



Accuracy of formulas used to predict post-transfusion packed cell volume rise in anemic dogs

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Abstract

Objective – To assess the accuracy of published formulas used to guide packed red blood cell (pRBC) transfusions in anemic dogs and to compare the predicted rise in packed cell volume (PCV) to the actual post-transfusion rise in PCV.

Design – Prospective observational study from April 2009 through July 2009.

Setting – A small animal emergency and specialty hospital.

Animals – Thirty-one anemic client-owned dogs that received pRBC transfusions for treatment of anemia.

Interventions – None

Measurements – Four formulas were evaluated to determine their predictive ability with respect to rise in PCV following transfusion with pRBC. Post-transfusion rise in PCV were compared to calculated rise in PCV using 4 different formulas. Bias and limits of agreement were investigated using Bland–Altman analyses.

Results – Accuracy of existing formulas to predict rise in PCV following transfusion varied significantly. Formula 1 (volume to be transfused [VT] [mL] = 1 mL × % PCV rise × kg body weight [BW]) overestimated the expected rise in PCV (mean difference, 6.30), while formula 2 (VT [mL] = 2 mL × % PCV rise × kg BW) underestimated the rise in PCV (mean difference, –3.01). Formula 3 (VT [mL] = 90 mL × kg BW × [(desired PCV – Patient PCV)/PCV of donor blood]) and formula 4 (VT [mL] = 1.5 mL × % PCV rise × kg BW) performed well (mean difference 0.23 and 0.09, respectively) in predicting rise in PCV following pRBC transfusion.

Conclusions – Agreement between 2 formulas, “VT (mL) = kg BW × blood volume (90 mL) × [(desired PCV – recipient PCV)/Donor PCV]” and “VT (mL) = 1.5 × desired rise in PCV × kg BW,” was found when they were compared to the actual rise in PCV following pRBC transfusion in anemic dogs. Further research is warranted to determine whether these formulas perform similarly well for other species.

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Abbreviations

BW body weight
Hb hemoglobin

HCT hematocrit
PCV packed cell volume
pRBC packed red blood cell
SD standard deviation
VT volume to transfuse

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Introduction

Anemia is often encountered in veterinary medicine and is defined as a decrease in the oxygen carrying capacity of blood.¹ In a normovolemic animal, anemia is characterized as having less number of red blood cells than the normal, decreased hemoglobin concentration (Hb), decreased hematocrit (HCT), or decreased packed cell volume (PCV) that causes the oxygen carrying capacity of blood, and thus oxygen delivery, to be decreased.² In a study involving healthy research dogs, oxygen uptake,

mixed venous partial pressure of oxygen, and oxygen delivery decreased abruptly at PCVs below 10%.³ It is unknown if this can be extrapolated to ill dogs; however, at this critical PCV, or possibly even higher in ill dogs, myocardial ischemia resulting in cardiac insufficiency, hypoperfusion, and tissue hypoxia may occur.⁴ Experimental human studies have shown the development of ECG ST-segment depression indicating myocardial ischemia at an Hb concentration of 50 g/L (5 g/dL).⁵

The goal of transfusion therapy is to improve oxygen delivery. Red blood cell transfusions allow veterinarians to correct anemia by increasing red cell volume; however, the decision to transfuse and volume of blood product to administer varies. Various transfusion dosages can be found in the veterinary literature that are based on a milliliter per kilogram (mL/kg) basis or use formulas to predict the rise the PCV within a certain number of percentage points, yet no veterinary consensus guidelines are available.

Although these recommendations exist, in clinical practice the volume of packed red blood cells (pRBCs) administered is often adjusted to the standard volume of pRBC unit(s) obtained from an animal blood bank. The volume of pRBCs administered should be calculated accurately in order to provide an increase in PCV similar to the expected rise, otherwise under- or over-transfusion may occur.

Patients that are undertransfused and require subsequent transfusion are exposed to increased risk, in addition to increased owner costs. Since all transfusions have the potential to transmit infection, cause immunosuppression, or lead to transfusion reactions, these adverse events may increase with each additional transfusion administered.⁶ On the other hand, over transfusion can also be deleterious and lead to volume overload or altered blood rheology.⁷ Studies in people have demonstrated higher mortality when post-transfusion HCT >36%.⁸ Meanwhile, patients with underlying oliguric or anuric renal failure, cardiac, or pulmonary disease are at greater risk of circulatory overload, especially if they are euvolemic prior to transfusion.⁹ In human medicine transfusing to a "restricted" (70 g/L [7.0 g/dL] of Hb) versus a "liberal" (100 g/L [10 g/dL] of Hb) concentration is considered safer transfusion practice.^{10,11} Nevertheless, the decision to transfuse and the amount administered should be based on the severity of anemia, illness severity, and comorbidities rather than a set Hb concentration.^{10,11} Despite risks of transfusion-related adverse events, severely anemic patients often require transfusions of pRBC and veterinarians must determine an appropriate volume of pRBCs to administer.

Several formulas have been published in the veterinary literature to predict the transfusion volume needed

Table 1: Commonly published transfusion guidelines.

- Administer 10 mL/kg to increase Hb concentration by 3 g or the PCV by 9 points or (volume of pRBC transfused × 2) / PCV of donor pRBC = expected rise in patient PCV⁶
- 10 mL/kg raises the PCV 10%^{6,12} or 1 mL/kg raises the PCV by 1%⁶
- 6–10 mL/kg of pRBC^{18,24} 10–15 mL/kg of pRBC with additives¹⁸
- 1–1.5 mL/kg of pRBC to raise HCT by 1%²⁵
- 2.2 mL/kg of blood raises the PCV by 1% when the PCV of the transfused blood is 40%²⁶
- Volume to transfuse (whole blood or pRBC) = desired PCV rise × BW (kg) × 2 to estimate the target PCV¹³

BW, body weight; Hb, hemoglobin; PCV, packed cell volume; HCT, hematocrit.

to achieve a desired post-transfusion PCV (see Table 1). These formulas result from theoretical calculations and have not been assessed clinically. Despite their common clinical use, controlled studies assessing the validity of these formulas are lacking. The authors' clinical impression is that the use of commonly described formulas in anemic dogs does not correlate with the actual rise in post-transfusion PCV. The objective of this study was to evaluate the accuracy of 4 formulas (three widely used formulas used in veterinary medicine and one less common formula used in neonatal human medicine) to transfuse anemic dogs in an emergency and specialty small animal hospital by comparing the calculated expected rise in PCV to the actual post-transfusion rise in PCV. Our hypothesis was that these formulas would not accurately predict the post-transfusion PCV rise in anemic dogs.

Methods and Materials

Client-owned dogs admitted to the Advanced Critical Care and Internal Medicine emergency and specialty hospital and diagnosed with anemia were prospectively enrolled in the study from April 2009 to July 2009. Any dog that received a pRBC transfusion was eligible for inclusion as long as the following information was available: age, breed, sex, body weight, known PCV prior to transfusion (pre-PCV), the volume of pRBCs administered, PCV of the donor pRBC, PCV within 1 hour after the transfusion (post-PCV), and classification of anemia (loss, destruction, or decreased production). Dogs that received other blood products such as whole blood or plasma, and blood substitutes, such as hemoglobin glutamer-200, were excluded.

All pRBC units were obtained from a commercial veterinary blood bank^a and were DEA 1.1 and 1.2 negative. pRBC units anticoagulated with citrate phosphate dextrose adenine (CPDA-1) solution were either 175 mL or 350 mL in volume with either the full unit or a portion of the unit administered without saline dilution. The PCV

Table 2: Formulas for pRBC transfusion dosage and expected rise in PCV^{6,12,13,14}

| Formula | Volume to be transfused (VT) (mL) | Expected rise in PCV (%) |
|---------|--|---------------------------------------|
| 1 | 1 mL × % PCV rise × kg BW | VT mL / kg BW |
| 2 | 2 mL × % PCV rise × kg BW | VT mL / (2 × kg BW) |
| 3 | 90 mL × kg BW × [(desired PCV – patient PCV) / PCV of donor blood] | (Donor PCV × VT mL) / (90 ml × kg BW) |
| 4 | 1.5 mL × % PCV rise × kg BW | (2 × VT mL) / (3 × kg BW) |

VT, volume to be transfused; PCV, packed cell volume; BW, body weight.

of the unit was measured by obtaining the blood from 2 “pigtail” volumes placed into an EDTA^b tube with the EDTA volume removed or sampling 1 mL from the transfusion line directly and placing it in the emptied EDTA tube. The PCV was then measured by filling a nonheparinized HCT tube and centrifuging for 5 minutes at a speed of 15,000 rpm. A micro hematocrit capillary reader chart was utilized to obtain the percent cell volume. Prior to transfusion, major crossmatches were performed in-hospital according to the referenced protocol and microscopically evaluated the recipients’ plasma against saline washed donor cells.⁶

The volume and the rate of the pRBC transfusion were determined by the attending clinician. Values obtained from the medical records were used to evaluate 4 different formulas: formula 1: 1 mL × desired rise in PCV × kg of body weight (BW)^{6,12}; formula 2: 2 mL × desired rise in PCV × kg BW¹³; formula 3: kg BW × blood volume (90 mL) × [(desired PCV – recipient PCV) / donor PCV]¹²; and formula 4: 1.5 × desired rise in PCV × kg BW¹⁴ (Table 2). The formulas were solved for the “desired rise in PCV” (Table 2). These converted formulas were used to calculate the expected rise in PCV for the actual volume of transfused pRBCs.

Statistical analysis

Descriptive statistics were calculated. Student’s *t*-test was used to assess the association of the post-transfusion rise with expected rise in PCV. For comparison of the formulas, a conventional Bland–Altman analysis was performed. The Bland–Altman technique plots the differences between 2 measurements against their mean and calculates the limits of agreement.¹⁵ Bias was determined as the calculated rise in PCV for formulas 1–4 minus the actual PCV rise. Bias was defined as the mean value of the difference between the calculated rise in PCV for formulas 1–4 and the actual PCV rise. Limits of agreement were defined as 1.96 standard deviations (SDs) of the differences, to include 95% confidence intervals. Results

were reported as mean (SD), unless otherwise stated. Results with *P* < 0.05 were considered statistically significant. All analyses were performed using statistical software.^c

Results

Thirty-one anemic dogs were included in the study. There were 13 neutered males, 14 spayed females, 3 intact females, and 1 intact male. A heterogeneous group of breeds were represented including: Labrador Retriever (*n* = 3), Pit bull-type dog (*n* = 2), Cocker Spaniel (*n* = 2), mix breeds (*n* = 6), and the remaining 16 dogs were other pure bred dogs. Median patient age was 6 years (range, 2–14 years). Median weight was 14.3 kg (range, 5.0–48.4 kg).

Thirty-seven transfusions were recorded with complete data. Twenty-seven dogs received a single pRBC transfusion. Two dogs received 2 pRBC transfusions and 2 dogs received 3 pRBC transfusions. The mean pre-transfusion PCV (pre-PCV) for all patients was 16.5% ± SD 0.76. The median volume of pRBCs transfused was 350 mL (range, 60–450 mL). Nineteen transfusions involved infusion of a 350 mL unit of pRBCs, while 10 dogs received a 175 mL unit of pRBCs, and 8 dogs received a fraction of or more than 1 unit. The median volume of pRBC transfused per kilogram of body weight was 16.5 mL/kg (range 7.2–40.3 mL/kg). The mean donor pRBC PCV was 60.9% ± SD 9.7. The mean post-transfusion PCV (post-PCV) was 28.8% ± SD 6.2 with a mean post-transfusion rise in PCV of 12.2% ± SD 6.1.

For each transfusion, the expected rise in PCV was calculated using the 4 formulas listed in Table 2. The results of the expected mean rise in PCV varied based on the calculation used. Direct comparisons of all 4 formulas compared to the actual rise in PCV are shown in Figure 1. Bland–Altman plots are shown in Figure 2, displaying the lines representing the “limits of agreement” (bias ± 2 SDs). These confirm a low bias for formulas 3 and 4 (mean difference 0.23 and 0.09, respectively) and a high bias for formulas 1 and 2 (Figure 2, Table 3). Formula 1 overestimated the expected rise in PCV compared to the actual rise in PCV, mean difference 6.30, whereas formula 2 underestimated the rise in PCV, mean difference –3.01 (Figure 22).

Eighteen transfusions (49%) were administered due to RBC destruction (eg, immune-mediated hemolytic anemia [IMHA]). Nineteen transfusions (51%) were administered due to internal or external blood loss (eg, trauma, surgical hemorrhage, gastrointestinal bleeding, anticoagulant rodenticide toxicity and hemoabdomen due to neoplasia). No patients in this study were transfused for non-regenerative anemia as the sole diagnosis.

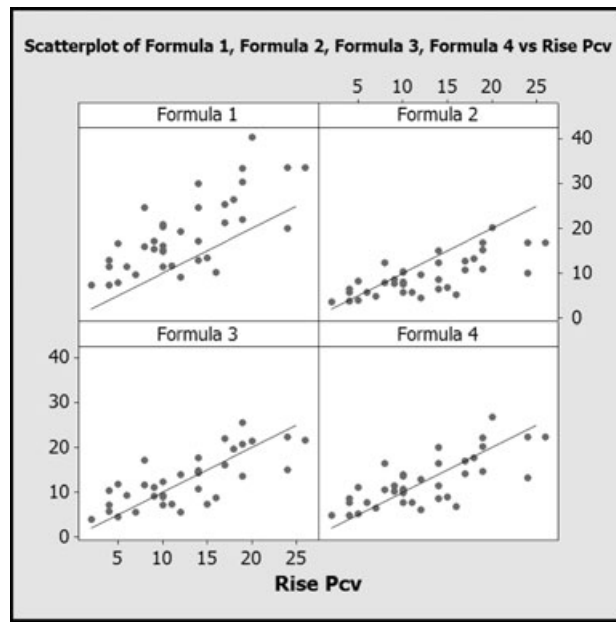


Figure 1: Scatter plot of the calculated rise in PCV for each formula (1–4) compared to the actual PCV. The straight line is the line of perfect concordance. Visual inspection of formulas 1 and 2 show that the majority of data points lie above and below the line of concordance, respectively. This reflects the Bland–Altman plot results, where formulas 1 and 2 are shown to over- and underestimate the actual PCV rise, respectively. The scatter of data around the line of concordance for formulas 3 and 4 reflect approximation of the actual rise in PCV.

Table 3: Results of Bland and Altman analysis for each of the formulas 1–4

| | Bias (%) | Limits of agreement (± 1.96 SD) |
|-----------|----------|--------------------------------------|
| Formula 1 | -6.30 | (4.94, -17.53) |
| Formula 2 | 3.01 | (11.14, -5.11) |
| Formula 3 | -0.23 | (8.02, -8.48) |
| Formula 4 | -.09 | (8.32, -8.50) |

Discussion

Currently, there is no consensus in veterinary medicine on deciding the volume of pRBCs to administer an anemic patient. The formulas evaluated in this study were chosen for a variety of reasons. Formula 1 is the most commonly cited.^{6,12,13,16–18} Formula 2 is a recently referenced formula with double the recommended volume. Because neither of these account for the donor PCV, we included formula 3. Finally, formula 4 has been used in neonatal human medicine for pRBC transfusion protocols and is the average of formulas 1 and 2. By evaluating these 4 formulas, we intended to include a range of dosages used to calculate the volume of pRBCs to transfuse and establish their accuracy when compared to their actual rise in PCV.

Bland–Altman analysis confirmed that there was a good agreement between formulas 3 and 4, whereas formulas 1 and 2 have increased bias (Figure 2).

Formula 1 overestimated the expected post-transfusion PCV by a mean difference of 6.30. This could result in increased patient morbidity since the patient would be under transfused and could potentially still be anemic requiring subsequent transfusions. Formula 2 underestimated the expected post-transfusion PCV by a mean difference of 3.01. Although the actual PCV would only be marginally increased, this could potentially, adversely impact euvoletic patients with comorbidity (eg, severe cardiac disease leading to volume overload). Both formula 1 and 2 were found to be unreliable models for predicting PCV rise in this patient population (Figure 2).

The advantage of utilizing either formula 3 or 4 is that both accurately predicted the post-transfusion PCV (mean difference 0.23 and 0.09, respectively; Figure 2). Formula 3 is the most accurate because it takes into account the patient’s PCV and the donor’s PCV, so the expected PCV rise can be calculated when a certain volume is given. The mean donor pRBC PCV in this study was 60.9% \pm SD 9.7, which is consistent with previous literature showing a donor PCV of 55–60% in pRBCs with additive solution.¹⁸ We believe that the reason formula 4 is nearly as accurate as formula 3 is that it includes a coefficient of 1.5, which is approximately the same as formula 3’s variable “90 mL/donor PCV” under most circumstances. The advantage of formula 4 is that it is easy to calculate since donor PCV is not required. Further studies are needed to investigate whether the cause

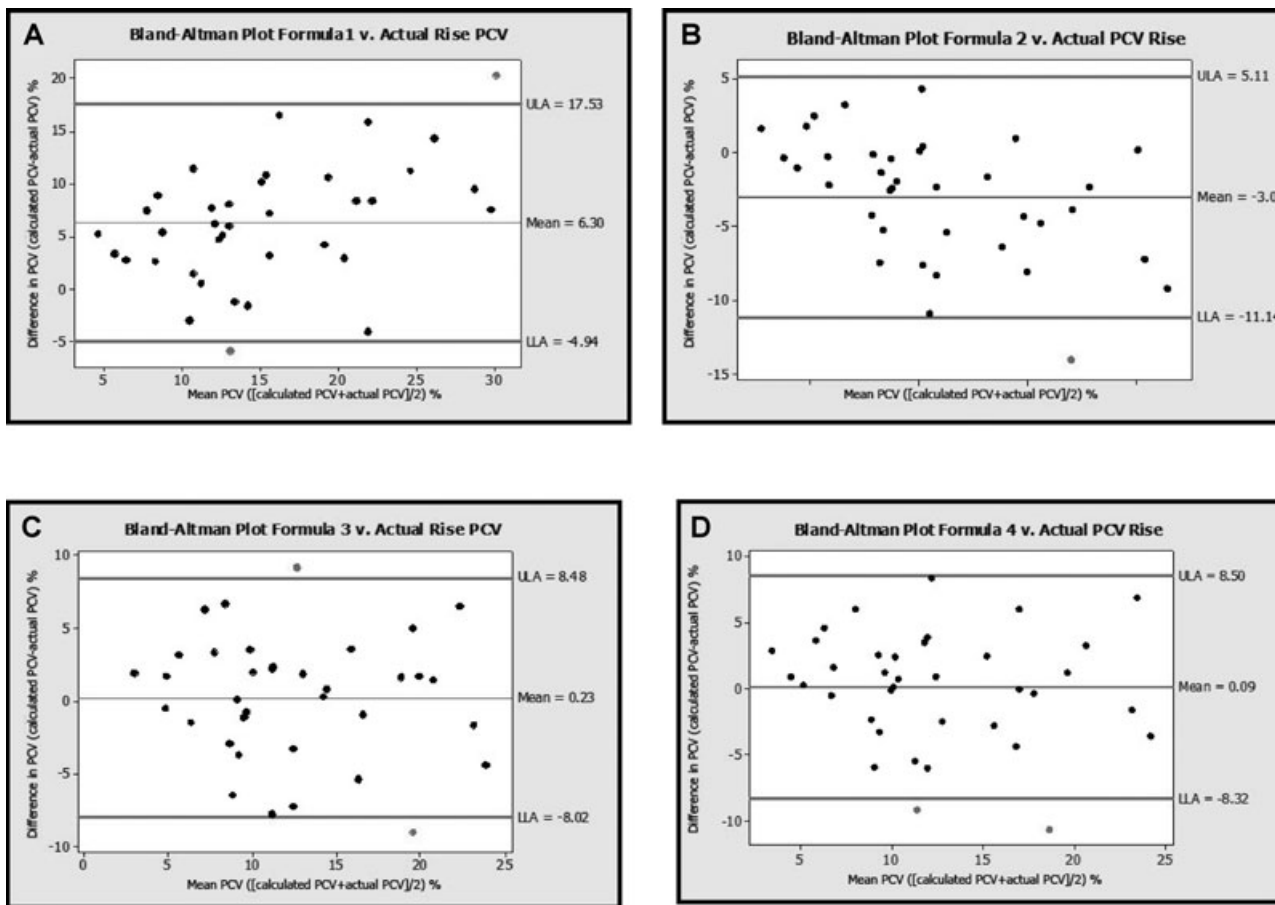


Figure 2: Figure 2: Bland-Altman plots. In Bland-Altman plots, $y = 0$ is the line of perfect average agreement, meaning that both techniques measure the parameter of interest to similar values. The light grey line represents the average agreement of the data while the 2 solid lines represent the 95% limits of agreement for the data. A positive or negative deflection of the line representing average agreement demonstrates that 1 technique tends to over- or underestimates the other, respectively. Wide 95% limits of agreement reflect larger variability of the data. (A) Comparison of Formula 1 to actual PCV rise. (B) Comparison of Formula 2 to actual PCV rise. (C) Comparison of Formula 3 to actual PCV rise. (D) Comparison of Formula 4 to actual PCV rise.

of anemia impacts the ability of these formulas to predict post-transfusion PCV relative to each formula.

The current study revealed a mean post-PCV of $28.8\% \pm \text{SD } 6.2$ with a mean post-transfusion rise in PCV of $12.3\% \pm \text{SD } 6.1$. This is consistent with previous veterinary literature where a post-transfusion PCV of 25%–30% is the goal in anemic dogs.¹²

This study evaluated pRBC units with an additive solution (CPDA-1) and, therefore, a mean donor PCV of 60.9%. pRBC units processed without additive solution may be more concentrated, with PCVs reaching 80%.^{6,12,19} In these instances, formula 3 may be more accurate as it incorporates the donor PCV. Alternatively, formula 1 may accurately predict the rise in PCV if the donor PCV is $>80\%$ as then the formula's coefficient would be close to 1. Similarly, formula 2 may be more precise for whole blood transfusions, as the PCV

of whole blood is about 45% and the coefficient would be near 0.5, which is analogous to formula 2.

There are certain limitations to the current study. The patient number per group is relatively small. Further studies with greater number of patients may help differentiate if the classification of anemia (eg, destruction versus loss versus decreased production) has a significant impact on post-transfusion PCV. We were unable to determine the duration of each transfusion and whether concomitant intravenous fluid therapy was administered during each transfusion. This may have influenced the results, particularly the use of other parenteral fluids as it may have resulted in hemodilution and therefore lowering of the PCV. Due to the observational nature of the study, the formula used by clinicians to determine the pRBC volume to be infused was not always available. Additionally, the volume of commercially obtained

pRBC units was not confirmed prior to administration. In cases in which a full unit was administered the amount given may have varied slightly and would have affected the resulting post-transfusion PCV from the formulas predicted PCV.

Ideally, the patient population for a study evaluating predictive formulas such as those evaluated here would be those patients without ongoing blood loss or hemolysis or concurrent intravenous fluid therapy during the transfusion period. In the current study, we aimed to minimize iatrogenic hemolysis due to transfusion incompatibility by performing a major crossmatch for each pRBC transfusion.¹¹ Additionally, all units used in this study came from DEA 1.1- and 1.2-negative donors. Blood typing of the recipient was not performed because no naturally occurring antibodies to DEA 1.1- and 1.2-negative have been identified to date.¹⁹ Ideally, blood typing of the recipient should be performed.

Eighteen transfusions were administered due to the known hemolytic anemia, and it is assumed that ongoing hemolysis was occurring during these transfusions. It is not possible to estimate the impact of this ongoing hemolysis on PCV. Similarly, the impact of ongoing blood loss in the 19 transfusions administered for patients with blood loss cannot be accurately estimated. Because of ongoing losses or concurrent intravenous fluid therapy, the lower-than-expected post-PCV would cause our formulas to underestimate the volume to be transfused. It must be noted that this may be one reason why formula 2 proved to be unreliable.

While we acknowledge that these ongoing losses influence post-PCV, we believe that the current patient population parallels those of other published studies detailing transfusion indications. In the study by Stone et al.²⁰ evaluating 315 dogs, the most frequent reasons for transfusions were acute blood loss due to trauma, surgery, or bleeding tumors, anemia most commonly due to IMHA or other hemolysis, and bleeding secondary to coagulopathy or other disease.²⁰ While indications for pRBC transfusion vary among studies^{21,22} and may be affected by geographic and temporal variations, we believe that the patient population in this study is representative of dogs requiring transfusion in the small animal emergency hospital.

The timing of post-PCV was standardized within 1 hour of transfusion completion. Thus, RBCs and blood volume may not have fully equilibrated within that timeframe. PCV, HCT, and Hb will increase rapidly, but it will take 12–24 hours for intravascular volume to return to baseline.²³ On the other hand, by standardizing the post-PCV within 1 hour, less time was available for further blood loss or hemolysis to occur. Further studies could evaluate dogs without confounding factors, such as ongoing hemolysis or blood loss and intravenous fluid

therapy. The accuracy of these 4 equations in a population with chronic or nonregenerative anemia has not been evaluated.

In summary, formulas used in everyday practice to estimate RBC transfusion volume requirements yield a wide range of results depending on the formula used. We believe this to be the first study evaluating the formulas used by many veterinarians for dosing RBC transfusions. The more complicated formula, $VT \text{ (mL)} = \text{kg BW} \times \text{blood volume (90 mL)} \times ((\text{desired PCV} - \text{recipient PCV}) / \text{donor PCV})$,¹ and the human formula, $VT \text{ (mL)} = 1.5 \times \text{desired rise in PCV} \times \text{kg BW}$,¹⁴ are the most accurate for determining the rise in PCV following the administration of a specific volume of pRBCs in anemic dogs. Adoption of formula 4, 1.5 mL/kg to raise PCV to 1%, is an easy method for accurately determining the volume of pRBC to administer to anemic dogs when the donor PCV is approximately 60%. Formula 1, 1 mL/kg to raise PCV by 1%, may be more suitable for extremely concentrated pRBC since the PCV can be >80%, while formula 2, 2 mL/kg to raise PCV by 1%, may be more appropriate when the PCV is similar to that of whole blood, around 45%. Further studies are warranted to evaluate these theories. The findings of this study support the application of formulas 3 and 4 for pRBC transfusions for anemic dogs; however, further studies will be needed to determine their application to other populations and to cats, as well as to develop more accurate formulas.

Footnotes

- ^a Animal Blood Bank, Inc, Dixon, CA.
- ^b EDTA lavender top 1.8 mL tube, Victor Medical Co, Irvine, CA.
- ^c Minitab, Inc, State College, PA.

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