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Multiple red cell transfusions in 27 cats (2003–2006): indications, complications and outcomes

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The objectives of this study were (1) to evaluate the indications, complications and outcomes of multiple red cell transfusions (MrcTs) in cats; of these cats (2) to describe those that received massive transfusion and (3) compare them with those who received MrcTs over a longer time course. Twenty-seven cats were identified which received a total of 110 transfusions, with a median of three transfusions (range 3–15) per cat. The transfusions consisted of 47 units of whole blood and 63 units of packed red blood cells. The median age of cats was 6 years (range 6 months to 15 years). Cats were hospitalized for a median of 6 days, with a range of 1–38 days. No acute transfusion reactions were documented, although due to the critical nature of the cats, they may not have been appreciated. Sixteen cats survived to discharge and 11 died or were euthanased. Indications (and % survival) for transfusions included bone marrow failure ($n = 8$; 50%); surgical loss ($n = 4$; 100%), sepsis ($n = 3$; 0%), neoplasia ($n = 3$; 33%), acute renal failure ($n = 3$; 66%), trauma ($n = 2$; 100%), gastrointestinal bleeding ($n = 1$; 100%), and cats with multiple disease processes ($n = 3$; 33%). MrcTs are well-tolerated in cats and may be associated with a favorable outcome.

Feline critical care in general, and transfusion medicine in particular, has been advancing over the last 20 years (Giger 1992, Griot-Wenk et al 1996, Castellanos et al 2004, Weingart et al 2004, Klaser et al 2005). Blood transfusions may be administered either as whole blood (WB) or as components including packed red blood cells (pRBCs) and fresh frozen plasma (FFP). Feline blood collection is widely considered more challenging than blood collection from dogs. Almost all feline donors require sedation to collect blood and the volume collected from each donor is typically 45–60 ml in total. Thus, feline blood is often at a premium and great care is taken to promote responsible use of blood products at times including the avoidance of transfusions to cats with a particularly grave prognosis. Hemoglobin-based oxygen carrier (HBOC) (Oxyglobin) has been used for this reason in an off-label fashion in some cats (Gibson et al 2002). However, Oxyglobin is expensive, has a short duration of effect, and commercial availability of this product has been intermittent in recent years.

One particular challenge in feline critical care is the individual cat that has catastrophic blood loss or hemolysis, occasionally in conjunction with inadequate erythropoiesis, which appears to require multiple transfusions in order to survive. This scenario is challenging due to the strain placed upon the blood bank by multiple transfusions and the possibility of lengthy period of depletion of red blood cells available for transfusion to other cats. In people, a specific term, massive transfusion (MT), has been coined to describe patients who receive either an entire blood volume (90 ml/kg) within 24 h, or one-half of a blood volume (45 ml/kg) within 3 h (Crosson 1996). This term has also been applied to dogs.

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In one retrospective study in dogs, four of 15 dogs treated with MT survived to discharge (Jutkowitz et al 2002). MT has not been reported in cats. However, in critically anemic cats, survival without multiple transfusions is unlikely. The goals of this study were (1) to evaluate the indications, complications and outcome of multiple red cell transfusions (MrcTs) in cats, of these cats (2) to describe those that received MT and (3) compare them with those who received MrcTs over a longer time course.

Material and methods

The blood transfusion log of Cummings School of Veterinary Medicine was searched for feline cases that had received MrcTs between February 2003 and May 2006. An MrcT was defined as three or more transfusions with pRBC, fresh WB or stored WB during a single stay at the hospital. An MT was defined as a transfusion with 60 ml/kg or greater over 24 h, or of 30 ml/kg over 3 h. This lower range was considered more appropriate for cats because their blood volume is significantly less than dogs and humans, ie, 60 ml/kg compared to 90 ml/kg (Mott 1968). An MT could consist of WB, pRBC and additionally plasma. A unit for transfusion of WB contained 50−60 ml of total volume, while a pRBC transfusion contained 20−25 ml. Signalment, blood type, retroviral status (if available), indications for transfusion and complications associated with the transfusion and outcome were recorded. Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) status were determined by enzyme-linked immunosorbent assay (ELISA) technology screening for FeLV antigen p27 and FIV antibodies (Idexx Snap FIV/FeLV test). Outcome was defined as survival to hospital discharge or death/euthanasia. Packed cell volume (PCV) values were measured with microhematocrit tubes in all cats. The decision to undertake a transfusion was made at the discretion of the clinician and not based on a cut-off PCV value. To evaluate the effect of MrcT on the PCV values, the PCV values before the first transfusion and after the last transfusion were compared. Ionized calcium (iCa) was measured by a critical care analyzer (NOVA Stat Profile Critical Care Xpress, Waltham, MA). The iCa reference range of this analyzer is 1.17−1.38 mmol/l, regardless of age. Hypocalcemia was considered as clinically relevant for iCa < 0.9 mmol/l and severe hypocalcemia was referred as iCa < 0.7 mmol/l as previously described (Jutkowitz et al 2002).

Transfusion with plasma or HBOC was additionally recorded, but did not contribute to the MrcT count. Descriptive statistics were used to evaluate the recipients as appropriate while χ^2 analysis was used to evaluate differences between survivors and non-survivors. The χ^2 test with Yates' correction was used for expected frequencies less than five. A paired Student's t-test was used to compare mean PCV before and after MrcT. Student's t-test was used to compare mean PCV values between survivors and non-survivors. Values of $P < 0.05$ were considered significant.

Results

Twenty-seven cats that met criteria were identified for study inclusion. These 27 cats received a total of 110 transfusions, with a median of three transfusions and a range of 3−15 transfusions. The transfusions consisted of 47 units of fresh or stored WB and 63 units of pRBC. During this study time, a total of 386 cats received a total of 568 pRBC or WB transfusions. Thus, the study group represents 7% of the transfused cats, which received 19% of the total red cell transfusions administered during the study period.

Twelve cats included in the study received plasma transfusion; nine cats received one unit of plasma, two cats received two units and one cat received three units. Thus 16 units of plasma were additionally transfused to the 27 cats within this study. Plasma was administered as therapy for either clinical or laboratory evidence of a coagulopathy. Five cats also received HBOC solutions, two of the five cats received two transfusions of HBOC, and the three others received only one. The median transfused volume of Oxyglobin was 10 ml per cat (range 8−30 ml).

The affected cats (Table 1) included 12 spayed females and 15 castrated males. The median age was 6 years with a range of 6 months to 15 years. Twenty-two cats were domestic short- or longhair, while four were purebreds. All cats were type A and all 22 cats tested for both FeLV and FIV were negative.

Data regarding the PCV were available in 24 cats. The mean PCV before the first transfusion was $12.8 \pm 4.2\%$ (median 13%, range 4−20%). The mean PCV after the last transfusion was significantly ($P < 0.01$) increased at $17.0 \pm 6.4\%$ (median 18%, range 4.8−33%). The mean increase in PCV following transfusion was not associated with survival.

Cats were hospitalized for a median of 6 days, with a range of 1−38 days. Sixteen cats (59%)

Table 1. The signalment and blood type of 27 cats and the number of transfusions received, indications for transfusion, category length of hospitalization and outcome in 27 cats with multiple red blood cell transfusions

Cat #	Breed	Sex	Age (years)	Blood type	Number of transfusions	Indication	Category	Length (days) of hospitalization	Status at discharge
1	DSH	CM	13	A	3	Bone marrow disease and brain tumor	Erythropoietic failure	6	Dead
2	DSH	SF	9	A	3	Hematemesis/pulmonary hemorrhage	Unknown/multiple	4	Alive
3	Himalayan	CM	10	A	3	Hemoabdomen due to hemangiosarcoma	Neoplasia	4	Alive
4	DLH	SF	2	A	3.5	Bone marrow aplasia	Erythropoietic failure	5	Dead
5	DSH	CM	1	A	6	Bone marrow aplasia	Erythropoietic failure	10	Alive
6	Siamese	SF	11	A	5	Inflammatory bowel disease	Gastrointestinal bleeding	7	Alive
7	DSH	SF	1	A	3	Acute renal failure from lily toxicity	Renal failure	5	Dead
8	DLH	SF	6	A	4	Acute renal failure from lily toxicity	Renal failure	13	Alive
9	DSH	CM	14	A	3	Chronic renal failure with bone marrow failure	Erythropoietic failure	5	Alive
10	DSH	CM	2	A	3	Acute renal failure, urethroliths	Renal failure	13	Alive
11	DSH	SF	10	A	6	Postoperative biliary surgery	SL	6	Alive
12	DSH	SF	4	A	4.5	Postoperative renal surgery	SL	8	Alive
13	DSH	SF	8 Months	A	15	Azathioprine toxicity	Erythropoietic failure	38	Dead
14	DSH	SF	8 Months	A	3.5	Azathioprine toxicity	Erythropoietic failure	16	Alive
15	British SH	CM	15	A	3	Postoperative thymoma	SL	8	Alive
16	DLH	CM	8	A	3	Postoperative biliary surgery	SL	9	Alive
17	DSH	CM	8 Months	A	3.5	Bone marrow aplasia	Erythropoietic failure	5	Alive
18	DSH	SF	2	A	6	Severe bite wounds/sepsis	Surgical loss	1	Dead
19	DSH	CM	8	A	3	Hit by car (HBC) trauma − liver hemorrhage	Trauma	12	Lived
20	DSH	CM	14	A	3	Bone marrow aplasia	Erythropoietic failure	1	Died
21	DSH	CM	9	A	3	Hematemesis due to gastric ulceration, chronic bone marrow disease	Unknown/multiple	5	Died
22	Maine Coon	CM	8	A	3	Hemangiosarcoma	Neoplasia	6	Lived
23	DSH	SF	6 Months	A	4	Pelvic fracture (polytrauma)	Trauma	11	Lived
24	DSH	CM	6	A	3	Septic abdomen	Surgical loss	17	Died
25	DLH	CM	6	A	3	Lymphoma	Neoplasia	4	Died
26	DSH	CM	8	A	3	Lymphoma with splenic rupture	Neoplasia	2	Died
27	DSH	SF	1	A	4	Severe bite wounds/sepsis	Surgical loss	8	Died

DSH = domestic shorthair, DLH = domestic longhair, CM = castrated male, and SF = spayed female. The categories were defined as erythropoietic failure ($n = 8$), neoplasia ($n = 4$), sepsis ($n = 3$), trauma ($n = 2$), renal failure ($n = 3$), surgical loss ($n = 4$), unknown/multiple ($n = 2$), and gastrointestinal bleeding ($n = 1$).

survived to discharge while 11 cats (41%) were non-survivors of which two died and nine were euthanased. It appeared from review of the medical records that in all cases the decision for euthanasia was based upon a perceived grave prognosis, not for financial concerns associated with treatment. MrcTs were administered over a median of 60 h, with a range of 2 h to 15 days. If transfusions were occurring over more than a 5-day period, blood was crossmatched before transfusion. In one case (cat 13), HBOC was given, as none of the blood units in the hospital were compatible with the recipient's blood.

The indications for transfusion included erythropoietic failure ($n = 8$), surgical blood loss ($n = 4$), sepsis ($n = 3$), neoplasia ($n = 4$), acute renal failure ($n = 3$), trauma ($n = 2$), gastrointestinal bleeding ($n = 1$), and multiple disease processes/sources of blood loss ($n = 2$).

Survival varied between the underlying causes necessitating the transfusion. All seven cats with surgical loss, traumatic loss and gastrointestinal-associated loss survived, while all three cats with sepsis died. Two of the three cats with renal failure survived, while four of the eight cats with erythropoietic failure survived. Two of four cats with neoplasia survived and one of the two cats with multiple processes survived. The number of units transfused and the length of stay in the hospital were not different between the survivors and the non-survivors. Using 8 years of age as a cut-off, there was no difference in outcome between younger cats ($n = 14$) and older cats ($n = 13$).

Of the 27 cats, three cats (cat-11, -18, and -21; see Table 1) met the criteria for MT receiving either 60 ml/kg within 24 h or 30 ml/kg within 3 h. The first cat (2.5 kg) received six transfusions within 3 h consisting of four units of pRBC and two units of frozen plasma for perioperative bleeding reason (classified in the surgical loss category). The second cat (4 kg) received seven transfusions within 24 h consisting of four units of pRBC, two units of WB and one unit of FFP for ongoing sepsis due to severe bite wounds (classified into sepsis category). The third cat (2.2 kg) received four transfusions within 24 h consisting of two units of pRBC, one unit of WB and one unit of FFP for multiple chronic ongoing disease (classified into unknown category). The first cat survived, the second cat died and the third cat was euthanased. No significant difference was detected between survivors and non-survivors in the group receiving MrcT vs MT.

No acute transfusion reactions were recorded in cats receiving MrcT, although given the dynamic condition of most cats; subtle reactions might have not been recorded. Additionally, fever may have been masked due to the influence of general anesthesia and surgery. One of the 27 cats developed signs of fluid overload as evidenced by auscultation of moist crackles and radiographic evidence of left atrial enlargement and pulmonary edema. In this cat, the transfusion had been stopped. Four cats developed hypocalcemia (iCa < 0.90 mmol/l), but none of the cats became severely hypocalcemic (iCa < 0.70 mmol/l). Among cats receiving MT, two developed hypocalcemia, this was not significantly higher than the MrcT group. In the MT group, one cat with hypocalcemia died whereas the other lived. Thus, no correlation was found with survival and the presence of hypocalcemia in this group. At least one plasma transfusion was administered to all cats in the MT group but only to nine of the 24 cats in the MrcT group, however, this difference was not significant. No other electrolyte abnormalities attributed to transfusions were documented.

Discussion

The results of this retrospective study support the idea that aggressive transfusion practices may be warranted in cats with severe anemia. The overall survival rate of 16/27 (59%) is similar to the survival rates previously published for the overall population of transfused cats and higher than those cats transfused with Oxyglobin (Castellanos et al 2004, Weingart et al 2004, Klaser et al 2005). However, the underlying disease process is almost certainly also related to the individual cat's prognosis. In this study, cats with massive blood loss whether surgical or trauma related had an excellent chance of survival while the three cats with severe sepsis died. Sepsis in cats in particular is challenging to both identify and to treat (Brady et al 2000).

No prognostic factors based upon age or biochemical abnormalities were identified in this study. However, the survival rates varied based upon the underlying indication for the transfusions, although due to sample size, these were not significant. In this small study, cats with acute, controllable loss such as perioperative blood loss or trauma did very well while cats with severe sepsis died. Thus, decisions to undertake multiple transfusions should be made in light of the underlying disease.

Multiple feline transfusions represent a significant drain upon a blood bank's resources, as well as substantial financial commitment. Twenty-seven cats in this study received almost 20% of the units of WB and pRBC in the study period. Thus, the decision to undertake MrcT should not be undertaken lightly, as feline blood products remain limited. It is possible that cats in this study would have responded as well or better to transfusion with HBOC. Our critical care service typically prefers WB and blood components to HBOC, primarily reflecting the general ready availability of blood products, the potential fear of volume overload due to the colloidal nature of HBOC, and the longer half-life of blood products (Chan et al 2001).

Of interest, evidence of major transfusion reactions was not detected in any cats in this study and minor complications concerned only four cats. This may reflect the critical condition of the cats, where subtle changes in heart rate or respiratory rate, or even vomiting, may not clearly be related to the transfusion and thus were not specifically noted in the medical record. It is possible that some cats experienced subtle transfusion reactions. No cat developed new icterus or evidence of hemolysis. It was impossible to determine shortened red cell survival due to the dynamic nature of the cats' disease.

In this study, three of the 27 cats met the criteria for MT. This is, to the best of our knowledge, the first report of MT in cats. The aim of MT is a rapid and effective restoration of an adequate blood volume maintaining blood composition within safe limits. While stored blood is a biocompatible product, it is not a physiological product: temperature of conservation is $4°C$, platelets are lost within 4 h, factors V and VIII are lost within 24 h, it contains an anticoagulant solution and there are some biochemical and morphological alterations (Rehak and Chiang 1988). Thus, MT is associated with numerous disturbances in people and in dogs such as hypocalcemia, hypomagnesemia, hyperkalemia or hypokalemia, acid/base disturbances, hypothermia, thrombocytopenia, coagulation factor depletion, etc. Hypocalcemia is a classic disorder after MT and citrate-related hypocalcemia is a well-described complication of MT (Rudolph and Boyd 1990). In a healthy adult, body stores of calcium are large and citrate is quickly metabolized by the liver following transfusion. In cases of MT or MrcT, rapid administration of citrate can lead to hypocalcemia especially in patients with severe liver disease, hypothermia or circulatory collapse

leading to inadequate hepatic blood flow. In a study in 471 human patients receiving MT, iCa concentrations were below normal (range 1.13−1.32 mmol/l) in 94% of patients and were very low (<0.70 mmol/l) in 46% (Wilson et al 1992). The mortality rate with severe hypocalcemia was 71 % (vs 40% in patients with more normal values) (Wilson et al 1992). In the only veterinary study describing MT in 15 dogs (Jutkowitz et al 2002), iCa concentrations before and after transfusion were available for 10 dogs. In these dogs, mean iCa concentration prior to transfusion $(1.17 \pm 0.14$ mmol/l) was significantly $(P < 0.005)$ higher than mean concentration after transfusion $(0.89 \pm 0.19$ mmol/l). iCa concentration was below the reference range following MT in all 10 dogs and was extremely low (<0.70 mmol/l) in two of these dogs. It is unknown if dogs with severe hypocalcemia following MT are more likely to die. In our study, it was difficult to conclude if severe hypocalcaemia in MT was a poor prognosis factor as only three cats met the criteria for MT. However, it seems that MT is most likely to lead to hypocalcemia (67% of the cats in this group) whereas in the MrcT group only 8% of cats developed hypocalcemia. In this study, probably due to the fact that more cats received MrcT $(n = 24)$ than MT $(n = 3)$, no other electrolytes' abnormalities that could be attributed to MT were noticed.

Coagulation abnormalities related to multiple administration of blood products were not documented in any cats. Of the 12 cats, which received a plasma transfusion, coagulopathy was present before transfusion or related to the ongoing disease or surgical misadventure rather than attributed directly to the transfusion. However, all cats that met the criteria for MT received at least one transfusion of plasma with or without evidence of coagulopathy. In people, the administration of one to two units of plasma for every five units of red blood cells has been recommended (Hellstern and Haubelt 2002). Other publications recommend the use of plasma or platelet concentrates based on coagulation parameters and clinical condition of the patient (Hardy et al 2006).

Limitations of this study include the retrospective nature of the study and the small number of cats reported. Blood was transfused based upon the attending clinician's discretion, thus cats may have received more blood than needed or cats that may have been successfully treated with MrcT were sub-optimally transfused and did not survive. Human studies evaluating

blood transfusion practices in emergency settings have frequently concluded that standardized protocols will improve the outcome due to improved resource allocation and prevention of coagulopathy (Malone et al 2006). The ultimate application of MrcT to animals remains to be determined.

Acknowledgments

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