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Retrospective Study

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Effect of premedication and other factors on the occurrence of acute transfusion reactions in dogs

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Abstract

Objective – To evaluate the effect of premedication on transfusion reactions (TRs) within 24 hours after blood product transfusions in dogs.
Design – Retrospective study between 2008 and 2011.
Setting – Private veterinary referral hospital.
Animals – Nine hundred and thirty-five transfusion events in 558 dogs.
Interventions – None.
Measurements and Main Results – Medical records of dogs receiving blood product transfusions were reviewed. Information collected included signalment, weight, transfusion product type, reason for transfusion, first or subsequent transfusion, whether an acute reaction occurred, type of reaction, whether the reaction was treated, premedication prior to the transfusion and the premedication used, other medications the animal was given, whether the animal had an immune-mediated process, and whether the transfusion was administered in the perioperative period. A total of 144 (15%) acute TRs were documented in 136 dogs. The most common TRs were fever alone (77/144 [53%]) and vomiting alone (26/144 [18%]). Six dogs died due to the TR (4%). TR was not associated with age ($P = 0.257$), sex ($P = 0.754$), weight ($P = 0.829$), or premedication ($P = 0.312$). The type of blood product transfused ($P < 0.001$) was significantly associated with TRs, with packed RBCs most likely associated with a TR, and plasma least likely. Immune disease ($P = 0.015$) was significantly associated with occurrence of a TR. Significantly fewer reactions were documented following transfusions given in the perioperative period ($P = 0.023$).
Conclusions – While most TRs were mild, there were some serious reactions observed including hemolysis, dyspnea, and 6 deaths. Immune-mediated disease was associated with development of a TR, while transfusion during the perioperative period was associated with lower likelihood of reaction. Packed RBC transfusions were associated with development of acute TRs. Overall occurrence of TR was not significantly altered with premedication; however, when evaluated alone, antihistamines decreased the incidence of acute allergic reactions.

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Keywords: canine, diphenhydramine, plasma, pRBC, whole blood

Abbreviations

DEA	dog erythrocyte antigen
FNHTR	febrile, nonhemolytic transfusion reaction
IMHA	immune-mediated hemolytic anemia
pRBC	packed red blood cell
TACO	transfusion-associated circulatory overload
TR	transfusion reaction
TRALI	transfusion-related acute lung injury

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Introduction

Blood product transfusions are common in veterinary medicine. The first reported canine blood transfusion in the modern era was in the mid 17th century.[1–3] Though many advances have been made since then, blood transfusions today are not benign. Transfusion reactions (TRs)

can occur from donor- or recipient-mediated processes, as well as from mishandling the component.[2,4,5]

Large investigations describing blood product transfusions and their associated reactions in small animals are limited. One retrospective study of 131 packed RBC (pRBC) transfusions in dogs found a reaction rate of 13%.[6] Another retrospective study evaluating 658 units of pRBC or whole blood transfused to dogs found reactions in only 3.3% of cases.[7] Both studies reported that reactions were mild and did not impact patient survival.

The most common TRs encountered are febrile nonhemolytic transfusion reactions (FNHTR) or mild allergic reactions.[2,4,5] The pathophysiology of FNHTRs is not well understood, but studies have shown them either to be mediated by inflammatory cytokines in donated components or to be a recipient response.[3,5,8–10] Life-threatening TRs have been documented,[2,4,5,11] and even mild reactions may increase morbidity and require additional treatments, cost, or hospitalization time.

Premedication with antihistamines and corticosteroids is controversial.[2,3,12,13] Historically, corticosteroids have been used in people in an effort to prevent FNHTRs, termed "chill-tremor syndrome."[14] Steroids had also been shown to treat posttransfusion purpura in people.[15] Antihistamines have also been used to decrease the likelihood of allergic reactions to transfusions.[8,16] Initially, antihistamines were injected into the transfusion product prior to administration to the patient.[8,16] Currently, antihistamines are administered directly to patients as premedications when deemed appropriate.[8]

In human hospitals, premedication has been performed with a combination of antihistamines and acetaminophen.[9,17–21] Several recent human studies have examined the use of premedication to prevent reaction, and most studies have not shown a significant benefit, though one study found benefit when people were premedicated with acetaminophen alone[17–21] A single veterinary study from the late 1950s found that 15 of 16 nonpremedicated dogs developed wheals when transfused with nonautologous plasma, but no reactions occurred in 8 dogs pretreated with the H_1 receptor inverse agonist, mepyramine.[22] The paucity of information regarding the benefits of premedication prior to transfusion in dogs warrants further investigation.

The objective of this study was to evaluate the effect of premedication with antihistamines or corticosteroids on the occurrence of acute TR in dogs. A secondary objective was to report other factors that may be associated with the occurrence of acute TRs.

Materials and Methods

The medical record database was searched for dogs that received blood product transfusions from January 2008 to April 2011. These were identified as fresh frozen plasma, fresh whole blood, or pRBC transfusions. Animals were excluded if the medical records were incomplete such that the objectives of this study could not be determined. Dogs were excluded if they were receiving immunosuppressive drugs other than steroids, if they received transfusion as part of an unsuccessful CPR, if they had an increased body temperature prior to transfusion, or if they died or were euthanized before the presence of a reaction could be ascertained. Data collected included breed, age, sex, weight, transfusion product type, reason for transfusion, first or subsequent transfusion, whether premedication was administered, which premedication was administered, occurrence of TRs, type of reaction if present, whether the reaction was treated and treatment performed, and whether the transfusion occurred perioperatively. The perioperative period was defined as all transfusions given from 6 hours prior to surgery to 4 hours postoperatively.

Blood typing and crossmatching were not routinely performed in patients receiving first time transfusions or in successive transfusions fewer than 5 days after the first. However, if a patient had received a transfusion more than 5 days previously, it was crossmatched with an in-house gel major crossmatch kit.[a] Transfusion products given to animals without a known blood type were always dog erythrocyte antigen (DEA) 1 negative.

Physical examination parameters considered normal included rectal temperatures of 37.8–39.2°C (100–102.5°F), pulse rates of 80–140/min depending on patient size, and respiratory rates of 15–32/min.[23,24] A TR was defined as a rectal temperature increase of over 1°C, or the development of urticaria, pruritus, facial edema, vomiting, tremors, tachycardia, tachypnea, dyspnea, pulmonary edema, or signs of substantial hemolysis (eg, development of icterus, hemoglobinuria, decreased PCV posttransfusion) within 24 hours of receiving a transfusion. Patients who were hypothermic prior to the start of the transfusion were included as a TR if their temperature increased greater than 1°C over the high end of the normal interval. Vomiting was considered a TR if it occurred in patients without evidence of vomiting prior to the transfusion and with no other cause for vomiting (such as disease or medications known to cause nausea) within 24 hours of a transfusion.

As part of standard hospital protocol, most transfusions were initiated slowly with gradual infusion rate increases if no reaction was noted. Transfused animals were monitored every 15 minutes for the first 2 hours and then hourly until the end of the transfusion. At the conclusion of the transfusion, more objective patient assessment (temperature, pulse rate, and respiratory rate) occurred every 4–6 hours as directed by the clinician. All patients were also visually assessed hourly after the

transfusion. Occasionally, transfusions were bolused in an emergency situation. These patients were included in analysis if a pretransfusion temperature, pulse rate, and respiratory rate were obtained, and if these parameters were monitored hourly for the first 2 hours after transfusion. After the first 2 hours post transfusion, patients were monitored as previously stated.

pRBCs and fresh frozen plasma were obtained from 1 of 2 commercial sources.[b,c] Donors from these sources were evaluated annually with CBC, biochemistry profile, urinalysis, brucellosis, and at least *Ehrlichia canis*, *Borrelia burgdorferi*, and *Dirofilaria immitis* testing from an independent laboratory.[d] In addition, dogs were DEA 1 typed and had plasma antibody tests using a standard blood typing laboratory protocol at the commercial sources. All whole blood transfusions were fresh whole blood from in-house donors. In-house donors were evaluated annually with complete blood count, biochemistry profile, urinalysis, and *Dirofilaria immitis*, and *Babesia* titers from an independent laboratory.[e] In addition, they were DEA tested with the RapidVet[a] kit and tested with an in-house Snap 4DX[d] test. Any equivocal blood typing results were confirmed by an independent laboratory.[e]

Statistical Methods

A commercially available statistical program was used for all statistical analyses.[f] Median and range were determined and reported for continuous data (age and weight). Frequencies of each category of discreet variables (gender, breed, transfusion product type, presence of immune disease, presence of TR, first versus subsequent transfusion, and occurrence of perioperative transfusion) were obtained. Variables with more than 2 levels were analyzed using both chi-square and Fisher's exact test statistics. Finally, a categorical data analysis was performed incorporating all factors. The data in the categorical analysis were assumed to follow a product multinomial distribution since observations in the medical database should be independent observations from multiple populations. Additionally, it was further assumed the probability vector estimated in the categorical analysis was approximately normally distributed as a result of central limit theory. The presence or absence of a reaction was the dependent variable. Independent variables included sex, premedication type, whether the dog had an immune disease, and whether the transfusion was administered in the perioperative period. The continuous variables of age and weight were tested for normality and were treated as covariates in the categorical data analysis. CATMOD was used to model analysis of variance for all data. Statistical significance was set at $P < 0.05$.

Results

A search of the medical record database returned 1130 transfusion events. Of the 1130 identified, 195 transfusions were excluded for the following reasons: in 89 cases the dog had received immunosuppressive drugs, 32 transfusions were administered to patients that were febrile prior to transfusion, 29 transfusions were bolused as part of an unsuccessful CPR event, 24 patients died before the presence of a reaction could be ascertained, 13 transfusion events had incomplete records, and 8 patients were euthanized before the presence of a reaction could be ascertained. A total of 935 transfusion events (458 pRBC transfusions, 412 plasma transfusions, 12 pRBC and plasma units given simultaneously, and 53 whole blood transfusions) in 558 dogs were evaluated in this study and used for statistical analysis.

The categorical analysis indicated that the type of blood product transfused, whether the dog had immune-mediated disease, and whether surgery was performed were significant sources of variation. The likelihood ratio statistic from the categorical data analysis was nonsignificant ($P = 0.99$), thus indicating the data distribution in this analysis was appropriate and indicating appropriate fit.

Two hundred and ninety-six dogs were female (29 intact, 267 spayed), and 262 were male (42 intact, 220 castrated). Ages ranged from 7 weeks to 17 years, with a median of 8 years. Weights ranged from 0.9 kg to 61.8 kg, with a median of 17.7 kg. The occurrence of reaction was not significantly associated with age ($P = 0.257$), sex ($P = 0.754$), or weight ($P = 0.829$). Many different breeds were represented. The most common breeds were mixed breed (216), Labrador Retriever (78), Golden Retriever (75), Cocker Spaniel (39), and Dachshund (31).

TRs occurred in 144 of the 935 (15%) transfusion events in the dogs evaluated in this study (Table 1). The most common reaction was fever. Fever was the sole reaction noted in 77 transfusions (53%) and was present in combination with at least one other clinical indicator of a TR in another 20 cases (14%). Vomiting alone was seen in 26 cases (18%) and with fever in another 12 cases (8%). Allergic reactions occurred in 13 cases (9%) and were characterized by facial swelling, urticaria, or pruritus. Dyspnea was noted with 10 transfusions (7%), and was seen in all 6 animals that died (4%). Tachycardia occurred in 4 cases (3%). Evidence of acute hemolysis was noted in 4 cases (3%). Of the 144 TR documented, 70 (49%) of these were deemed mild enough that the clinician did not elect to treat or discontinue the transfusion.

Four patients had reactions of acute hemolysis. Two of these patients were being treated for gastric blood loss, one for immune-mediated hemolytic anemia (IMHA), and the other for an unknown cause of anemia. None

Table 1: Documented transfusion reactions by transfusion product type

Transfusion reaction	Percentage of pRBC transfusions	Percentage of plasma transfusions	Percentage of whole blood transfusions	Percentage of pRBC and plasma simultaneously	Totals
Fever alone	11% (52/458)	5% (19/412)	9% (5/53)	8% (1/12)	8% (77/935)
Vomiting alone	5% (21/458)	1% (3/412)	2% (1/53)	8% (1/12)	3% (26/935)
Fever and vomiting	2% (7/458)	<1% (2/412)	2% (1/52)	0	1% (10/935)
Dyspnea	2% (9/458)	0	2% (1/53)	0	1% (10/935)
Facial swelling, urticaria, pruritus	1% (6/458)	2% (7/412)	0	0	1% (13/935)
Tachycardia	<1% (1/458)	1% (3/412)	0	0	<1% (4/935)
Hemolysis	1% (4/458)	0	0	0	<1% (4/935)
Total	22% (100/458)	8% (34/412)	15% (8/53)	17% (2/12)	15% (144/935)

pRBC, packed RBCs.

of these patients had received prior transfusions or had previous pregnancies; therefore, none of these patients had been crossmatched prior to transfusion. In 3 patients, the PCV rose after the transfusion, but not as high as would be expected. Within 8 hours, these patients became icteric. All 3 developed pigmenturia, hemoglobinemia, or hyperbilirubinemia. One of the 3 developed a fever during the transfusion. In the fourth case, the PCV never rose and the patient became clinically icteric within 2 hours of transfusion. A second transfusion was given to this dog after premedication and the PCV again did not rise as expected. These 4 patients did not show signs of shock and the first 3 eventually recovered and survived to hospital discharge. The fourth case was eventually euthanized due to poor response and financial constraints.

Ten cases of dyspnea were reported (Table 2). Five cases had radiographs either before or after the transfusion or both. Two cases were furosemide-responsive and suspected to be cases of transfusion-associated circulatory overload (TACO). In the other 8 cases, the cause of the dyspnea could not be definitively determined.

The type of blood product administered was associated with presence of TR ($P < 0.001$). TRs were seen in 100 of 458 (22%) pRBC transfusions, in 2 of 12 (17%) simultaneous transfusions, in 8 of 53 (15%) whole blood transfusions, and in 34 of 412 (8%) plasma transfusions.

Many of the animals in this study were transfused due to an immune-mediated disease such as IMHA or immune-mediated thrombocytopenia (Table 3). One hundred twenty-one dogs (199 transfusions) had been diagnosed with immune-mediated disease while 437 dogs (736 transfusions) were transfused due to other reasons. The presence of immune-mediated disease was significantly associated with an increased likelihood of TR ($P = 0.015$).

Forty-seven dogs (56 transfusions) received transfusions in the perioperative period, whereas 511 dogs (879 transfusions) did not. Two perioperative cases developed TR; both reported reactions were fever. TRs were detected less frequently in the perioperative period ($P = 0.023$).

Animals in this study were placed into 1 of 4 premedication groups: no premedication, premedication with steroids alone, premedication with antihistamines alone, and premedication with both steroids and antihistamines (Table 4). Of the 935 transfusions, premedication was not administered in 312 transfusions and 272 (87%) had no reaction. Steroids were given in 147 cases, of which 121 (82%) had no reaction; diphenhydramine in 305 transfusions, of which 260 (86%) had no reaction; and a combination of the 2 in 171 transfusions, of which 138 (81%) showed no reactions. Dexamethasone sodium phosphate was the most common steroid administered, but other steroids used included prednisone, dexamethasone, methylprednisolone, and hydrocortisone. All steroid dosages were at least 0.5 mg/kg of prednisone equivalent (mean 1.8 mg/kg, range 0.5–43). Diphenhydramine was given at dosages of at least 0.5 mg/kg (mean 1.7 mg/kg, range 0.5–6.3).[25] Premedication did not significantly affect the likelihood of TR ($P = 0.312$).

The effect of each premedication type on the specific reaction classes was also evaluated (Tables 5 and 6). Diphenhydramine decreased the number of acute allergic reactions ($P = 0.004$), but none of the other reaction classes. Steroid premedication was not found to be of benefit in relation to febrile reactions ($P = 0.406$) or any other reaction class. There was increased risk of dyspnea in patients given corticosteroids ($P = 0.038$).

The patients evaluated in this study averaged 1.7 transfusions per dog, which allowed evaluation of reaction occurrence between first and subsequent transfusions (Table 7). Of the 935 transfusions, 558 (60%) were first time transfusions and 377 (40%) were subsequent transfusions. Four hundred sixty-one (83%) of first time transfusions develop a reaction, whereas 97 (17%) had a documented reaction. Of subsequent transfusions, 330 (88%) did not have a reaction, whereas 47 (12%) did.

Table 2: Ten cases of dyspnea after transfusion and the suspected cause of the dyspnea

Signalment	Transfused component and etiology	Pretreatment	Pretransfusion radiographs/ diagnostics	Posttransfusion radiographs/ diagnostics	Treatment and response	Suspected diagnosis
11 years M/N Pekingese mix	pRBC for IMHA	None	None	None	Furosemide and oxygen. Quick response to treatment	TACO
10 years F/S Pomeranian	pRBC for IMHA	Dex SP	None	None	Acute respiratory arrest. CPR unsuccessful	Open
10 years F/S Golden Retriever	pRBC for anemia and thrombocytopenia	Dex SP and diphenhydramine	Radiographs unremarkable	Pulse oximetry after dyspnea of 60%. No radiographs	Oxygen. Arrested 4 hours later	Open
13 years F/S Chihuahua	Whole blood due to anemia from TCC of bladder	Diphenhydramine	Radiographs unremarkable	Radiographs: focal area of alveolar disease in dorsal aspect of right caudal lung lobe	Oxygen and furosemide. Arrested 3 hours later	Non cardiogenic pulmonary edema, TRALI, or broncho-pneumonia
16 years M/N Maltese	pRBC for hemoabdomen	Diphenhydramine	Radiographs unremarkable	2-hour posttrans systolic BP 115 mmHg	Furosemide and oxygen. Improved over 24 hours	Probable TACO
4 years F/S Dachshund	pRBC for IMHA	Dex SP	Radiographs unremarkable. Systolic BP 150 mmHg	Radiographs: air bronchograms throughout lung fields, more prominent in caudal lobes	Furosemide and oxygen. Arrested 3 hours later	Possible TRALI
13 years F/S Golden Retriever	pRBC for hemoabdomen	Diphenhydramine	Radiographs: Broncho-pneumonia (resolving from prior). Pulse ox 91%	Pulse ox 75%. No radiographs	Furosemide and oxygen. Euthanized due to poor prognosis	Open
12 years F/S Rat Terrier	pRBC blood for IMHA	Diphenhydramine and Dex SP	None	Major crossmatch. No radiographs	Oxygen. Arrested 2 hours later	Open
4 years F/S Maltese mix	pRBC for ITP	Diphenhydramine and Dex SP	None	None	Stop transfusion. Oxygen. Acute respiratory arrest. CPR unsuccessful	Open
9 years M/N Standard Poodle	pRBC for IMHA	Diphenhydramine and Dex SP	None	None	Oxygen. Euthanized due to poor prognosis	Open

BP, blood pressure; Dex SP, dexamethasone sodium phosphate; F/S, female spayed; IMHA, immune-mediated hemolytic anemia; ITP, immune-mediated thrombocytopenia; M/N, male neutered; pRBC, packed RBCs; Pulse ox, pulse oximetry; TACO, transfusion-associated circulatory overload; TCC, transitional cell carcinoma; TRALI, transfusion-related acute lung injury.

Table 3: Reactions observed in the group with immune-mediated disease versus without immune-mediated disease

Reactions	Reactions with immune disease	Reactions without immune disease
Fever alone	30 (57.7%)	47 (51.6%)
Vomiting alone	8 (15.4%)	16 (17.6%)
Fever and vomiting	3 (5.8%)	8 (8.8%)
Dyspnea	6 (11.5%)	4 (4.4%)
Allergic	4 (7.7%)	9 (9.9%)
Hemolysis	1 (1.9%)	3 (3.3%)
Tachycardia	0	4 (4.4%)
Total	52 (26.1%)	91 (12.4%)

Table 4: Reactions and percentage encountered in each premedication group

Reactions	No premedication	Diphenhydramine alone	Steroids alone	Steroids and diphenhydramine
Fever alone	23 (57.5%)	24 (53.3%)	13 (50.0%)	17 (51.5%)
Vomiting alone	3 (7.5%)	9 (20.0%)	6 (23.1%)	7 (21.2%)
Fever and vomiting	3 (7.5%)	4 (8.9%)	0	4 (12.1%)
Dyspnea	0	3 (6.7%)	2 (7.7%)	5 (15.2%)
Allergic reactions	7 (17.5%)	1 (2.2%)	5 (19.2%)	0
Hemolysis	1 (2.5%)	3 (6.7%)	0	0
Tachycardia	3 (7.5%)	1 (2.2%)	0	0
Total	40	45	26	33

Table 5: Diphenhydramine's effect on transfusion reaction classes

	Allergic	Fever	Dyspnea	Hemolysis	Vomiting	Fever and vomiting	Tachycardia	Total
Diphenhydramine	1	41	8	3	16	8	1	482
No diphenhydramine	12	36	2	1	9	3	3	453

Statistical analysis revealed no significant difference between likelihood of a reaction with the first versus subsequent transfusion ($P = 0.111$).

Discussion

In the present study, TRs occurred in 15% of transfusion events and were generally not affected by premedication. However, diphenhydramine did decrease the occurrence of acute allergic reactions. Although 49% of reactions were mild and were not deemed to warrant clinical treatment, the other 51% required intervention and 6 animals died within hours of transfusion. Dogs with immune disease appeared to be more prone to reactions, while fewer reactions were noted in patients given blood products perioperatively.

TRs in veterinary medicine are described as either acute or delayed, and as either nonimmunologic or immunologic (Table 8).[2–5,12] Acute TRs usually begin within minutes or hours of transfusion, but may occur up to 48 hours after transfusion, whereas delayed reactions occur 48 or more hours post transfusion.[4,12]

Table 6: Corticosteroids' effects on transfusion reaction classes

	Allergic	Fever	Dyspnea	Hemolysis	Vomiting	Fever and vomiting	Tachycardia	Total admin
Corticosteroids	5	30	7	0	13	4	0	318
No corticosteroids	8	47	3	4	12	7	4	617

Table 7: Reactions in first time transfusions versus subsequent transfusions

	First transfusion	Subsequent transfusions
Reaction	97/558 (17%)	47/377 (12%)
No reaction	461/558 (83%)	330/377 (88%)

Table 8: Types of transfusion reactions in dogs

Immunologic	Acute	Hemolysis (intravascular or extravascular) Nonhemolytic febrile reaction Acute hypersensitivity reaction TRALI
	Delayed	Hemolysis (intravascular or extravascular) Neonatal isoerythrolysis Immunosuppression
Non immunologic	Acute	Bacterial contamination TACO Hypocalcemia Dilutional coagulopathy Air embolism Pulmonary thromboembolism Hemolysis (due to inappropriate handling/administration)
	Delayed	Disease transmission

TACO, transfusion-associated circulatory overload. TRALI, transfusion related acute lung injury.

Nonimmunologic reactions occur due to contamination or inappropriate storage or administration of the product.[5,11,12,26] Hemolysis of donor product can occur before introduction to the recipient due to the component being outdated, warmed, contaminated, mishandled, or transfused with excessive pressure through a small catheter.[11,12,26–28] This typically does not cause a clinical reaction, though the component is clinically less effective.[28] In addition, recipients of such units can develop hemolyzed serum and hemoglobinuria, which can be confused with an immune hemolytic reaction.

Febrile, nonhemolytic TRs are immunologic reactions to the leukocytes or platelets in transfused blood.[2–5,29] These are characterized in veterinary literature as an increase in body temperature of at least 1°C when no other cause for fever is found.[2,4,5] It is also important to rule out the possibility of sepsis or a hemolytic TR in febrile patients, both of which are usually accompanied by other signs such as tachycardia, icterus, or shock. These immune reactions are the subject of much research in people, and at this time there are multiple theories on the cause of FNHTRs. Initially, it was thought that these reactions were due to the white blood cell fraction of the blood components.[3,10,29] A suspected interaction between donor white blood cells and recipient antigens was implicated.[3,10,28,30] Human medicine has moved to leukoreduction of blood components,[3,10,18,30] which has dramatically decreased but not completely eliminated FNHTRs.[10,18,30] Because of this, a second theory has been presented: that stored, leukoreduced components produce inflammatory cytokines over time and these cytokines produce FNHTRs when transfused.[9,19,28,30] Supporting this theory is the fact that FNHTRs are significantly more common after administration of products that have been stored longer.[9,19] In the present study, FNHTRs were the most common reaction encountered. These reactions occurred most commonly with pRBC transfusions, followed by whole blood.

As mentioned previously, FNHTRs are mediated by donor white blood cells and inflammatory cytokines.[9,19] These cytokines cause fever by production of prostaglandins that act on the hypothalamus.[9,19] Some studies have shown that corticosteroids decrease the production of inflammatory cytokines, lymphocyte proliferation, and the production of prostaglandins.[31,32] Steroids also decrease lymphocyte IgG production.[31,32] However, steroids are not tissue specific and can have detrimental effects.[31] Since steroids decrease cytokine production by decreasing their transcription, it is possible that steroids may only decrease cytokines if given hours prior to transfusion.[28,31,32] In this study, premedication with steroids did not decrease the occurrence of FNHTRs. In fact, patients with immune-mediated disease were at increased risk of TR even though 83% were premedicated with a steroid, and 79% of their reactions were FNHTRs.

Some veterinary blood banks have implemented leukoreduction of blood components in an effort to decrease the incidence of FNHTRs. We know from human literature that this will not likely eliminate these reactions; decreasing the storage time of these components should also be a goal to minimize FNHTRs.[21,28,30]

A large number of the reactions observed were cases of vomiting. One third of the vomiting cases occurred with fever and may represent part of a broader FNHTR syndrome. Human literature includes nausea and vomiting in the FNHTR syndrome, but the only criterion for FNHTR in veterinary medicine is a temperature increase of at least 1°C.[5,28,33,34] Some human articles advocate including patients in the FNHTR category even without fever as long as they have chills and other signs

often associated with this syndrome.[34,35] It is therefore possible that some or all of the vomiting cases here could be classified as FNHTRs. Another possible cause of the vomiting was allergic or anaphylactoid reactions. Since such a large number of cases had vomiting as the only perceived sign, these could have been hypersensitivity-type reactions. Based on the retrospective nature of this study, it was impossible to further classify these cases into a specific group. Monitoring transfused patients for chills or shivering is not common practice in veterinary medicine, but should be added to the list of possible reactions. This could help better classify cases of vomiting in future studies. It did not appear that any of the premedication groups influenced vomiting reactions.

The second most common reaction observed in this study was acute allergic reaction. Allergic reactions are a type I hypersensitivity mediated by IgE, which stimulates mast cell degranulation.[2–5,12] These reactions are characterized by pruritus, urticaria, and facial swelling. Acute allergic reactions have been reported more commonly with plasma transfusion, which is supported by findings in this study. Diphenhydramine should block H_1 receptors and theoretically prevent the majority of allergic reactions.[19] However, histamine's action at H_2 receptors and some other vasoactive substances mediate some vasodilation associated with allergic reaction.[19] In the present study, premedication with diphenhydramine decreased the likelihood of acute allergic reaction. However, acute allergic reactions only occurred in 2.6% of patients who did not receive diphenhydramine. Further studies are warranted to determine clinical features that might predict which patients are at risk for acute allergic reactions, which would allow judicious use of diphenhydramine as a premedication.

Dyspnea was seen after transfusion in 10 cases. The most common causes of dyspnea post transfusion include transfusion-associated circulatory overload, transfusion-related acute lung injury (TRALI), and pulmonary thromboembolism.[5,36–38] Determining whether an episode of dyspnea was from a pulmonary thromboembolism, TACO, or TRALI was difficult. Determination of which process occurred was determined from doctors' notes, physical examination forms, response to treatment, and radiographic assessment when available. It is known that there is an increased risk of pulmonary thromboembolism with IMHA.[38] Many dyspnea episodes were excluded due to suspicion of thromboembolism. Of the remaining dyspnea reactions attributed to the transfusion, 4 of 10 were in patients diagnosed with IMHA. It is possible that there is some crossover of cases, resulting in inaccurate reporting of the incidence of suspected TRALI. This discrepancy would be small, however, and should not affect the statistical analysis of the data. Statistical analysis found that premedication with steroids increased the risk of dyspnea. This finding is likely partially due to the number of IMHA cases present in the current study.

Transfusion-related circulatory overload is a non-immunologic reaction.[4,5,10,12,28] It can be seen with rapid administration of large volumes of blood, or when blood transfusions are administered to normovolemic patients.[5,10,26] Patients with concurrent cardiac, respiratory, or renal disease are at increased risk of TACO.[5,26,36] Patients with TACO exhibit signs of furosemide-responsive congestive heart failure, and pulmonary edema may be appreciated on thoracic radiographs.[5,10,28] Human studies have shown an increased risk of TACO in patients under 3 years or over 60 years of age.[36] The number of blood products transfused and surgery within 48 hours of transfusion have also been correlated with increased risk of TACO.[36]

TRALI is the leading cause of mortality associated with transfusion in people, and it is thought to be underdiagnosed.[39] It occurs up to 6 hours post transfusion in patients without lung injury prior to the transfusion.[5,10,28,40–44] Clinically, TRALI is similar to acute respiratory distress syndrome with signs of tachypnea, fever, tachycardia, hypoxemia, and pulmonary edema without evidence of circulatory overload.[5,10,28,40] The exact mechanism of TRALI is being investigated, but it is thought to be a two-step process.[5,39,40,44] A predisposing event activates the endothelium; thereafter, an immunologic reaction to components in the plasma, white blood cells, or platelets occurs during transfusion, leading to endothelial damage and leakage of the pulmonary vasculature.[10,39,40,44] In people, TRALI is most often associated with plasma products from multiparous female donors, and incidence decreases when using plasma from males or nulliparous females.[26,39] The incidence of TRALI in veterinary medicine is unknown, and it has yet to be described in dogs. Its diagnosis is difficult because the clinical signs are nonspecific and are typically based on bilateral pulmonary infiltrates without evidence of left ventricular failure and neutropenia.[37,45] In people, left atrial pressures are routinely measured, as is protein concentration of sputum.[37,45] Finding antileukocyte antibody-antigen pairs also supports the diagnosis.[45] The present study included cases of transfusion-associated dyspnea with bilateral pulmonary infiltrates unresponsive to furosemide therapy; these cases may have had TRALI. However, the retrospective nature of the study makes this diagnosis speculative. Future studies are needed to further elucidate this potential complication in dogs.

The cases of tachycardia are impossible to categorize. Tachycardia can be seen with either acute allergic reactions or FNHTRs.[5,6] Half of the tachycardia cases occurred with fever, making FNHTRs more likely;

however, 75% of the tachycardia cases were seen with plasma transfusions, which commonly produce allergic reactions. For this reason, they were defined as their own group.

Less than 1% of TRs in the present study showed evidence of acute hemolysis. Hemolytic TRs are a type II hypersensitivity mediated by either IgG or IgM.[2,4,5,12] Major incompatibility is caused by a reaction between antibodies in the recipient's plasma with antigens on the donor RBCs.[46] Minor incompatibility reactions are between antibodies in the donor plasma and antigens on the recipient's RBCs.[46] Hemolysis can be via intravascular and extravascular means, but usually one route predominates.[46] These reactions can cause complement fixation, release of vasoactive substances, and release of inflammatory cytokines.[2,4,12,46] If complement activation is complete, intravascular hemolysis occurs.[46] Extravascular hemolysis occurs when complement activation is incomplete.[46] If complement and IgG antibodies are both present on the RBC surface, liver macrophages will phagocytose the cell.[46] If only IgG is present on the cell surface, it is usually removed from circulation by the spleen.[46] The severity of hemolysis is dependent on the titer of the antibody and the number of incompatible RBCs.[46] If severe, hemolytic reactions can cause disseminated intravascular coagulation, shock, acute kidney injury, and death.[2,4,5,12,29,46] Intravascular hemolysis initially causes hemoglobinemia and can cause hemoglobinuria.[46] These abnormalities can be verified by centrifugation of the blood or urine and presence of a red supernatant.[46] Free hemoglobin in the blood is broken down by the reticulo-endothelial system, which is then followed by a rise in indirect bilirubin and prehepatic icterus in the first hour after hemolysis.[46] Bilirubinemia peaks 5–7 hours after hemolysis.[46]

All of the hemolysis reactions in this study occurred in first time transfusions. These patients were not blood typed or crossmatched. Thus, these authors recommend compatibility testing even before first time transfusions. All patients should be blood typed and crossmatched to each specific transfused unit. In the current study, only DEA 1 negative blood was used. This is not universal donor blood because other antigens can still be present.[3,29,33,47] Universal donors are negative for all DEAs except DEA 4.[3,29,33,47] Crossmatching would still be pertinent due to the potential for previously unidentified antigens. Both blood typing and crossmatching kits are readily available for clinic use, and their ease of use allows rapid testing even in the critical patient.

Due to the retrospective nature of this study, it was impossible to definitively diagnose these cases as acute hemolytic TRs. They were included in the analysis due to the initial inadequate rise in PCV following transfusion in 3 cases, presence of fever in one case, lack of PCV response in one case, and presence of new icterus in all cases. No other signs of shock occurred, making sepsis unlikely. Hemolysis of the transfused units prior to or during administration cannot be definitively ruled out. It is very possible that 3 of these cases involved low-grade hemolysis, possibly due to a less reactive DEA or due to a low recipient antibody titer.

In the present study, TR was perceived to be ultimately fatal in 6 cases (4%), which is higher than reported in previous studies. This discrepancy could be due to the large number of cases evaluated in the present study. All of these cases were in patients with respiratory distress. Some of these dogs may have experienced respiratory distress from pulmonary thromboembolism associated with IMHA, which would have falsely increased the number of deaths associated with transfusion. However, due to the retrospective nature of the study, it is impossible to determine the exact cause of the dyspnea episodes.

Another factor evaluated in the present study was the occurrence of transfusions in the perioperative period. Fifty-six dogs (6%) received a transfusion in the perioperative period. Of these, 25 were pRBC (45%), 22 were plasma (39%), 5 were both simultaneously (9%), and 4 were whole blood (7%). Only 2 of these 56 dogs (4%) had a TR, both of which were fever. One dog was taken to surgery for a bleeding, perforated gastric ulcer, and the other had a liver mass removed. The dog with gastric ulceration received pRBC while the other received whole blood. The dog with the gastric ulcer received the transfusion 4 hours prior to surgery and had started to develop fever prior to surgery. The fever resulted in a rapid rise in temperature postoperatively as well. The animal with the liver mass received the transfusion intraoperatively and developed fever postoperatively. Giving a transfusion in the perioperative period was significantly associated with a decrease in detection of a TR ($P = 0.023$). This was expected because the most common TR is fever, and since animals undergoing surgical procedures become mildly hypothermic and are given large doses of IV fluids, a febrile reaction may be masked. Mild hypothermia and fluids should not have affected other causes of reaction, though.

Another possible explanation for the low number of reactions seen in perioperative transfusion recipients lies in the probable link between general anesthesia and decreased immune function. Many studies in people have evaluated the effects of anesthetics on immunosuppression.[48–53] Inhalant anesthetics have been found to suppress inflammatory cytokine production.[49,51] Studies have also shown that many injectable anesthetics suppress monocyte, macrophage, neutrophil, and lymphocyte functions.[48,49,51] In addition, surgical stress has shown to depress inflammatory cells and upregulate

the anti-inflammatory cytokine IL-10.[49,50] These anti-inflammatory effects have a positive correlation with blood loss in surgery.[50] Half of the surgical patients in the current study received either pRBC or whole blood due to intraoperative anemia. Neither patient numbers nor reaction numbers in the perioperative group were sufficient for evaluation of different anesthetic protocols or intraoperative hemorrhage on outcomes.

Animals were excluded from analysis for multiple reasons including cases in which transfusions were given during unsuccessful CPR, patients febrile prior to transfusion, patients that died or were euthanized due to worsening disease, incomplete records, or the concurrent use of nonglucocorticoid immunosuppressive drugs. Patients who underwent unsuccessful CPR did not live long enough to exclude the possibility of a reaction. Patients who received other immunosuppressive drugs were excluded from analysis for multiple reasons. At our hospital, cyclosporine is the adjunct drug of choice in immune-mediated disease. There were a small number of cases that received leflunomide or azathioprine. Azathioprine is thought to act mainly by cell-mediated immunity, and therefore would not have application in the prevention of TRs.[32] Leflunomide's clinical use in dogs is fairly recent, and its effects on TRs are unknown.[32] It was excluded because its onset of action in dogs is unknown, it was being used in only 14 transfusion cases, and because it was always used in conjunction with other medications. Consequently, it would have been impossible to determine its effectiveness. Cyclosporine has some immunomodulatory effects on many inflammatory cytokines, as well as mast cells.[32] Therefore, it may help prevent some TRs. Patients receiving cyclosporine were excluded from this study due to insufficient knowledge of cyclosporine's onset of immunomodulation.

This study was retrospective in nature, and therefore is subject to many limitations. There is no control over the completeness of records, so it is possible that excluded, incomplete records could have influenced the data reported. It is also possible that the staff evaluating the patients during and after the transfusion did not perceive or record TRs. Since TRs were reported in 15% of cases, as opposed to the previously reported 3% to 13%,[7,29] missed reactions seem unlikely to have been common.

The reported dose range of diphenhydramine used for pretreatment of allergic reactions varies from 0.5 to 4 mg/kg.[23,25] Due to this discrepancy, it is possible that a subtherapeutic dose of diphenhydramine was used in some patients in the current study. The only patient who was premedicated with diphenhydramine and had an acute allergic reaction was premedicated with a 0.5 mg/kg dose. However, of the 482 patients that were premedicated, the median dose was only 1.95 mg/kg, which is below the more widely accepted dose of 2 mg/kg. Further prospective studies are needed to determine a more exact therapeutic dose for premedications.

Despite its retrospective nature, the large number of cases reported here makes this a valuable study. We also report here the first possible case(s) of canine TRALI in the literature. Very little data are available on the effect of premedication on acute TRs. Based on information gathered in this study, there is no benefit to premedicating dogs with diphenhydramine or glucocorticoids prior to transfusion, though diphenhydramine did decrease the likelihood of acute allergic TR specifically. A large prospective study is warranted to further investigate the effect of premedication on TRs in dogs.

Footnotes

[a] RapidVet major crossmatch, DMS Laboratories, Flemington, NJ.
[b] Animal Blood Resources International, Stockbridge, MI.
[c] Blue Ridge Veterinary Blood Bank, Purcellville, VA.
[d] IDEXX Laboratories, Westbrook, ME.
[e] Antech Laboratories, Irvine, CA.
[f] SAS statistical software, SAS Institute, Cary, NC.

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