions were compared prior to and posttransfusion using the Wilcoxon rank sum test. For all comparisons, values of $P < 0.05$ were considered significant. All statistical analyses were performed using commercially available statistical software programs.[d,e]

Table 3: Demographic data for 43 thrombocytopenic dogs receiving cryopreserved platelet concentrate and 43 thrombocytopenic control dogs

Parameter	cPC Treated dogs	Control dogs	*P* value
Age (years)	7.26, 8 (1–13)*	7.56, 7 (1–15)	0.79
Sex (*n*)			0.77
Female	1	0	
Female spayed	24	23	
Male	3	3	
Male castrated	15	17	
Body weight (kg)	16.94, 14.1 (3–49.8)	17.64, 11.15 (0–59.9)	0.89

*Values listed as mean, median (range).
cPC, cryopreserved platelet concentrate.

Table 4: Final diagnoses in 43 thrombocytopenic dogs receiving cPC and 43 thrombocytopenic control dogs

Final diagnosis	Treatment	Control
Immune-mediated	28	28
IMT	22	26
Evan's syndrome	6	2
Other	15	15
DIC	3	0
Neoplasia	5	6
Not specified	2	2
Hepatotoxicity/hepatic failure	2	2
Rickettsial infection	0	3
Splenic torsion	1	1
Chemotherapy toxicosis	2	1

IMT, immune-mediated thrombocytopenia; DIC, disseminated intravas cular coagulopathy.

Results

Based on information obtained from the medical record database, 49 cPC transfusion events in 44 thrombocytopenic dogs were identified. Data could not be extracted for 1 dog, leaving 43 treated dogs in the study. A control population of 43 thrombocytopenic dogs not receiving cPC were identified from the same medical record database during the same time period (except 1 dog, which was treated in 2005, 2 years before cPC use began at the authors' institution).

Of the 43 treatment-group dogs, there were 6 mixed-breed dogs, 4 Maltese, 4 Miniature Dachshunds, 3 Beagles, 3 Cocker Spaniels, 3 Labrador Retrievers, 2 Boxers, 2 West Highland White Terriers, and 1 each of 16 other breeds. Of the 43 control group dogs, there were 10 mixed-breed dogs, 3 Maltese, 3 Miniature Schnauzers, 2 Bichon Frisé, 2 Chihuahuas, 2 Jack Russell Terriers, 2 Labrador Retrievers, 2 Rat Terriers, 2 Standard Poodles, and 1 each of 15 other breeds. There were no significant differences in age, sex, or body weight between treatment and control groups (Table 3).

The same number of dogs in treatment and control groups were classified according to disease as "idiopathic immune-mediated" or "other." The cause of thrombocytopenia was idiopathic IMT in 65% of dogs in both groups. Categories of final diagnoses are listed in Table 4.

Bleeding was absent, minor, or major in 11 and 15, 15 and 18, and 17 and 10 treated and control dogs, respectively. This was not different between groups ($P = 0.23$). Also, there were significantly more dogs in the treatment group ($n = 40$) than the control group ($n = 31$) with triggers present at presentation ($P = 0.01$). Twenty-six dogs (60%) received cPC prophylactically and 17 (40%) therapeutically (Table 2). Two cPC transfusions were administered prophylactically to patients undergoing surgery; otherwise, cPC was given to prevent major bleeding.

Treated dogs had significantly lower HCT at presentation compared to control dogs ($P = 0.01$). The HCT at presentation was not recorded for one control dog. Treated dogs had significantly lower platelet counts at presentation compared to control dogs ($P = 0.009$). There was no significant difference in platelet counts between the two groups approximately 24 hours post-cPC transfusion (treatment dogs) or 24 hours postpresentation (control dogs) ($P = 0.07$) (Table 5). However, there was a significant increase in platelet count in treated dogs approximately 24 hours post-cPC transfusion ($P = 0.002$) compared to count at presentation (Figure 1). No clumps were present upon blood smear evaluation of the samples for which a platelet count was provided. Platelet counts were unavailable for 4 dogs in the treatment group 24 hours post-cPC and for 20 dogs in the control group, 24 hours after presentation.

In addition, there was no significant difference between the two groups in the number of dogs with improvement in clinical bleeding within 24 hours of receipt of cPC (13/28 in the treatment group) or of presentation (4/16 in the control group) ($P = 0.16$) (Table 5). Change in clinical bleeding was not recorded in 15 treatment and 27 control dogs.

Dogs received a mean cPC dosage of 13.5 mL/kg (median 10.8 mL/kg, range 2.6–40 mL/kg) per transfusion event. One dog received 2 cPC transfusions over 2 days; 1 dog received 3 cPC transfusions over 5 days; and 1 dog received 3 cPC transfusions over 3 days. Over the course of hospitalization, 26/43 (60%) dogs in the treatment group received at least 1 additional type of blood product, while 12/43 (28%) dogs in the control group received at least 1 blood product (Table 6).

There were no significant differences between the 2 groups in days of hospitalization ($P = 0.63$), survival to discharge ($P = 0.11$), or days to discharge or death ($P = 0.65$) (Table 5). No acute adverse transfusion reactions to cPC were reported for any dog.

Table 5: Characteristics and outcomes of thrombocytopenic dogs receiving cPC and a control population of thrombocytopenic dogs

Parameter	Treatment	Control	*P* value
HCT on presentation (%)	26.6 (8.1–57.2)	35.4 (10.8–56.3); $n = 42$	0.01[a]
HCT post cPC treatment (%)	24 (10–51); $n = 38$	35 (17–57); $n = 16$	0.02[a]
Change in HCT	0.25 (−27.8 to 17.9); $n = 38$	0.95 (−10.6 to 25.2); $n = 16$	0.2
Platelet count on presentation ($\times 10^9$/L)	10 (0–77)	17 (1–69)	0.009[b]
Platelet count post cPC treatment (treatment) or 24 hours post presentation (control) ($\times 10^9$/L)	13 (3–144); $n = 39$	28 (4–150); $n = 23$	0.07[b]
Change in platelet count ($\times 10^9$/L)	5 (−13 to 135); $n = 39$	−1 (−34 to 23); $n = 23$	0.08
Number of dogs (%) survived to discharge	31 (72%)	37 (86%)	0.11
Days of hospitalization	3 (0–9)	3 (0–11)	0.63
Number of dogs (%) with improvement in clinical bleeding	13 (46%); $n = 28$	4 (25%); $n = 16$	0.16
Days to death or euthanasia	3.5 (1–9); $n = 12$	1 (0–3); $n = 6$	0.65

Values listed as median (range) or percentage of total population. $N = 43$ unless otherwise noted.
Differences between values with the same superscript letters were statistically significant ($P < 0.05$).
HCT, hematocrit.

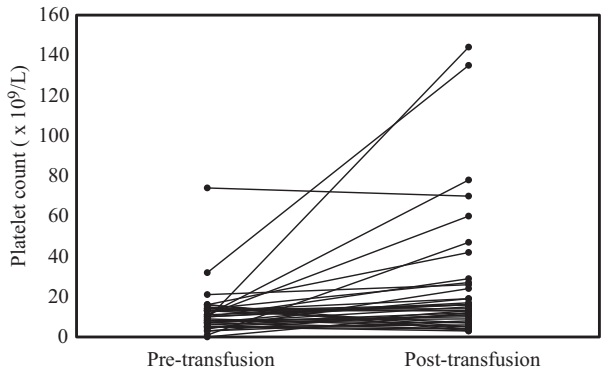

Figure 1: Distribution of platelet count in thrombocytopenic dogs ($n = 43$) prior to cryopreserved platelet concentrate (cPC) transfusion and approximately 24 hour post-cPC transfusion ($n = 39$).

Table 6: Dogs that received non-cPC blood products during hospitalization

Number transfusion events	Treatment	Control
FFP		
1	2 (4.6%)	2 (4.6%)
2	1 (2.3%)	0
pRBC		
1	13 (30.2%)	7 (16.3%)
2	5 (11.6%)	0
3	1 (2.3%)	0
FWB		
1	1 (2.3%)	0
Combination		
1 FFP + 1 pRBC	3 (6.9%)	2 (4.6%)
1 FWB + 1 pRBC	0	1 (2.3%)
Total	26 (60.4%)	12 (27.9%)

Treatment, $N = 43$. Control, $N = 43$.
cPC, cryopreserved platelet concentrate; FFP, fresh frozen plasma; pRBC, packed red blood cells; FWB, fresh whole blood.

Discussion

There is minimal clinical literature providing guidelines for the use of PC in dogs, including indications, efficacy when used either prophylactically or therapeutically, appropriate triggers, and adverse reaction rates.[11,12] This retrospective study describes the clinical characteristics and outcomes of 43 dogs that received cPC transfusions. The attending clinicians ordered cPC transfusions for dogs with lower platelet counts and lower HCTs compared to age- and disease-matched thrombocytopenic control dogs. Significantly more dogs receiving cPC transfusions had a prophylactic trigger based on platelet count than did dogs that did not receive cPC transfusions. Because the treatment group had diverse clinical characteristics and case management, no conclusions could be drawn regarding the clinical efficacy of cPC compared to a control population of dogs. The administration of cPC appeared to be safe, as no adverse transfusion reactions were reported. This retrospective information provides further insight into the use of cPC in veterinary patients.

Disease categories varied in this study, although immune-mediated disease (primary IMT and Evan's syndrome) was the cause of thrombocytopenia in the majority of dogs in this study population. In this study, 65% of dogs given platelet support had a diagnosis of immune-mediated disease. The rest of the population

received platelet support for non-immune-mediated causes. This is similar to other studies that report the most common cause of thrombocytopenia is primary IMT.[6,11,23]

In people, platelet half-life is greater in patients with hypoplastic rather than immune causes of thrombocytopenia,[24,25] and platelet transfusion is an atypical first-line therapy for IMT, but it can be beneficial in some cases.[26] Thus, in people, most PC transfusions are used in patients with hypoproliferative bone marrow, such as occurs with chemotherapy; the efficacy and safety of PC in management of IMT is controversial, so PC is typically reserved for intracranial or other life-threatening bleeding.[9–11,27]

Although PC is administered most commonly prophylactically to prevent major bleeding in patients with marked thrombocytopenia or those with additional risk factors for bleeding (sepsis, disseminated intravascular coagulation), it may also be administered prior to an invasive procedure.[9] Less commonly, PC is administered therapeutically in people to decrease bleeding associated with thrombocytopenia.[9] In our study, cPC was administered prophylactically in 60% of the dogs and therapeutically in 40%. In another prospective study, approximately 30% of dogs receiving PC prophylactically were dogs without major bleeding or prior to surgery.[12] In our study, one dog received cPC prophylactically to prevent surgical bleeding; otherwise, cPC was administered to prevent spontaneous, major hemorrhage. The high rate of prophylactic use was unexpected due to the high cost of cPC. More clinical prospective research is needed to determine if PC or other platelet products positively influence outcome in dogs with increased platelet destruction and if PC is more beneficial when given prophylactically rather than therapeutically.

Within the medical field, the appropriate trigger (or platelet threshold) for PC administration is debated, although recent studies support lowering the threshold for prophylactic transfusions from 20 to 10×10^9/L (20 to $10 \times 10^3/\mu$L) in patients without other risk factors for bleeding.[9–11] Treated dogs were more likely to present with a platelet transfusion trigger, and lower HCT and platelet count compared to age and disease-matched thrombocytopenic dogs. These results were anticipated, as clinicians may be more likely to recommend use of cPC in patients they perceive as having more severe clinical disease.

In this study, doses of cPC transfusion ranged from 2.63 to 40 mL/kg, with a mean of 13.5 mL/kg. The currently recommended cPC dose is 10 mL/kg or 100 mL (1 unit) per 10 kg body weight.[16] This dose is based on efficacy to halt active bleeding in thrombocytopenic dogs.[16,18] Administration of 1 unit of fresh PC containing approximately 70×10^9/L ($70 \times 10^3/\mu$L) platelets per 10 kg body weight can theoretically result in a maximum platelet increase of 40×10^9/L ($40 \times 10^3/\mu$L) within 1 hour.[11] Cryopreserved units usually have an approximate 30% loss of platelets due to the freeze-thaw cycle plus a lower in vivo recovery compared to fresh PC.[14,18,28] Therefore, 1 unit of cPC is not expected to increase platelet count as much as 1 unit of fresh PC, and it is thought that approximately 2.5 units of cPC are equivalent to 1 unit of fresh PC.[20] However, a higher platelet dose may result in a higher platelet count for a greater length of time than a lower platelet dose, suggesting better clinical outcomes in patients receiving higher doses.[29,30] Patients in the current study appeared to be administered cPC based on the nearest rounded unit likely because of the expense. Therefore, some patients were overdosed while others were underdosed according to current recommendations. Although these doses appeared to be safe and well tolerated, the optimal dose for clinical efficacy is still unclear.

Because of the paucity of literature describing use of PC in clinical patients, it is difficult to determine its efficacy in dogs with thrombocytopenia. In this study, clinical efficacy was defined as an improvement in clinical bleeding and platelet count post-cPC administration, and increased survival compared to the control population. Treated dogs had a statistically significant increase in platelet count, but neither an improvement in clinical bleeding or survival rate compared to the control group.

There was a statistically significant increase in platelet count from presentation (10×10^9/L [$10 \times 10^3/\mu$L]) to after cPC transfusion (13×10^9/L [$13 \times 10^3/\mu$L]) in the treatment group. This finding is different from another study that reported neither transfusion of lyophilized platelets nor fresh PC significantly increased platelet counts.[12] However, the change in platelet count in this study should be interpreted cautiously, as there was variability in timing of pre- and posttransfusion platelet counts. It is recommended that a platelet count be performed at 1–2 hours and again at 24 hours posttransfusion.[6,17] This recommendation is based on the finding that in some dogs, in vivo recovery of platelets is higher at 24 hours posttransfusion than at 1–2 hours.[18] These higher platelet counts 24 hours posttransfusion may be due to temporary sequestration of transfused platelets in either the spleen or liver.[14] The true effect of platelet transfusion on platelet count is also difficult to determine because transfused platelets are rapidly recruited for platelet plugs, thereby decreasing the count.[31] Although there was a significant difference in pre- and post transfusion platelet counts, the change in platelet count was not significantly different from the change in platelet count in the control group. It is reasonable to suspect that platelet counts did not improve in many of the dogs with IMT because of the unique pathology

of the disease causing rapid destruction of transfused platelets.[12]

Although cryopreservation in DMSO improves storage time, it alters platelet morphology and function and reduces posttransfusion recovery of platelets in comparison to fresh platelets.[14,20,28] Specifically, cPC platelets have demonstrated increased premature platelet activation,[28] impaired platelet aggregation, and reduced platelet response to hypotonic shock in vitro.[19] Fresh PC has better in vivo survival (approximately 80% survival) 1–2 hours posttransfusion compared to cPC (approximately 50% survival) in lethally irradiated thrombocytopenic dogs.[6,18] The half-life of platelets is also significantly longer in fresh PC at 3.5 days compared to 2 days in cPC.[18] In vitro performance and in vivo recovery raise concerns of the clinical efficacy of cPC. To complicate matters, it is thought that platelets administered to dogs with thrombocytopenia due to immune-mediated disease are destroyed or consumed within minutes to hours of transfusion.[32] However, no data exists regarding platelet survival posttransfusion in such dogs.

Among the 43 dogs that received cPC transfusions in this study, 13 (30%) improved in regard to clinical bleeding, and 15 (35%) did not improve; unfortunately, because of the retrospective nature of the study, information was unavailable for 15 of the treatment-group dogs (35%). Therefore, results of this retrospective study do not provide adequate information to conclude whether cPC transfusion makes a difference in clinical bleeding. Marked clinical improvement was seen in 1 dog in which neurologic signs consistent with intracranial hemorrhage resolved within 2 hours and hyphema resolved within 12 hours of receipt of cPC. Another dog with 7×10^9/L ($7 \times 10^3/\mu$L) platelets received cPC immediately prior to surgery and did not develop intra- or postoperative bleeding while undergoing cholecystectomy. The goal of platelet transfusion is to prevent or arrest life-threatening, major bleeding.[11] In a study evaluating the effect of cPC in dogs with experimentally induced thrombocytopenia, cPC provided adequate hemostasis to improve clinical bleeding and prevented death from a bleeding diathesis.[18] In another published report on use of PC (fresh and lyophilized), improvement in clinical bleeding was seen in 35% of dogs within the 24 hours of transfusion.[12] Prospective studies, rigorously assessing clinical bleeding by using standardized bleeding scores at multiple time points, are necessary.[12] In addition, this study was unable to document the effect of HCT on clinical bleeding or cPC efficacy. Previous studies have reported that the presence of anemia in thrombocytopenic human patients decreases platelet function more so than thrombocytopenic patients without anemia.[12,33] Transfusion of red blood cells to increase HCT in thrombocytopenic patients with anemia can improve bleeding times and reduce the risk of bleeding.[33–35] It is possible that clinical bleeding could have been affected by the presence of anemia in this population of dogs, regardless of cPC transfusion. However, this information was not available due to the retrospective nature of the study.

Although more dogs died after receiving cPC than not receiving cPC, the difference in mortality was not statistically significant, and reasons for death or euthanasia were not captured. Therefore, it is unknown if these dogs died or were euthanized specifically from excessive bleeding due to thrombocytopenia. It is suspected that the individual clinicians elected to give cPC transfusions to the thrombocytopenic dogs with more severe clinical disease, and thus poorer prognosis and higher mortality rate would exist regardless of intervention. The other clinical outcomes recorded, including change in HCT, days of hospitalization, and days to death or euthanasia, revealed no differences between the treatment and control groups.

The cPC formulation of canine platelets cryopreserved in 6% DMSO was well tolerated with no documented transfusion reactions. The absence of transfusion reaction is important to note, as the safety of cPC administration in critically ill dogs has yet to be validated. One study reported 1 transient transfusion event out of 22 healthy research dogs that received cPC transfusions.[6,14] The dog exhibited pallor of the mucous membranes that resolved after discontinuing the transfusion for 10 minutes. That dog continued to receive the rest of the transfusion without complications but developed facial swelling 1 hour posttransfusion.[14] There are also concerns about adverse effects developing when administering DMSO to a critically ill dog, but it was determined that the washing of platelets to remove DMSO was not necessary if a dog was receiving ≤10 mL/kg cPC.[14] Although the mean transfusion dosage was 13.5 mL/kg in the current study, 1 dog received up to 40 mL/kg without adverse reaction.

In people, adverse reactions to fresh PC range from 2–14% and manifest as nausea, fever, and abdominal pain to more severe systemic signs such as dyspnea and cardiovascular disturbances.[36–38] It is worth noting that in the current study, all dogs with immune-mediated disease had received immunosuppressive doses of glucocorticoids or other agents, which may have suppressed the development of transfusion reactions in these dogs. In addition, some dogs also received diphenhydramine prior to transfusion, which may have prevented adverse events. Since follow up for cPC recipients was variable, occurrences of delayed transfusion reactions could not be assessed. In a previous clinical study, a transfusion reaction rate of 14% and 13% was found in 22 dogs

receiving lyophilized PC and 15 dogs receiving fresh PC, respectively.[12] Regardless, cPC transfusion appears to be safe and well tolerated in thrombocytopenic dogs.

Limitations of the study are primarily due to its retrospective nature, as diagnostics and therapies were not standardized, multiple clinicians managed both treated and control patients, and animals euthanized due to financial reasons were not excluded from survival analysis. Furthermore, this retrospective review did not include all data points nor measures of platelet counts at 1–2 hours post transfusion. Even though there was a statistically significant increase in platelet count after cPC transfusion within the treatment group, this increase still resulted in a very low median platelet count, putting the animals are at risk of spontaneous hemorrhage. Moreover, the impact of HCT on clinical efficacy was unable to be assessed due to the paucity of dogs. However, to the authors' knowledge, this is the largest clinical study describing a population of dogs receiving cPC, which is the form of PC that is currently most readily available. Further prospective, controlled studies are needed to determine the indications for and efficacy of platelet transfusions in dogs, particularly in dogs with idiopathic IMT.

This study retrospectively reviewed the medical records of 43 dogs receiving cPC over 75 months at a referral institution. The cPC was well tolerated in a variety of dogs with thrombocytopenia with no documented transfusion reactions. The results suggest that administration of cPC for active bleeding due to thrombocytopenia and for prevention of bleeding in thrombocytopenic dogs undergoing invasive procedures may be performed without adverse reactions. Overall, in this study, clinicians were more likely to give cPC to thrombocytopenic dogs with more severe clinical disease characterized by lower platelet counts and lower HCT. Further prospective studies are needed to evaluate the clinical efficacy of cPC transfusions, to better identify indications for transfusion, and to determine optimal cPC product characteristics and dosing.

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Footnotes

[a] ThromboSol, LifeCell, Bridgewater, NJ.
[b] Cryopreserved platelets in 6% DMSO, Animal Blood Resources International, Stockbridge, MI.
[c] Advia 120 hematology system, Siemens, Malvern, PA.
[d] Analyse-it, v2.0, Leeds, UK.
[e] MedCalc Software, version 13.0.2, Ostend, Belgium.

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