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Quantitative assessment of infusion pump-mediated haemolysis in feline packed red blood cell transfusions

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Abstract

Objectives Haemolysis caused by the use of peristaltic infusion pumps (PIPs) has been described in human and canine packed red blood cells (pRBCs). The aim of this study was to evaluate the effects of two different linear PIPs on the haemolysis of feline pRBC units stored for a long time.

Methods Feline pRBC units stored with adenine, dextrose, mannitol and sodium chloride (SAGM) were manufactured. After 35–42 days of storage at 2–4°C, a line administration system with a 180 µm filter was attached to every pRBC bag, the system was drained by gravity alone (8 drops/min) and a 1.3 ml sample was collected (G). A NIKI V4 pump was then used at a flow rate of 25 ml/h, the flow was stopped when the infusion system was filled with blood coming from the infusion pump and another 1.3 ml sample was collected (NK). Finally, an Infusomat FmS pump was evaluated, collecting another 1.3 ml sample (IM). Packed cell volume (PCV) was measured in all samples by microhaematocrit centrifugation, total haemoglobin (HGB) was measured using a specific haemoglobin analyser and, after centrifugation, free HGB was determined by spectrophotometry. The percentage of haemolysis was calculated. Friedman's test was used to compare the samples.

Results Fifteen feline pRBC units were evaluated. The average degree of haemolysis for sample G (gravity-assisted) was 1.12%. Comparison of the degree of gravity-assisted haemolysis with haemolysis in PIP NK (1.13%) and IM (1.14%) samples revealed no significant differences, with differences of only 0.01% and 0.02%, respectively.

Conclusions and relevance The results of this study demonstrate that the use of two common PIPs in veterinary hospitals does not produce levels of haemolysis that are significantly different than that caused by gravity alone during transfusion of feline pRBCs at a rate of 25 ml/h.

Keywords: Transfusion; pRBC; infusion pump; haemolysis; blood; NIKI V4; Infusomat FmS

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Introduction

Transfusion of packed red blood cells (pRBCs) is a common practice in the treatment of feline anaemia. The percentage of haemolysis and serum free haemoglobin (HGB) in pRBCs are markers of RBC integrity that are used as a safety and quality-related characteristic.[1] All units have a baseline haemolysis level, which can increase during administration to a patient, and the use of infusion pumps could potentially contribute to this haemolysis.[2]

Haemolysis leads not only to a functional reduction in HGB, but also to the release into the circulation of cell components such as potassium or free HGB, which have the potential to exacerbate or provoke renal or cardiovascular complications.[1,3,4] Free HGB transfusion to the

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recipient could also be associated with a decrease in nitric oxide, vasoconstriction, hypertension, and contribute to pro-inflammatory and pro-thrombotic states.[3]

pRBCs may be administered by allowing the fluid to flow by gravity through the administration system, or by using infusion pumps. The latter are devices that regulate administration rates by applying positive pressure to the system.[3] In feline medicine, the need for low transfusion rates, particularly in patients at high risk of volume overload, hampers infusion by gravity due to the difficulty associated with calculating and maintaining at a constant rate an adequately slow flow. Because of this, there may be advantages to using positive pressure pumps. Peristaltic infusion pumps (PIPs) are widely used for transfusion of feline pRBCs, but their effects on RBC integrity are unknown.

Haemolysis caused by the use of PIPs has been described with both human and canine pRBCs.[1,3,5,6] The degree of haemolysis depends on factors such as infusion rate, blood haematocrit, preservative solution and administration catheter diameter.[3,4] Increased levels of haemolysis have also been observed when very low or high rates are used, and the storage time of pRBCs may also have a major effect on pump-induced haemolysis.[7,8]

Feline RBCs have haemorheological differences to dog RBCs, including a smaller size and a greater increase of stiffness under hypoxic conditions.[9,10] This loss of elasticity could potentially result in a higher cell fragility and subsequent haemolysis when PIPs are used for transfusion of feline RBCs. The effect of PIPs on feline erythrocytes is unclear, and therefore it is unknown whether their use in the species is safe.

The aim of this study was to evaluate the effects of two widely used linear PIPs on feline RBC integrity by measuring haemolysis biomarkers in units of pRBCs stored for 35–42 days.

Materials and methods

Animals

All donors were indoor healthy cats weighing 4–9 kg that had been vaccinated and dewormed. Complete blood counts and chemistry profiles prior to the collection procedures were within normal reference intervals. No animals were specifically recruited for this study, and all data was obtained from the routine standardised procedures performed at the Animal Blood Bank (Banco de Sangre Animal, Barcelona, Spain). All units included in this study were due to be discarded owing to expired storage life and stock excess. Plasma units were used for clinical purpose. All units of blood were collected after signed informed owner consent. This study was conducted according to European legislation on the Protection of Animals Used for Experimental and Other Scientific Purposes (86/609/EU).

Blood collection and processing

Whole blood units were collected by using a specific feline semi-closed system without leukocyte depletion filters, consisting of a 50 ml syringe attached to a 20 G needle with an extension set and a primary blood bag attached to the syringe with a sterile connector (CompoDock; Fresenius). The collection system was sealed, sterilised with ethylene oxide and 8 ml tri-sodium citrate, sodium phosphate and dextrose (CPD) was added as anticoagulant to the syringe, under sterile conditions using a laminar flow hood (Cruma FL-1; Diantech Solutions).

After a complete physical examination of each donor cat, an intravenous catheter was placed and mild sedation was administered using ketamine and diazepam.[11,12] Once sedated, donors were placed in sternal recumbency, and the puncture area over the jugular vein was clipped of hair and aseptically prepared using chlorhexidine and alcohol. Jugular venepuncture was performed and blood was withdrawn by gently manually pulling the syringe plunger. A maximum of 10 ml/kg (donor weight) was collected.[11] During collection, the syringe was gently agitated to allow proper contact of the blood with the anticoagulant. The collected blood was then transferred to the blood bag through the sterile connection ensuring the maintenance of a closed environment. The tubing was then sealed (Composeal; Fresenius Kabi), units of whole blood were stored at room temperature (20–22°C) and processed into separate units of pRBCs and plasma within 24 h.

Units were gently mixed and placed in centrifuge cups (Megafuge 40R; Thermo Scientific) eliminating void space by using manufactured plastic adaptors. Weight differences <0.3 g between opposite cups were tolerated. Whole blood units were centrifuged at 2000 *g* for 15 mins at 20°C (64.4°F), with 80 s of acceleration and 110 s of deceleration. Plasma was then expressed into a secondary transfer bag by using a sterile connection of polyvinyl chloride tubing (CompoDock; Fresenius). Finally, 10 ml of additive solution of adenine, dextrose, mannitol and sodium chloride (SAGM) was aseptically added to the pRBC units, after one last sterile connection.

The volume of each pRBC unit was calculated on the basis of its weight, considering that 1 ml of pRBCs weighs 1.085 g.[13]

Storage and haemolysis biomarker measurement

After 35–42 days of storage at 2–4°C in a dedicated refrigerator (Medika 250; Fiocchetti), units were allowed to achieve room temperature over 30 mins. A line administration system with a 180 µm filter (Infusomat Space Line; B Braun) was attached to every pRBC bag, the system was drained by gravity (approximately 8 drops/min) and, after discarding the first 3 ml, a sample of 1.3 ml was collected (G). This sample was used to assess the percentage

Table 1 Comparison of indices of haemolysis after administration of feline packed red blood cells by gravity and use of two different peristaltic infusion pumps (NIKI V4 and Infusomat FmS)

	Gravity	NIKI V4		Infusomat FmS	
	Mean ± SD (median)	Mean ± SD (median)	NK – G	Mean ± SD	IM – G
Haemolysis (%)	1.12 ± 0.84 (0.96)	1.13 ± 0.78 (0.92)	0.01	1.14 ± 0.84 (0.85)	0.02
Free haemoglobin (g/dl)	0.336 ± 0.29 (0.26)	0.34 ± 0.29 (0.30)	0.004	0.345 ± 0.31 (0.26)	0.009
Total haemoglobin (g/dl)	15.32 ± 2.13 (15.5)	15.24 ± 2.25 (15.1)		15.38 ± 2.27 (15.6)	
PCV (%)	45.47 ± 7.37 (46)	45.2 ± 7.63 (46)		45.4 ± 7.5 (46)	

No statistically significant differences were observed between the three groups regarding haemolysis ($P = 0.356$), packed cell volume (PCV; $P = 0.380$), total haemoglobin ($P = 0.618$) and free haemoglobin ($P = 0.507$)
NK – G = difference between mean value for NIKI V4 and mean value for gravity; IM – G = difference between mean value for Infusomat FmS and mean value for gravity

of haemolysis and free HGB of the unit without the effect of any PIP.

A NIKI V4 (Everest) infusion pump was then attached to the system and set to deliver 25 ml/h. The authors had previously measured the volume of the line and the flow was stopped when the transfused volume exceeded this volume by at least 3 ml, to ensure that the infusion system was filled only with blood coming from the infusion pump. Subsequently, another sample of 1.3 ml was taken (NK). This sample was used to assess the percentage of haemolysis associated with the NIKI V4 pump. Finally, an Infusomat FmS (B Braun) pump was applied, and the same procedure was performed, taking a third sample of 1.3 ml (IM). This sample was used to assess the percentage of haemolysis associated with the Infusomat FmS pump. The entire process from connection of the line administration system to collection of the final sample was completed within 96 mins.

Packed cell volume (PCV) was measured in all samples by microhaematocrit centrifugation, total HGB was measured using a specific analyser (Hb 201 System; HemoCue) and, after centrifugation, free HGB was determined by spectrophotometry (Plasma Low Hb; HemoCue). The percentage of haemolysis was obtained using the following formula:

$$\%\text{haemolysis} = \text{free HGB (g/l)} \times (100\text{–PCV}) / \text{total HGB (g/l)}$$ [3,4]

As n = 15 (<30), non-parametric tests were chosen, and thus normality of the distribution was not checked. The Friedman test is a non-parametric test suitable for comparing between paired samples, and was used to compare % haemolysis, total HGB, free HGB and PCV of the samples at G, NK and IM in our study. A P value ⩽0.05 was considered to be statistically significant.

Results

Fifteen feline pRBC units were included. Five units were stored for 4 weeks, six units for 5 weeks and four units for 6 weeks.

The mean ± SD haemolysis level in sample G (administration by gravity) was 1.12 ± 0.84%, while mean haemolysis in sample NK and sample IM (the two PIPs) was 1.13 ± 0.78% and 1.14 ± 0.84%, showing an increase of 0.01% and 0.02%, respectively. When comparing the percentage of haemolysis in gravity-administered samples with samples administered by PIP infusion, there were no significant differences between methods.

The mean free HGB level in sample G (administration by gravity) was 0.336 ± 0.29 g/dl, while mean free HGB in sample NK and sample IM (the two PIPs) was 0.340 ± 0.29 g/dl and 0.345 ± 0.31 g/dl, showing an increase of 0.004 g/dl and 0.0087 g/dl, respectively. When comparing free HGB in gravity-administered samples with samples that were administered by PIP infusion, there were no significant differences between methods.

The mean total HGB and PCV levels in sample G (administration by gravity) was 15.32 ± 2.13 g/dl and 45.47 ± 7.37%, respectively, while mean total haemoglobin in sample NK and sample IM (the two PIPs) was 15.24 ± 2.25 g/dl and 15.38 ± 2.27 g/dl, and mean PCV was 45.20 ± 7.63% and 45.40 ± 7.5%, respectively. When comparing the mean total HGB and PCV levels in gravity-administered samples with samples that were administered by PIP infusion, there were no significant differences between methods. In 6/15 units (40%), levels of haemolysis after gravity-assisted administration were higher than 1%, reaching a maximum level of 3.3% in one unit. From these six units that had more than 1% basal haemolysis level, four had been stored for 6 weeks, one for 5 weeks and one for 4 weeks. All results are shown in Table 1.

Discussion

This study investigated RBC damage produced during simulated feline pRBC transfusion using two different PIPs vs gravity-assisted administration. PIPs can be classified based on their pump mechanisms (eg, linear peristaltic, rotary peristaltic, reciprocating piston or piston-actuated diaphragm pumps). There is no consensus on the type of pump that induces less RBC damage. Some

authors state that linear peristaltic pumps might be the most susceptible to producing haemolysis, although, in practice, they remain the most commonly used pumps.[3,5] Linear PIPs have been found to increase the free HGB concentration (a marker of RBC damage) in human pRBCs, possibly due to direct compression of erythrocytes within the intravenous tube.[14,15] Two widely used linear PIPs in veterinary medicine were chosen for this study, the NIKI V4 and Infusomat FmS.

Multiple biomarkers of RBC damage have been described in human and veterinary transfusion medicine research, including free HGB, percentage haemolysis, band-3 protein, CD47 and phosphatidylserine exposure, potassium, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase concentrations, micro-vesicle release, osmotic fragility and changes in RBC morphology.[3,16,17] Free haemoglobin and haemolysis were analysed in the present study because they are considered good markers of RBC integrity and are widely used in human research. Free HGB is the biomarker most present in human publications investigating the relationship between infusion pumps and RBC damage in transfusion, and percent haemolysis is considered to be the standard in human medicine and is used as a marker for failure of RBC processing or administration techniques.[3,18] Potassium concentrations are another widely used biomarker of RBC damage, but their use is not recommended when aged pRBCs are tested, as in our study.[6]

A clinical situation with potential maximum risk for haemolysis was simulated by selecting pRBC units that were near or at the end of their recommended storage life (35–42 days). During storage, blood cells continue to exhibit metabolic activity. When adenosine triphosphate reserves decrease, metabolic activity begins to fail, membrane elasticity is reduced and morphological changes occur, predisposing to increased cell fragility.[3,4,19] Additionally, for ethical reasons, units nearing or at expiration dates were used, and only when a high number of units were available.

In addition, there are different studies in which, using a PIP, a higher degree of haemolysis was observed at low velocities such as those used in cats.[5,14,19] Exposure time and stress levels are the two main parameters that determine the degree of RBC damage due to shear stress, which can result in haemolysis and fragmentation of erythrocytes.[20] At lower flow rates, exposure time to mechanical shear force increases, and this may induce higher levels of RBC haemolysis.[5] Veterinary textbooks recommend transfusion rates of 2–10 ml/kg, and a maximum rate of 10–20 ml/kg/h, to avoid circulatory overload.[21,22] In a previous study, rates of approximately 10 ml/kg/h for normovolaemic cats showed no complications attributable to the rates used.[23] A flow rate of 25 ml/h was chosen in this study to cover those of common feline transfusions, matching calculated rates for cats weighing 2.5 kg at 10 ml/kg or 5 kg at 5 ml/kg.

Although mean increases of free HGB in the range of 0.004 and 0.0087 g/dl were observed when using NIKI V4 and Infusomat FMS PIPs, respectively, the differences were considered non-significant when compared with administration by gravity. These results are similar to a previously published study using human pRBCs, in which a mean increase in free HGB of 0.006 g/dl was observed when using different types of PIP.[14] In human medicine, an increase of <0.06 g/dl of free HGB is considered not to be clinically significant.[5]

In another study conducted with human erythrocytes administered at 30 ml/h, median increases in the percentage of haemolysis of 0.016% (shuttle pump), 0.026% (piston pump) and 0.241% (PIP Infusomat-Space) were described.[1] Our results (0.017% [NIKI V4] and 0.022% [Infusomat-FMS]) were comparable to those reported in the previous human study with non-peristaltic pumps, but were associated with far less haemolysis than that associated with the use of the PIP Infusomat-Space in human erythrocytes. This difference could be explained by the fact that an anti-siphon valve was applied when testing the PIP Infusomat-Space in the human study, or by other variables such as morphological and metabolic variability between species, pre-transfusion blood storage times or dissimilar unit PCV. Another study performed in human pRBCs that tested two different linear PIPs at 100 ml/h and 300 ml/h infusion rates found that there was a mean haemolysis increase of 0.08% at 100 ml/h.[6] No anti-siphon valve was used in this second study, but infusion was performed at higher speeds than in our study.

In veterinary medicine there has only been one study performed with canine whole blood using free HGB alone as a biomarker and comparing three types of PIP. Free HGB increases of 7% to 228% were observed, depending on the pump type used.[19] In our study, a mean free HGB increase of 1.19% was detected when using the NIKI V4 and 2.68% when using the Infusomat-FMS pump. To our knowledge, the only published comparable study in feline medicine used syringe infusion pumps and autologous whole blood, and tested post-transfusion survival of RBCs in the recipient, but not erythrocyte damage or haemolysis.[24]

Six of 15 units in this study had haemolysis levels that were higher than the US Food and Drug Administration (FDA) human medicine 'recommended limit' of 1%, even when administered by gravity.[25] A previous study reported that 13.88% and 19.49% of feline pRBC units have >1% haemolysis levels after 28–35 and 35–42 days of storage, respectively.[4] In our study the percentage of units with over 1% haemolysis was higher than previously reported, with 40% of the units (n = 6/15) surpassing the recommended limit. For our study, the initial degree of haemolysis was not considered to be an exclusion criterion. This higher proportion of haemolysed units was probably due to the differences in storage durations between the units tested. Four of the six units with >1%

haemolysis had been stored for 6 weeks, the maximum currently accepted time limit for storage. We cannot rule out a contributing effect of the filter and infusion system used on haemolysis levels, although in human medicine, needle gauge, tubing length and tubing diameter appear to have no effect on haemolysis.[26]

Although the FDA-recommended haemolysis limit is 1% in human transfusion medicine, it has been reported that much higher levels of haemolysis can be tolerated by humans without apparent untoward effects.[27,28] The pathophysiological effects of exposure to such levels of free HGB in feline patients have not been evaluated. In one study performed in healthy dogs, kidney injury was reported when an infusion of 4 g/kg of canine HGB was administered.[29] To administer the same quantity of free HGB to a cat, and considering the mean PCV and total HGB of the present study, a unit with 7.12% of haemolysis (and 2 g/dl free HGB) would have to be administered at a dosage of 20 ml/kg.[29]

This study had some limitations that are inherent to an in vitro investigation. We studied laboratory markers of haemolysis which, while considered to be good markers of erythrocyte damage, might not be representative of post-transfusion in vivo erythrocyte circulating half-life. Additional in vivo studies are warranted. Another limitation was the fact that only units that had been stored for a long duration were investigated. Old units may have the highest risk of shear stress haemolysis due to a lower viscosity and loss of membrane integrity. Multiple articles performed in human pRBCs, however, show no difference in pump-induced haemolysis between units stored for short or long periods.[1,30] The impact of duration of storage has not been yet demonstrated in feline pRBCs.

Regarding the study design, a crossover study including different groups with different PIP order would have been preferable. In our study, the IM pump was always evaluated last, and this could have affected the results owing to different times of exposure to non-refrigerated temperatures before transfusion. The longer blood sits at room temperature, the higher the risk of increasing haemolysis levels.[31] To avoid different total exposure time to room temperature, samples from each pRBC unit were held until all were collected and tested at the same time. In our study, no statistical difference was noted between methods, and thus it is unlikely that this lack of crossover would have had a significant effect over the results. Another limitation was that no power analysis was performed, and as such the study may be underpowered to detect a difference. Therefore, a failure to detect statistically significant differences in this study does not necessarily imply that there is no difference. A minor limitation was that no basal sample was collected before blood was passed through the infusion set, so the full transfusion process could have also been studied, including the effect of the infusion system, but this was not the objective of this study. The study was designed to evaluate the effect of the infusion pumps on RBCs and not the effect of the infusion set and filter.

Conclusions

Our study has demonstrated that the level of haemolysis of pRBC units caused by the use of two different linear PIPs (Infusomat FmS [B Braun] and NIKI V4 [Everest]) at a rate of 25 ml/h, after 35–42 days of storage at 4°C, is not significantly different than that seen with gravity infusion.

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Ethical approval This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not specifically required for publication in *JFMS*.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken (either prospective or retrospective studies). No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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