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CASE REPORT

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Evaluation of the safety and feasibility of extracorporeal therapy: therapeutic plasma exchange in dogs - report of five cases

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Abstract

Background Therapeutic plasma exchange (TPE) has been used in immunological diseases, conditions of hyperviscosity, and the removal of protein-bound drugs and toxins. Although complications may be encountered, its use has been reported to offer some degree of safety and clinical improvement for dogs. This case report aimed to describe the feasibility and safety of TPE in dogs.

Case presentation Five dogs with immune-mediated hemolytic anemia (IMHA) and/or canine visceral leishmaniasis (CVL) not responsive to immunosuppressive treatment underwent TPE by centrifugation. Physical, laboratory, and cardiovascular parameters were assessed pre- and post-TPE. Although one dog presented with angioedema and another dog presented with neurological signs (nystagmus) during the procedure, no other significant hemodynamic or hemostatic complications were observed, and both the physical and cardiovascular parameters remained stable post-TPE. Both angioedema and nystagmus were controlled at post-TPE. A tendency for a decrease in serum protein and ionic calcium was the main laboratory finding.

Conclusions Centrifugation-based TPE is a safe and feasible therapy in dogs with IMHA and CVL. Attention should be given to hypocalcemia, the tendency toward hypoproteinemia, and secondary complications such as the occurrence of neurological signs.

Keywords Apheresis, Blood component, Immunological disease, Centrifugation, Canine

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Background

Therapeutic plasma exchange (TPE) is an apheresis therapy that enables the separation of blood components in an extracorporeal circuit, followed by specific substitution of the plasma [1, 2]. The therapy is indicated for the removal of high-molecular-weight biological substances such as antibodies, immune complexes, and toxins (which bind to plasma proteins). In most cases, it is a very useful complementary therapy in the removal of compounds resulting from immune-mediated disorders. However, it does not prevent their production if the underlying issue is not treated or resolved [3, 4]. Thus, TPE is known to improve the response to standard treatment for immune-mediated diseases, hyperviscosity syndrome, and intoxications, increasing the possibility of recovery in veterinary [5–8] and human patients [3, 9, 10].

TPE has been advocated for hematological, nephrological, neurological, and gastrointestinal disorders in humans [11–14] and is a relatively safe and controlled procedure [15]. In veterinary medicine, TPE is an emerging therapy, but it is understudied because of the high cost of equipment and the need for specialized personnel [8]. However, there may be limitations in the use of this technique in very small animals due to excessive extracorporeal volume and very low blood flow rates [16]. It has been recommended as an adjuvant treatment for conditions resulting in hypergammaglobulinemia, autoimmune and immune-mediated diseases, and those arising from immune complex deposition [17]. Most studies describe the application of TPE in dogs via the filtration technique for the treatment of hematological diseases such as immune-mediated hemolytic anemia (IMHA) and immune-mediated thrombocytopenia (IMT) [18–20], neurological conditions (myasthenia gravis) [21], immune-mediated disorders (systemic lupus erythematosus) [22], vascular disease (cutaneous and renal glomerular vasculopathy) [23], hyperproteinemia secondary to canine visceral leishmaniasis (CVL) [24], drug intoxication [6, 7], and hyperviscosity syndrome [25.26], with its use also reported in cats for the latter condition [25].

In TPE, the removal of target substances can be performed through centrifugation or membrane separation (filtration) [3, 26], with both methods being designed primarily to remove high-molecular-weight substances (>15.0 kDa). The centrifugation-based separation method relies on the substance density and gravitational force, whereas filtration relies on the membrane pore size and molecular substance size [2, 9, 10, 27]. Regardless of the removal process, it occurs nonselectively, removing both pathological and nonpathological components, such as albumin and coagulation factors, from the plasma. Thus, apheresis should be complemented with simultaneous infusion of replacement solutions, which may include fresh frozen plasma (FFP), albumin, colloid fluids, and crystalloids, aiming to maintain the colloid osmotic pressure and compensate for losses, ensuring the patient's volume status [9, 28].

In this apheresis technique, the volume of exchange per session and the frequency of the procedure must be defined on the basis of factors that directly influence the removal efficiency, such as the molecular weight of the target substance, the volume of distribution, and binding to plasma proteins [2]. In humans, a volume of 1 to 1.5 plasma generally achieves satisfactory removal of the target substance under most conditions [28], and larger exchange volumes progressively become less efficient and more challenging [29].

The utilization of this therapeutic modality in veterinary medicine requires visibility and technical recognition, given the potential to enhance the treatment of immunological diseases. In light of this perspective, this prospective study aims to document the effects of a session of TPE on the physical, laboratory, and cardiac characteristics of five dogs diagnosed with immune-mediated hemolytic anemia (IMHA) and/or canine visceral leishmaniasis (CVL) that did not respond to conventional therapy, highlighting the feasibility and safety of this apheresis therapy.

Cases presentation

Materials and methods

Data from five dogs undergoing TPE via centrifugation were evaluated, including procedure details, physical examination findings, laboratory results, and cardiac imaging. The history of the animals and subsequent indications for the apheresis procedure included the diagnosis of IMHA and/or CVL refractory to immunosuppressive treatment. For animals with IMHA, the diagnosis was determined on the basis of the ACVIM consensus statement on the diagnosis of immune-mediated hemolytic anemia in dogs and cats [30] and on serological tests for those with CVL.

Central vascular access was obtained via the Seldinger technique [31, 32], with a double-lumen catheter in the right jugular vein and the distal end of the catheter positioned at the junction of the cranial vena cava with the right atrium. Catheters of 8 Fr × 12.5 cm (Joline®, Joline GmbH & Co., Hechingen, Baden-Württemberg, Germany) or 11 Fr × 20 cm (Joline®, Joline GmbH & Co., Hechingen, Baden-Württemberg, Germany) were used for animals up to 10 kg and over 10 kg, respectively. Radiographic examination was performed to confirm the correct positioning of the catheter. The removal of the double-lumen catheter was performed 24 h after the end of the procedure.

In all five dogs, TPE sessions were performed via the Spectra Optia® system (Terumo BCT Inc., Lakewood,

CO, USA) set to achieve an exchange volume corresponding to one time the plasma volume of each animal. Considering the total blood volume (TBV) of each animal, the extracorporeal circuit (141 mL) was initially filled with a priming fluid: 0.9% NaCl solution or red blood cell concentrate (according to the patient's weight) from a compatible donor for blood transfusion. The choice of the priming solution to be used was based on the extracorporeal volume considering the circuit volume of 141 mL and the volume of the channel (10 mL), which must respect a proportion of < 15% of the hematic volume. The choice of red blood cell concentrate should respect both the extracorporeal volume below 141 mL and the volume of the channel lower than 15%. Otherwise, NaCl 0.9% can be used as a priming solution to remove air from the circuit. A regional citrate anticoagulation bag (2200 mg/100 mL of sodium citrate) was used to prevent coagulation of the system (JP Indústria Farmacêutica S.A., Ribeirão Preto, São Paulo), with a ratio of 10:1 required by the manufacturer. Simultaneously, with plasma removal, the infusion of replacement solution was composed of FFP (at least 50%) and 0.9% NaCl.

Equipment parameters represented by fluid balance, plasma volume to be withdrawn and session time were individually configured on the basis of total blood volume (TBV = weight (kg) × 0.08), hematic volume (HV = TBV (mL) × hematocrit (%)) and plasma volume (PV = TBV (mL) – HV). During the procedure, the dogs were physically restrained on a stainless steel table.

A blood sample from the left jugular vein was collected for a complete blood count (CBC) and serum biochemical analysis before and after each session. The red blood cell count was performed manually with the aid of a hemocytometer, while the platelet and leukocyte counts were quantified via a Poch-100iV Diff analyzer. The determination of total plasma protein was performed manually via a portable refractometer. The serum biochemical analysis included the determination of urea, creatinine, alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total protein, albumin, globulin, calcium, and phosphorus concentrations. These parameters were confirmed via a Roche Cobas Mira Plus enzymatic analyzer following the manufacturer's instructions and the available commercial kits (Bioclin®, Roche Diagnostic, Belo Horizonte, Minas Gerais, Brazil). Another sample was collected for venous blood gas analysis to evaluate the blood pH, partial pressure of carbon dioxide (PCO_2), base excess, sodium bicarbonate, ionized calcium (iCa), sodium, and potassium. Blood gas and electrolyte assays were conducted in a portable device (i-Stat 1 Handheld, Abbott, USA).

Electrocardiographic and echocardiographic examinations were performed and interpreted by the Veterinary Cardiology Service of São Paulo State University (UNESP)– Botucatu– SP– Brazil immediately before and after TPE sessions. Computerized electrocardiography was used, and the results were evaluated via the TEB ECG-PC VET®, São Paulo, São Paulo, Brazil. Alligator clip-type electrodes were placed on the skin surface of the humero-radial-ulnar and femoro-tibial-patellar joints. The three bipolar leads (I, II, and III) and augmented unipolar leads (aVR, aVL, and aVF) were recorded at a speed of 25 mm/second and calibrated so that one centimeter equaled 1 mV. For electrocardiographic interpretation, heart rate (HR), morphological analysis, polarity, duration and amplitude of P waves, QRS complexes, and T waves, as well as the duration of the PR and QT intervals, were measured via lead II.

Echocardiography (GE Healthcare device, LOGIQ®, GE Medical Systems (China) CO. LTD., Jiangsu, China) was performed via 6 S and 3 S probes according to the animal's weight. The examination included transthoracic evaluation in 2D mode, M mode, and Doppler. The animals were positioned in right and left lateral decubitus using manual restraint, without sedation or anesthesia, to perform the transthoracic echocardiographic examination in two-dimensional, M-mode and Doppler modes. The reference echocardiographic values used were according to the patients' body weight [33].

To prevent any adverse reactions to the procedure, the dogs included in the study received 2 mg/kg diphenhydramine subcutaneously and 50 mg/kg hydrocortisone intravenously thirty minutes before the beginning of the session. Physical and clinical evaluations of the dogs were conducted in the pre, trans- (30, 60, and 90 min after the start of the session), and postsession periods. Data on systolic blood pressure (SBP), rectal temperature (RT), heart rate (HR), and respiratory rate (RR) were recorded.

The collected data are presented descriptively, and considering the low number of observations, they are represented by median and interquartile ranges (Q1 and Q3), with comparisons between parameters before and after TPE by the nonparametric Wilcoxon test for paired data.

Results

Four females and one male dog were subjected to the procedure, with a median weight of 6.8 kg (range, 5.1–14.7) and an age of 7.4 years (range, 3.5–11.2), from four different breeds (Schnauzer, Bull Terrier, German Spitz, and two Pugs). Two Pugs had disorders associated with immune complex deposition due to CVL, *Leishmania infantum* infection confirmed by serological tests, and two (Schnauzer and Bull Terrier) had IMHA (anemia, positive saline agglutination, reticulocytosis, and spherocytosis). The fifth dog (German Spitz) presented a simultaneous picture of the CVL and IMHA. All dogs were refractory to clinical treatment for the underlying disease. None of the dogs improved with conventional

Table 1 Demographic and clinical characteristics of the five dogs that underwent centrifugal-based TPE

Characteristic	Dog				
	1	2	3	4	5
Gender	Female	Female	Female	Male	Female
Breed	Pug	Schnauzer	Bull Terrier	Spitz Alemão	Pug
Age (year)	3.4	12.2	10.2	7.4	3.5
Weight (kg)	7.4	4.9	22.1	5.4	6.8
Disease	CVL	IMHA	IMHA	CVL and IMHA	CVL
Immunosuppressive treatment + others	Corticotherapy[1]	Corticotherapy[1] + Micophenolate[2]	Corticotherapy[1] + Ciclosporine[3]	Corticotherapy[1] + Micophenolate[2]	Corticotherapy[1]
Blood transfusion therapy	No	2X (red blood cell concentrate)	2X (red blood cell concentrate)	3X (red blood cell concentrate)	No

CVL, canine visceral leishmaniasis; IMHA, immune-mediated hemolytic anemia; [1]2 mg/kg/once a day; [2]10 mg/kg/twice a day; [3]10 mg/kg/once a day

Table 2 TPE session parameters for the treatment of the five dogs

Parameter	Dog				
	1	2	3	4	5
Session time (minute)	113	123	78	108	98
Total blood volume (mL)	600	400	1,760	424	560
Plasma volume (mL)	444	328	1,566	301	381
Extracorporeal volume (%)	23.5	35.3	8.0	33.3	25.2
Removed plasma volume (mL)	396	304	941	292	356
Plasma volume exchange per TPE session	0.9	1.0	0.6	1.1	1.1
Replacement solution - NaCl 0.9% (%)	30	20	0	30	30
Replacement solution– FFP (%)	70	80	100	70	70
Volume of anticoagulant infused (mL)	23	21	16	26	28
Priming with red blood cell concentrate	Yes	Yes	Non	Yes	Yes

TPE, therapeutic plasma exchange; FFP, fresh frozen plasma

medical treatment for the underlying disease. The demographic and clinical characteristics of the participants are summarized in Table 1.

Given the objective of the study in evaluating the feasibility and safety of the apheresis therapy in dogs, each dog underwent only one session of TPE. The parameters established for each dog are described in Table 2. Dog 3 did not reach the previously established volume for a plasma exchange, as the session had to be interrupted owing to the occurrence of neurological signs (lateral nystagmus and decreased responsiveness to environmental stimuli). Additionally, dog 1 did not achieve the prescribed exchange volume, even though there were no complications and the session was completed.

The median and range for each biochemical parameter, considering all five dogs (urea, creatinine, ALT, ALP, GGT, total protein, albumin, globulin, calcium, phosphorus, sodium, and potassium) at pre- and post-TPE are presented in Table 3. Although no significance was reached, the plasma protein content tended to decrease post-TPE.

Table 3 Median (range) of biochemical parameters at pre- and post–TPE

Parameter	Pre-TPE	Post-TPE	*p*
Urea (mg/dL)	32 (22.5–267.5)	44 (27.5–266)	0.313
Creatinine (mg/dL)	0.7 (0.6–4.4)	0.7 (0.6–4.4)	0.438
Alanine aminotransferase (UI/L)	101 (85–169.5)	163 (55.5–163.0)	0.438
Alkaline phosphatase (UI/L)	422 (178.5–781.5)	165 (89.5–349.0)	0.063
Gamma-glutamyltransferase (UI/L)	10 (3.4–32.7)	3.6 (1.9–15.2)	0.063
Total protein (g/dL)	7.1 (5.2–9.8)	5.8 (4.4–6.5)	0.063
Albumin (g/dL)	2.3 (2.3–3.1)	2.1 (1,9–2.6)	0.058
Globulin (g/dL)	3.9 (3.0–7.2)	3.2 (2.5–4.2)	0.063
Calcium (mg/dL)	9.8 (9.3–10.3)	8.2 (6.2–9.9)	0.250
Phosphorus (mg/dL)	5.0 (4.3–5.3)	5.4 (4.6–5.8)	0.581
Sodium (mEg/L)	131 (128.3–148)	149.5 (132.3–168.3)	0.125
Potassium (mEg/L)	4.7 (3.9–5.0)	3.9 (3.2–4.2)	0.197

TPE, therapeutic plasma exchange

Table 4 Median (range) of hematological parameters at pre-TPE and post-TPE

Parameter	Pre-TPE	Post-TPE	*p*
Red blood cells (10^6/μL)	4.1 (2.6–4.2)	6.3 (3.2–7.0)	0.125
Hemoglobin (g/dL)	9.2 (5.9–9.5)	14.4 (7.5–15.5)	0.125
Hematocrit (%)	28 (15.3–31.0)	44.5 (22.5–48.5)	0.125
MCV (fL)	68.2 (66.9–74.8)	70.0 (66.7–72.8)	1.000
MCHC (%)	33.8 (29.4–34.3)	32.8 (31.2–33.7)	1.000
Plasma protein (g/dL)	9.7 (6.5–11.4)	6.4 (5.3–7)	0.125
RDW (%)	18.3 (14–19.2)	16.5 (14.2–16.6)	0.500
Platelets (x10^3/μL)	354 (86–662)	301 (98–617)	0.500
Metarubrocytes (/100)	7 (1.3–26.3)	4 (0.5–12.0)	0.250
Total leukocytes (x10^3/μL)	18.2 (11.6–29.6)	21.0 (19.3–29.7)	0.625
Segmented (10^3/μL)	15.3 (9.4– 26.5)	18.9 (17.3–26.6)	0.375
Lymphocytes (10^3/μL)	1.300 (1.2–1.3)	0.85 (0.45–1.3)	0.250
Eosinophils (10^3/μL)	0.1 (0.0–0.2)	0.0 (0.0–0.150)	1
Monocytes (10^3/μL)	1.6 (0.7–4.3)	1.6 (0.73–2.3)	0.789

TPE, therapeutic plasma exchange; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width

In Table 4, the results of the hemograms (red blood cells, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelets, metarubricytes, plasma protein, leukocytes, lymphocytes, eosinophils, and monocytes) are described. Although no significance was reached, a tendency toward an increase in red blood cells, hemoglobin, and hematocrit was observed post-TPE.

The results obtained pre- and post-TPE for venous blood gas and electrolytes (pH, PCO2, sodium, bicarbonate, base deficit, potassium, and ionized calcium) are summarized in Table 5. The dog that developed neurological signs (previously described) after the interruption of the session presented a decrease in ionized calcium values between the pre- and post-TPE periods, requiring supplementation with this electrolyte (10% calcium gluconate – 1.5 mL/kg).

All animals presented electrocardiographic parameters within the normal range in the pre- and post-TPE periods. Heart rate (HR), duration, and amplitude of electrocardiographic parameters did not significantly change. No ventricular or supraventricular arrhythmias, conduction disturbances, or sinus pauses/blocks were detected.

In the pre- and post-TPE Doppler echocardiogram, there were no clinically relevant alterations in the anatomical or hemodynamic parameters. Systolic and diastolic functions were preserved, and blood flow in major vessels and valves was within normal limits.

Physiological parameters such as HR, respiratory rate (RR), rectal temperature (RT), and systolic blood pressure (SBP) remained within the species' reference values during and after TPE (Fig. 1). One dog developed angioedema after the administration of FFP, which quickly resolved after the administration of hydrocortisone (50 mg/kg).

Table 5 Median (range) of hemogasometric and electrolytic parameters at pre- and post-TPE

Parameter	Pre-TPE	Post-TPE	*p*
Blood pH	7.37 (7.35–7.40)	7.34 (7.29–7.36)	0.438
PCO_2 (mmHg)	35.6 (26.5–36.0)	33.8 (27.3–45.2)	0.313
Sodium (nmol/L)	143 (142–148)	143 (142.5–151.5)	0.423
Bicarbonate (mmol/L)	19.1 (15–22.5)	17.7 (14.8–23.2)	0.813
Base excess (mmol/L)	-5.4 (-9.5– -2.5)	-7.2 (-9.9– -3)	0.197
Potassium (mmol/L)	4.1 (3.6–4.3)	3.4 (3.2–4.1)	0.188
Ionized calcium (mmol/L)	1.3 (1.2–1.4)	0.9 (0.7–1.2)	0.058

TPE: therapeutic plasma exchange

Discussion and conclusions

The present study successfully conducted TPE therapy in five dogs that did not respond properly to conventional immunosuppressive drug therapy. Although angioedema has been observed in one dog and nystagmus in another dog, a single TPE session seemed to be safe in dogs, with no reports of major complications such as hypovolemia, hypotension, and/or hemodilution. To the best of the authors' knowledge, these major risks were avoided because of the use of blood priming in these animals, a

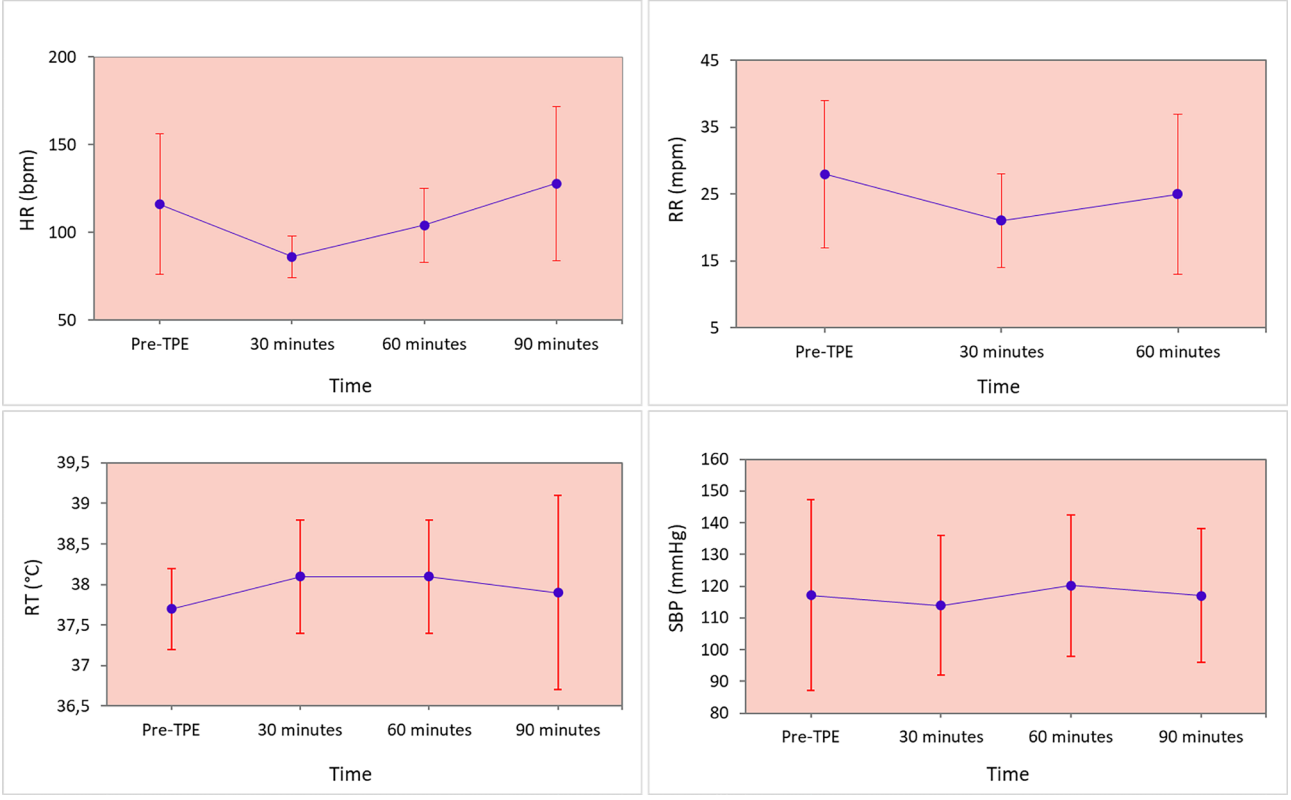

Fig. 1 Median (range) of physical parameters before and during therapeutic plasma exchange. HR (heart rate), RR (respiratory frequency), RT (rectal temperature) and SBP (systolic blood pressure)

procedure that limits the extracorporeal blood volume to less than 20% of the patient's TBV [20].

In human medicine, TPE is commonly used to treat Guillain–Barré syndrome, Goodpasture syndrome, myasthenia gravis, IMHA, IMT, and acute liver failure before liver transplantation [19]. In veterinary medicine, the use of TPE has been reported in IMHA [20, 34], IMT [20], myasthenia gravis [21], systemic lupus erythematosus [22], cutaneous and renal glomerular vasculopathy [23], hyperviscosity syndrome [35, 36], and toxicity caused by protein-bound solutes [6, 7]. Falling into this spectrum of immunological diseases, the dogs in this report were diagnosed with IMHA and/or CVL, making them candidates to benefit from the described apheresis therapy. The pathophysiology of both CVL and IMHA involves an exacerbated immune response, leading to excessive production of immunoglobulins and antigen–antibody complexes [37–40]. These components can be detrimental to the patient's clinical condition, as they trigger a dysfunctional immune response and increase the risk of normal cell destruction, particularly in the case of IMHA [39]. Additionally, immune complexes may deposit in various tissues (particularly in the case of CVL) [40, 41], inducing a deleterious inflammatory response. Thus, by removing these substances and promoting a potential immunomodulatory effect, TPE may offer a relevant therapeutic approach in these specific cases, helping to mitigate complications arising from the exaggerated immune response [2, 24, 34].

In this study, a combination of FFP (comprising at least 70% of the total replacement volume) and crystalloid solution (0.9% NaCl solution) was used as replacement fluids. Even after preprocedure administration of diphenhydramine and hydrocortisone, one dog experienced angioedema after the use of FFP. In this case, the animal quickly recovered after the administration of hydrocortisone, and TPE was continued. A similar condition was also described by Francey and Schweighauser [16]. Given the above, to minimize the potential occurrence of transfusion-related allergic reactions in a larger number of animals undergoing TPE, the use of premedication should be considered, particularly in protocols where FFP is included as one of the replacement fluid components. This is because, even in protocols where FFP does not constitute the entirety of the replacement fluid (as in the present study), multiple units of this blood component, derived from different donors, are required in each TPE session to achieve the necessary volume, thereby increasing the risk of transfusion reactions associated with this therapy [42].

FFP or albumin are widely used replacement solutions in human medicine because they provide desired properties, such as volume of replacement, maintenance of oncotic pressure, and replenishment of coagulation factors [19]. However, the use of FFP has been associated with greater adverse effects, causing human albumin diluted in saline solution to be commonly employed as a replacement solution in people [43]. Conversely, in veterinary medicine, replacement solutions have been based on previously described options for dogs and cats, including FFP and/or human albumin and/or crystalloid solutions (such as 0.9% saline) and/or synthetic colloids [16, 20, 23, 34]. This knowledge is based on the replacement solution's choice applied to the five dogs in this study.

As described by de Back et al. [28], a volume of 1 to 1.5 exchanges per session predicts an approximately 60–80% reduction in the pathogenic substance(s), respectively. Larger exchange volumes are proportionally less efficient due to the exponential kinetics of the procedure and require larger volumes of replacement solutions [28, 29]. In the present report, although the prescription was made to achieve at least the volume of 1 plasma exchange in all dogs, this volume was actually achieved in 3 animals. The reason why dog 1 did not reach this minimum exchange volume may be that the effective volume of plasma removed did not match the volume of plasma processed [44]. Therefore, prescriptions exceeding the volume of one exchange may be necessary to achieve the required removal efficiency. On the other hand, dog 3 did not reach the prescribed exchange volume because its session was interrupted due to neurological clinical complications. Despite this, this animal also presented a trend toward a decrease in total protein and globulin values posttreatment.

In this study, as previously described, all animals were subjected to a prescription of a volume of plasma exchange, which decreased the concentration of immunoglobulins by 60% in a single procedure [9]. This therapeutic benefit may, in part, explain the trends toward a decrease in globulin levels observed in the animals in this study. Additionally, part of this outcome may be attributed to plasma hemodilution caused by the small amount of 0.9% NaCl solution (20–30%) used to compose the replacement solution. Despite this, considering the distribution volume and recovery rate of the target substance, the vast majority of the conditions already described in humans require additional sessions in a short period of time or even daily for better results [9, 12], which tends to be extrapolated to veterinary medicine as well.

Indeed, most electrolytes, venous blood gases, and complete blood counts remained stable after treatment. In four dogs, normocytic normochromic anemia rapidly reversed after blood transfusion, justifying the results observed in the post-TPE hemogram. The decrease in protein concentration in the hemogram, total plasma proteins, and globulins in serum biochemistry observed post-TPE is consistent with findings in dogs in other

studies [16, 19, 24]. However, the assessment of a specific group of proteins, including the immunoglobulin group, tended to be decreased by the procedure, which could be complemented through the use of electrophoresis and/or proteomics and/or specific assays [36, 45, 46].

The acid–base balance of the dogs remained within the expected range for the species, although hypocalcemia was observed shortly after the session in all patients. This finding corroborates findings in dogs described by Crump and Seshadri [19] and Francey and Schweighauser [16]. This alteration is commonly observed in patients undergoing TPE, as the use of citrate as an anticoagulant binds to ionized calcium to inhibit the coagulation cascade [47]. For this reason, with the prospect of hypocalcemia during the procedure, intravenous calcium supplementation throughout TPE has been described [16, 19, 20]. Only one dog experienced complications during the procedure, with rapid recovery after intervention (procedure interruption, blood return to the patient, and administration of 10% calcium gluconate). Potassium replacement has also been described in humans because of the possibility of similar reductions in this electrolyte and hypokalemia during the procedure [48]. Although angioedema and nystagmus have been observed in one dog each, it is reliable to state that, overall, the dogs presented clinical stability, and vital signs remained within the expected range for the species during the procedure. Thus, on the basis of the results described and evaluated in this study, along with previously reported descriptions [16, 19, 20], prophylactic supplementation with calcium gluconate during the TPE procedure, aimed at preventing hypocalcemia and its secondary clinical manifestations, should be considered an essential practice in protocols that use sodium citrate as an anticoagulant for the extracorporeal circuit and fresh frozen plasma as part of the replacement fluid.

From a cardiac examination perspective in the animals of this pilot study, TPE resulted in stability for the dogs undergoing the procedure, as cardiac exams were observed within the expected interval for the species.

One limitation of this study is the small number of animals evaluated, which may not have captured all the possible adverse effects. Additionally, the number of animals limited our assessments to descriptive data. Furthermore, the therapeutic evaluation of TPE for the diseases in question was not the focus of this report, so only one session of TPE was evaluated. After the TPE session, the animals returned for follow-up during clinical treatment.

In conclusion, therapeutic plasma exchange by centrifugation is a feasible and rapid extracorporeal technique that is safe (during delivery and immediately after the procedure) when used in dogs with IMHA and/or CVL. Special attention should be given to possible transfusion reactions and the occurrence of signs secondary to hypocalcemia during the procedure. To avoid or minimize the consequences of hypocalcemia, the choice of the fluid used for replacement needs special attention, and adequate proportions must be used for each patient individually. Although no significant results were found, a tendency toward a decrease in serum protein was observed after TPE in the dogs reported here. The therapeutic effect of TPE on this specific tendency toward the reduction of target molecules has not been evaluated. Therefore, further studies are needed to complement the therapeutic action of centrifugation-based TPE in veterinary patients affected by potentially immunological conditions.

Abbreviations

TPE	Therapeutic Plasma Exchange
IMHA	Immune-mediated hemolytic anemia
IMT	Immune-mediated thrombocytopenia
CVL	Canine visceral leishmaniasis
TBV	Total blood volume
HV	Hematic volume
PV	Plasma volume
CBC	Complete blood count
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
GGT	Gamma-glutamyl transferase
PCO2	Partial pressure of carbon dioxide
ICa	Ionized calcium
SBP	Systolic blood pressure
RT	Rectal temperature
HR	Heart rate
RR	Respiratory rate
MCV	Mean corpuscular volume
MCHC	Medium corpuscular hemoglobin concentration

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Author contributions

SRM, RSM, SSG, and MGPA - made substantial contributions to data curation; writing– original draft preparation and investigation, formal analysis. SRM and RSM made substantial contributions to writing review and editing. AGS - participated in the data curation and investigation. MABM - participated in the conceptualization and investigation. AA - participated in the writing original draft preparation; investigation and formal analysis. HDMG and RG - performed the formal analysis. ASO, AM, MLGL, RKT, FFS, and RG - made substantial contributions to conceptualization; data curation, investigation, and writing review and editing. PTCGO - made substantial contributions to conceptualization; methodology; project administration; investigation; formal analysis, writing original draft preparation; writing review and editing, and supervision.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the ethical precepts recommended by the National Council for Animal Control and

Experimentation (CONCEA) and approved by the Institutional Animal Use Ethics Committee (number 0100/2021). Prior to admitting the dogs, informed consent forms were obtained from all owners, permitting the use of all clinical data generated during their visit to the veterinary hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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