Use of a hemoglobin-based oxygen-carrying solution in cats: 72 cases (1998–2000)

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Objective—To determine clinical features and outcome associated with use of a hemoglobin-based oxygen-carrying (HBOC) solution in cats.

Design—Retrospective study.

Animals—72 cats.

Procedure—Medical records of cats that received an HBOC solution were reviewed.

Results—The most common clinical signs and physical examination findings prior to infusion of the HBOC solution were associated with anemia; vomiting, neurologic signs, and respiratory abnormalities were also detected. The HBOC solution was given as a supportive measure in treatment of anemia in 70 cats, most often because compatible blood was not readily available. There were 80 separate HBOC solution infusion events (mean dose, 14.6 ml/kg [6.6 mg/lb]; mean rate of infusion, 4.8 ml/kg [2.2 ml/lb] per hour). Improvements in 37 of 43 of the more closely monitored cats included increased rectal temperature, blood hemoglobin concentration, blood pressure, appetite, and activity. Adverse events in 44 cats included pulmonary edema (n = 8), pleural effusion (21), mucous membrane discoloration (21), pigmenturia (11), vomiting (4), and neurologic abnormalities (4). Twenty-three cats were discharged from the hospital, and 49 cats died or were euthanatized. Necropsy examination of 23 cats did not reveal evidence of renal or hepatic toxicosis associated with HBOC administration.

Conclusions and Clinical Relevance—Although administration of an HBOC solution may provide temporary support to anemic cats, the development of pulmonary edema or pleural effusion potentially associated with rapid infusion rate and large volume of infusion of the HBOC solution should be investigated further before use of the solution can be recommended in cats. (*J Am Vet Med Assoc* 2002;221:96–102)

There has been an increase in the use of blood products during the past decade, and the demand for blood products for use in cats is much greater than the supply. Most veterinarians obtain blood from in-hospital donors or client-owned pets at the time of need or purchase blood products from the few commercially available sources. Donors are limited, and most cats donate small volumes (35 to 50 ml) of blood every 4 weeks at maximum. The direct cost associated with maintaining and health-screening in-hospital donors is likely not recovered, considering the price charged for each blood unit to the owner. Furthermore, there are some risks to the donor associated with adverse reactions to sedation and the potential development of hypovolemic shock following donation. Risks to the recipient include transmission of infectious diseases and transfusion reactions. The AB blood-type compatibility issues are of major concern because of naturally occurring alloantibodies that require typing of donor and recipient blood. Because of the small amount of blood collected from each cat and the lack of commercially available closed blood collection systems for small blood volumes, feline blood component preparation is uncommon and has been limited to a few commercial veterinary blood banks, teaching hospitals, and large veterinary centers. The use of an RBC substitute in cats could be life saving when compatible RBC are not immediately available for transfusion.

In 1998, the FDA approved a **hemoglobin-based oxygen-carrying (HBOC)**[a] solution for use in anemic dogs. The HBOC solution is an ultrapurified, polymerized bovine **hemoglobin (Hb)** solution that is free of RBC stroma and membranes and contains 13 g of Hb/dl in a modified lactated Ringer's solution. Because it is a cell-membrane-free solution distributed in the plasma, there is no barrier to diffusion of oxygen. The solution improves rheologic variables and effectively delivers oxygen to tissues. In addition to its documented clinical efficacy in dogs with anemia caused by hemorrhage, hemolysis, or ineffective erythropoiesis, HBOC solutions have been used in an anemic miniature horse with ovarian hemorrhage, which allowed surgical correction,[1] and for support for a foal with neonatal isoerythrolysis.[2] The HBOC solution has been experimentally used in various animal species and provides temporary support in models of hemorrhagic shock in dogs[3] and pigs,[4] isovolemic hemodilution in dogs,[5] and total exchange transfusion in sheep.[6] Although limited experimental studies have assessed the safety of this HBOC solution in cats,[7] there have been few anecdotal case reports of its clinical use in cats.[8,9] Since FDA approval was obtained for dogs, the HBOC solution has been administered to cats at the **Veterinary Hospital of the University of Pennsylvania (VHUP)** under off-label use with owner consent. The purpose of this retrospective study was to determine clinical features and outcome associated with use of the HBOC solution in cats.

Criteria for Selection of Cases

The medical records and pharmacy databases at VHUP were searched for records of cats that had received the HBOC solution between June 1998 and December 2000.

Procedures

The following information was retrieved when available: signalment, medical history, physical examination findings, clinical signs, treatment, reason for

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The authors thank Dr. Frances S. Shofer for assistance with statistical analysis.

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administration of the HBOC solution, response to infusion, adverse events, and patient outcome. For cats that were anemic, the major cause of anemia was classified as hemolysis, hemorrhage, ineffective erythropoiesis, or unclassified (if there was not enough recorded information to determine the cause).

Data used to evaluate an effect of the HBOC solution were pre- and postinfusion whole blood Hb concentration [Hb], body temperature, heart and respiratory rates, and appetite or activity. The period of evaluation determined to include the greatest number of cats was within 5 hours preceding to 24 hours following the initiation of the HBOC infusion. Preinfusion [Hb] was obtained from results of CBC performed by use of an automated hematology analyzer[b] or a Hb point-of-care instrument,[10,c,d] or estimated to be a third of the preinfusion PCV.[11] The postinfusion [Hb] was obtained from the Hb point-of-care instrument[c] or results of CBC. The dose of the HBOC solution per infusion and rate of administration were recorded, and the total dose of HBOC solution infused per cat was calculated. If a cat received > 1 dose of HBOC solution > 24 hours apart, the administrations were evaluated as separate infusion events.[12] Any blood transfusions that were administered were also recorded. An attempt was made to determine the reason for using the HBOC solution rather than feline blood or **packed RBC (PRBC)** in each case. Preinfusion temperature, pulse rate, and respiration rate were recorded from the medical record by use of the vital signs measured closest but not > 5 hours prior to infusion of the HBOC solution. The first measurements after infusion were recorded and, if possible, were obtained at the same time as the postinfusion PCV and [Hb] measurements. Immediate outcome was evaluated to determine how many cats had a positive response to receiving the HBOC solution. A positive response was defined as an increase in whole blood [Hb], an increase in temperature of > 0.5 C (1.0 F) from an initial temperature of < 37.8 C (100.0 F), return of heart rate or blood pressure to reference ranges, or an improvement in appetite or attitude. Any adverse events that were possibly associated with infusion of the HBOC solution were noted. The cause of death and reason for euthanasia were sought, and necropsy findings were reviewed.

Statistical analyses—Data were summarized via mean ± SD, median, and range for continuous variables (eg, PCV, [Hb]), and frequency and percentages for categoric data (eg, breed, sex). Paired *t* tests were used to compare parameters before and after infusion of the HBOC solution. The Student *t* test was used to compare pulmonary edema or pleural effusion to the rate of administration and dose of HBOC solution. All analyses were performed by use of commercial software[e]; P values < 0.05 were considered significant.

Results

Signalment—A search of the medical records identified 72 cats that had received the HBOC solution between June 1998 and December 2000. There were 63 domestic shorthair cats, 3 domestic longhair cats, 2 Siamese, and 1 Persian, Maine Coon, Abyssinian, and Birman cat. There were 34 female cats (29 neutered and 5 sexually intact) and 38 male cats (32 neutered and 6 sexually intact). Age ranged from 0.3 to 18 years with a mean of 8.0 ± 5.0 years (median, 7.4 years; n = 72). Body weight range was 0.6 to 8.2 kg (1.3 to 18.1 lb; mean, 4.3 ± 1.7 kg [9.5 ± 3.7 lb]; median, 4.2 kg [9.2 lb; n = 70]). Body condition, as subjectively rated on the initial examination, was cachectic (n = 10), underweight (25), normal (21), overweight (10), or obese (4); body weight and condition were not recorded in 2 cats. Fifty-three cats were strictly housed indoors, 12 were indoor-outdoor cats, 3 always stayed outdoors, and in 4 cats the living situation was not recorded.

Clinical signs—The most common signs at initial evaluation were decreased appetite or anorexia (n = 38) and signs of depression or lethargy (29). Weakness (n = 16), vomiting (15), weight loss (14), respiratory distress or increased respiratory effort (14), gastrointestinal tract hemorrhage (3), and ataxia (2) were also reported. Seventeen cats were referred to VHUP because of anemia that required RBC transfusion, and 3 cats were referred for renal transplantation. Other listed complaints included FeLV-associated anemia, aortic thromboembolism, ischemia of the distal portion of a limb (splint complication), and icterus.

Physical examination—The most common initial physical examination findings were consistent with anemia and included white or pale pink mucous membranes (n = 49), icteric mucous membranes (8), poor or weak femoral pulses (16), bounding or snappy femoral pulses (2), hypothermia (29), heart murmur (17), gallop rhythm (8), and tachycardia (heart rate > 220 beats/min; 6). Respiratory system abnormalities were reported in 39 cats and included increased respiratory rate (> 32 breaths/min; n = 34), increased respiratory effort or respiratory distress (20), muffled lung sounds (6), pulmonary crackles (4), increased bronchovesicular sounds (4), stridor (2), and respiratory arrest (2). Many cats were described as mentally dull and having signs of depression (n = 16), unresponsive (12), or weak or recumbent (10). Other physical examination findings included a palpable abdominal mass (n = 9), bradycardia (< 130 beats/min; 7), hepatomegaly (4), and splenomegaly, absence of femoral pulses, and distal limb necrosis (1 cat each).

Administration of HBOC solution—Except for 2 cats, all were given the HBOC solution as a supportive measure in the treatment of anemia. The predominant cause of anemia was hemorrhage (n = 29) followed by ineffective erythropoiesis (24) and hemolysis (11). The cause of anemia could not be determined in 6 cats. One cat received the HBOC solution in an attempt to augment tissue oxygenation in an ischemic limb, and another cat with aortic thromboembolism, hypotension, and impaired perfusion was administered the HBOC solution as a colloidal solution that may have also improved oxygenation of tissues distal to the thrombus, on the basis of experimental evidence that HBOC solutions are able to maintain normal oxygena-

tion in tissues distal to a site of 95% stenosis in blood vessels.[13]

There were 80 separate HBOC infusion events in 72 cats. Mean dose administered per infusion event was 14.6 ± 13.1 ml/kg (6.6 ± 6 ml/lb; median, 11 ml/kg [5 ml/lb]), with a range of 2 to 89 ml/kg (0.9 to 40.5 ml/lb; n = 75 infusion events). Mean rate of infusion was 4.8 ± 6.2 ml/kg per hour (2.2 ± 2.8 ml/lb per hour; median, 3.7 ml/kg [1.7 ml/lb] per hour; n = 77 infusion events). Mean total dose was 17.1 ± 14.5 ml/kg (7.8 ± 6.6 ml/lb; n = 64 cats), with a range of 2 to 89 ml/kg (0.9 to 40.5 ml/lb; median, 12.5 ml/kg [5.7 ml/lb]). Six cats received 2 HBOC solution infusions, and 1 cat received 3 infusions. Information for calculation of the total dose infused was incomplete for 8 cats.

Thirty-nine cats received blood in addition to the HBOC solution. Twenty of these cats received blood during the same 24-hour evaluation interval within which the HBOC solution was administered; therefore, these cats were excluded from the subsequent evaluation of improvement but were included in reviewing adverse events and patient status.

The reason for choosing the HBOC solution rather than feline PRBC or blood was available for 60 cats. The HBOC solution was administered because of a lack of readily available feline blood in 50 cats. Thirty of these cats ultimately also received blood. Five of these 50 cats received the HBOC solution as part of an attempt to resuscitate them after respiratory arrest when feline blood was not immediately available for transfusion. Three cats were given the HBOC solution because of a lack of compatible RBC for transfusion; 1 was a renal transplant recipient that destroyed transfused RBC immediately after infusion (6 units of feline blood prior to infusion of HBOC solution), and 2 cats required type B blood when no type B donors or insufficient quantities of type B blood were available (1 cat also received 2 units of blood). Five cats were given the HBOC solution rather than feline blood as a temporary supportive treatment, pending the diagnosis and owner's decision regarding continued treatment, in an attempt to limit the use of feline RBC. Two cats received the HBOC solution in attempts to improve tissue oxygenation distal to a site of thrombosis.

Response to HBOC infusion—Limited information was available to assess the efficacy of the HBOC solution, and data were confounded by concurrent administration of blood and other treatments. Among 43 cats that received the HBOC solution during a time interval that did not include administration of a RBC transfusion and had sufficient information recorded in their medical records, 37 (86%) cats had improvement in at least 1 of the evaluated variables, whereas in the others the clinical or laboratory findings either remained unchanged (n = 4) or deteriorated (2; **Table 1**). There was no information to assess the reason for deterioration in 1 cat; however, the other cat had ongoing gastrointestinal tract hemorrhage because of enterocolitis, and endocarditis was detected at necropsy.

The preinfusion [Hb] was obtained from the CBC (n = 4) or Hb point-of-care instrument (10), or was calculated from the PCV (21). The postinfusion [Hb] was obtained via the Hb point-of-care instrument in all but 1 cat in which it was recorded from the CBC. An increase in [Hb] was noted in 30 of 35 infusion events (27 of 32 cats) in which a pre- and postinfusion [Hb] was recorded or calculated (Table 1). Mean change in [Hb] was +1.54 ± 1.63 g/dl ($P < 0.001$). The [Hb] increase was < 0.5 g/dl in 4, ≥ 0.5 and < 1 g/dl in 9, ≥ 1 but < 2 g/dl in 4, and ≥ 2 g/dl in 13 measurements. The increase in [Hb] was dose-dependent. The postinfusion [Hb] decreased slightly in 5 cats (mean, –0.63 g/dl; range, –0.2 to –0.9 g/dl); the preinfusion [Hb] was estimated in all of these cats and therefore may have been inaccurate. In contrast, an overall significant ($P < 0.001$) decline in PCV was detected after the initial infusion of HBOC solution, with a mean pre- and postinfusion PCV of 12.9 ± 4.7% and 10.6 ± 5.1%, respectively. The PCV decreased in 24 cats by 1 to 2% (n = 9), 3 to 4% (7), 5 to 6% (3), and 7 to 9% (5); increased in 6 cats by 1% (4), 3% (1), and 5% (1); and remained the same in 4 cats. In the case where the PCV increased 5%, there was a possibility that the preinfusion PCV was obtained from a diluted blood sample drawn from a catheter; therefore, the preinfusion PCV may have been erroneously low.

The pre- and postinfusion body temperatures were recorded for 45 infusion events (39 cats; Table 1). There was a significant ($P < 0.05$) increase in mean body temperature. Body temperature after HBOC infusion was increased, decreased, or remained the same in 28, 16, and 1 cat, respectively. Improved body temperature (> 0.5 C [1.0 F]) was noted in 11 of 20 cats with initial temperatures < 37.8 C (100.0 F). There were no significant differences between pre- and postinfusion heart rates or respiratory rates, although heart rate returned to reference range in 6 cats, and 1 cat no longer required supplemental oxygen.

Table 1—Variables used to assess response to administration of a hemoglobin-based oxygen-carrying solution in cats

Variable	No. of infusion events	Preinfusion		Postinfusion		*P* value
		Mean (SD)	Median (range)	Mean (SD)	Median (range)	
PCV (%)	34	12.9 (4.7)	12 (6–26)	10.6 (5.1)	9 (3–29)	0.001
Blood Hb (g/dL)	35	4.2 (1.5)	3.9 (2–8.7)	5.7 (2.3)	5.5 (3.0–13.4)	< 0.001
Temperature (C)	45	37.4 (1.9)	38.0 (32.8–40.1)	38.0 (1.5)	38.3 (34.7–39.9)	0.01
Heart rate (bpm)	43	178 (34)	180 (12–90)	173 (27)	172 (108–240)	0.37
Respiration rate (rpm)	40	41 (19)	37 (12–90)	43 (22)	39 (16–100)	0.48
Systolic blood pressure (mm Hg)	15	93 (40)	80 (44–190)	120 (30)	122 (63–180)	0.008

Hb = Hemoglobin. bpm = Beats per minute. rpm = Respirations per minute.
To convert C to F, multiply value by 9/5 and add 32.

Systolic blood pressure during 15 infusions in 13 cats increased after 12 infusion events and decreased after 3 infusion events. Mean change in systolic blood pressure was +27 ± 34 mm Hg (P = 0.008). All 13 cats also received other medications during the infusions, which may have influenced blood pressure measurement; crystalloid fluids (n = 13), blood transfusions (5), continuous rate infusions of dopamine (4), continuous rate infusions of epinephrine (1), mannitol (1), and hetastarch (1) were administered. Two cats that had undetectable peripheral blood pressure before infusion were not included in analysis of blood pressure. Improved pulse quality was observed in 4 cats.

Overall, improvement in clinical parameters was noted in 21 cats. Improvement in activity, attitude, or both, including improved posture, resumed grooming behavior, or improved social interaction, was noted in 13 cats and improved appetite (when appetite was recorded before and after infusion) was detected in 14 cats.

Adverse events—Adverse events were noted in 44 cats after the infusion of the HBOC. The most common adverse events were pleural effusion, pulmonary edema, or both (25 cats). However, of the 21 cats with pleural effusion, 8 cats had evidence of pleural effusion prior to the administration of the HBOC solution. Five cats had no evidence of pleural effusion, and this information was not available for 8 cats. In 18 cats, cardiac or respiratory abnormalities or both were detected prior to administration of the HBOC solution and included the need for supplemental oxygen (n = 6), cardiomegaly (4), heart murmur (2), crackles (2), thoracic trauma (2), and hypertrophic cardiomyopathy, restrictive cardiomyopathy, endomyocarditis, bronchoalveolar carcinoma, respiratory arrest, pneumonia, and pyothorax (1 each). Myocardial fibrosis was diagnosed in 1 cat at necropsy. Only 4 of these cats required any additional treatment as a consequence of the pleural effusion within the first 24 hours after infusion, such as supplemental oxygen (n = 4), diuretics (2), and thoracocentesis (1).

Pulmonary edema was detected in 8 cats after administration of the HBOC solution, although 2 cats had radiographic evidence of pulmonary edema prior to infusion, 1 cat had no radiographic signs of pulmonary edema, and for 5 cats this information was not available. Of these 8 cats, 4 also had pleural effusion. All of these cats had cardiac or respiratory abnormalities prior to infusion, which included the need for supplemental oxygen (n = 4), hypertrophic cardiomyopathy (2), intrathoracic neoplasia (2), and cor triatriatum sinister, endomyocarditis, heart murmur, thoracic trauma, pulmonary crackles, respiratory arrest, pyothorax and pneumonia, and ventilator therapy (1 each). Only 1 of these cats had changes enough to alter treatment to include administration of supplemental oxygen and a diuretic. Mean dosage of HBOC solution administered was greater in the group that developed pulmonary edema than in the group that did not (20.6 ml/kg [9.4 ml/lb] vs 14.5 ml/kg [6.6 ml/lb]), but this difference was not significant (P = 0.3).

Change in respiratory rate was also assessed for 56 infusion events (50 cats), including cats that received concurrent blood transfusions. Mean pre- and postinfusion respiratory rates were 42 ± 19 breaths/min (range, 12 to 90 breaths/min) and 42 ± 21 breaths/min (range, 16 to 100 breaths/min), respectively (P = 0.92). These mean respiratory rates varied little from those of the group that did not receive concurrent blood transfusions (Table 1). The range of change in respiratory rate was –51 to +56 breaths/min. An increase in respiratory rate was observed during 24 infusion events, no change occurred during 9 infusion events, and a decrease in respiratory rate occurred during 23 infusion events. Respiratory rate increased, decreased, and remained the same in 10, 7, and 4 cats with pleural effusion, respectively. Respiratory rate increased, decreased, remained the same, and was not assessed in 2, 3, 1, and 2 of the cats with pulmonary edema, respectively.

Mucous membrane discoloration (muddy pink, icteric, orange, or brown) and pigmenturia (orange-brown) were detected in 21 and 11 cats, respectively, in which these observations were recorded before and after administration of the HBOC solution. One cat had reddish-brown iris discoloration for approximately 24 hours after administration of HBOC solution.

Vomiting was detected in 4 cats during the postinfusion assessment interval; however, they all had a history of recent vomiting.

Neurologic abnormalities were detected in 4 cats, all of which had prior neurologic abnormalities. One cat that had a seizure 10 hours after administration of HBOC solution had a history of seizures and a portosystemic shunt ligation 5 years previously; the cat was discharged from the hospital after administration of HBOC solution without further report of seizures or neurologic abnormalities. The second cat had a 3-year history of seizures, and the seizure observed 14 hours after administration of HBOC solution occurred after septic peritonitis, cardiopulmonary arrest, and resuscitation. This cat died 15 hours after resuscitation and at necropsy was found to have gastric lymphosarcoma with gastric rupture and peritonitis. Neurologic abnormalities in a third cat began approximately 8 hours after infusion of the HBOC solution and included ataxia, extensor rigidity, vertical nystagmus, and vocalization. Prior to infusion of the HBOC solution, this cat's mental status was described as obtunded, and tremors of the head and limbs had been seen. Because of overall clinical deterioration, the cat was euthanatized 21 hours after administration of HBOC solution. Clinical evaluation and necropsy revealed anemia caused by hemobartonellosis but failed to determine the cause for the neurologic abnormalities. The fourth cat was dyspneic, had obtunded mental status, did not have voluntary motor ability prior to receiving the HBOC solution, and had progressive neurologic signs within 3 hours after administration of HBOC solution; the cat was euthanatized, and a necropsy was not performed.

Outcome—Twenty-three of 72 (32%) cats were discharged from the hospital. All 13 (18%) cats that died and 36 (50%) that were euthanatized had severe underlying disease prior to receiving the HBOC solu-

tion. The most common single final diagnoses were hematologic disorders (n = 26), including myelodysplastic syndrome (5), immune-mediated hemolytic anemia (4), FeLV-associated anemia (4), hemobartonellosis (3), flea-bite anemia (3), coagulopathy (3), RBC maturation arrest (1), unknown cause of anemia (3), and neoplasia (16). Other illnesses included hepatic disease (6), renal disease (5), gastrointestinal tract disease (4), cardiac disease (3), severe trauma (3), respiratory disease (2), toxin (2), necrotizing pancreatitis, septicemia, post-parturient illness, limb ischemia, and unknown neurologic disease (1 cat each). The general reason for euthanasia of 35 cats was a poor prognosis associated with severe underlying disease (reason for euthanasia was not recorded for 1 cat). Thirty-eight cats were euthanatized (n = 27) or died (11) within the first day. Three cats were euthanatized and 1 died on the second day after infusion. Six cats were euthanatized and 1 cat died 2 to 14 days after infusion.

Necropsies were performed in 23 cats, each of which had evidence of severe underlying disease processes. Necropsy of 14 cats revealed that 10 cats had pleural effusions, and 6 cats had pulmonary edema. Of these cats, 7 had pulmonary disease and 9 had heart disease. Two did not have substantial heart or respiratory tract disease. Of the 9 cats that did not have pleural effusion or pulmonary edema, 5 had heart disease, 5 had primary lung disease, and 2 of the cats had antemortem effusion or edema. Two cats were without substantial heart or respiratory disease.

Hepatic lesions consistent with acute disease were found in 13 cats and included bile stasis (n = 8), acute centrilobular necrosis (4), and single-cell hepatocellular necrosis (3). Other findings included pancreatic necrosis (n = 6), pancreatic inflammation (2), and gastrointestinal hemorrhage and melena (3). Acute renal ischemic necrosis was found in 1 cat with endocardial fibrosis and acute thromboembolism, and acute tubular necrosis was identified in 1 cat with presumed toxicosis. Other isolated findings include ischemic encephalopathy along with respiratory and heart disease, mild hemorrhage of the leptomeninges, and mild focal choroid plexitis.

Discussion

Intense commercial research has focused on development of HBOC solutions as RBC substitutes when compatible blood is not available. The solution used in this study[a] promises to become an excellent alternative because of its readily available source, chloride-dependent oxygen release to tissue, extended stability at room temperature, and negligible antigenicity in any studied species. This HBOC solution is the only product approved by the FDA for use as a temporary oxygen carrier in anemic dogs; approval was obtained on the basis of experimental canine studies and a large multicenter clinical trial in anemic dogs.[14] The HBOC has been used clinically in a few cats,[8,9] although it has not been approved for use in cats. In the study reported here, some cats appear to have benefited from HBOC administration. The cause of pulmonary edema and pleural effusion in 35% of the cats after administration of the HBOC solution is uncertain and may be related to underlying diseases as well as the rapid infusion rate and large dose of HBOC solution. Although difficult to assess in these critically ill cats, deaths did not appear to be related to treatment for anemia but rather to the grave underlying diseases.

The dose of the HBOC solution administered to the cats of this retrospective study was variable, ranging from as little as 2 ml/kg to an extreme of 89 ml/kg in 1 cat, but mean and median doses administered per infusion were 14.6 and 11 ml/kg, respectively. The mean and median rates of infusion of the HBOC to cats were 4.8 and 3.7 ml/kg per hour, respectively. Thus, the need for additional oxygen-carrying ability, and, therefore, the volume of the HBOC solution or RBC transfusion to be administered, varied greatly depending on the cat's underlying disorder.

In our retrospective study, 16 cats received an RBC transfusion after the HBOC solution, because they were deemed to be in need of additional oxygen-carrying ability; however, there was neither a positive nor negative control group for comparison.

The cats of this study were severely ill, as indicated by their underlying diseases and failure of administration of the HBOC solution to resuscitate 5 anemic cats after respiratory arrest. In addition, there may have been a clinician bias to give gravely ill cats the HBOC solution rather than RBC because of their poor prognosis and the limited availability of feline blood. Fifty-three percent of the cats died or were euthanatized within the first 24 hours of hospitalization. The reason for euthanasia given in 97% of the cats was a poor prognosis associated with the underlying disease, rather than anemia alone.

Despite the low survival rate and the difficulty in assessing the efficacy of the HBOC solution (because positive [RBC transfusion] and negative [no treatment] control groups were not evaluated), the HBOC solution appeared to have certain beneficial effects. Positive responses included an increase in whole blood [Hb], which is an indirect measure of increase in the oxygen content of the blood and possibly of improved oxygen delivery to tissues. Whole blood [Hb] rather than plasma [Hb] was recorded for most cats of this study, and [Hb] concentrations before and after administration were available for only 35 of 80 infusion events. However, an increase in whole blood [Hb] was recorded in 30 of 35 infusion events, with an increase of > 2 g/dl in 13 infusion events. The small decrease in [Hb] in 5 cats after infusion of the HBOC solution may be attributable to ongoing loss of RBC. The decrease in PCV after 30 infusion events was attributed to a dilutional effect because of the volume-expanding effects of the HBOC solution, rather than hemorrhage; mean systolic blood pressure increased from 93 mm Hg to 120 mm Hg after infusion, and the pulse quality was reported to be improved in 4 cats. However, a limiting factor in this study was that parameters of clinical efficacy of the HBOC solution were not evaluated in all cats or at the same time intervals from the start of the HBOC infusion, and central venous pressure was only measured in 1 cat in this study.

Subjective parameters of improvement in clinical signs (ie, appetite, activity, improved pulse quality)

assessed shortly after infusion are important in assessing the efficacy of the HBOC solution, as with monitoring response to RBC transfusions. Twenty-one cats had improved activity, appetite, or both after administration of the HBOC solution. It was impossible to remove the influences of all other treatments when we assessed each cat's response to the HBOC solution; however, 20 cats that did receive concurrent blood transfusions, a treatment most likely to confound results of HBOC administration, were not included in evaluation of responses. Nevertheless, the clinical changes that may have indicated a positive response to the HBOC solution may also have been caused by concurrent treatments or factors other than administration of the HBOC solution.

The impression of a beneficial response in cats is supported by results of a previous experimental study that compared an HBOC solution, 6% **hydroxyethyl starch (HES)**, and autologous blood for treatment of hemorrhagic shock in cats. The HBOC solution and autologous blood were equally effective in restoring arterial blood pressure and oxygen transport parameters, including heart rate, arterial and venous oxygen contents, oxygen extraction, and blood gas values, whereas HES resulted in improvement in blood pressure, but oxygen transport parameters remained decreased.[7] In other experimental reports on the treatment of hemorrhagic shock in dogs[3] and pigs[4] and isovolemic blood exchange in dogs[14] and sheep,[6] administration of an HBOC solution resulted in improved tissue oxygenation.

A sustained clinical improvement in signs associated with anemia is expected in patients after RBC transfusion, unless there is ongoing hemolysis or blood loss. However, the HBOC solution has a short intravascular half-life that is dose-dependent, typically 30 to 40 hours at 30 ml/kg (13.6 ml/lb) in healthy dogs.[16] The half-life of the HBOC solution in cats has not yet been determined but is likely similar. Therefore, administration of an HBOC to any species is intended to provide temporary oxygen-carrying support until the patient's bone marrow has adequate time to respond with increased erythropoiesis or compatible RBC are available for transfusion.

Two of the cats in this study received the HBOC solution not for anemia but in an attempt to deliver oxygen to sites of thrombosis. The low viscosity of the HBOC solution enhances perfusion of tissues and allows oxygen delivery to tissues despite disruption of RBC flow. In experimental models, oxygenation was maintained distal to severe (95%) arterial stenosis with the HBOC solution.[13] Unfortunately, neither of these cats appeared to benefit from the HBOC solution; 1 cat with underlying cardiac disease was euthanatized, and amputation of the ischemic limb was necessary in a cat with a splint complication. Other experimental uses of HBOC solutions in rats for conditions other than anemia, such as solid tumor oxygenation prior to radiotherapy[17] and organ perfusion during transplantation,[18] have been successful and may be considered in clinical veterinary medicine.

Adverse events associated with administration of the HBOC solution to the cats of this study were similar to those reported in a multicenter canine clinical trial.[14] It should be pointed out that allergic reactions to the solution, which is bovine Hb product, were not observed in the canine clinical trial or in our study. In dogs treated with the HBOC solution, transient discoloration of mucous membranes, sclera, urine, and skin, and increased central venous pressure with development of pulmonary edema, vomiting, and diarrhea were reported.[16] Transient discoloration of mucous membranes, skin, sclera, and urine is expected after administration of HBOC solution, regardless of species.[14] Potentially the most worrisome of the adverse events is the development of circulatory overload. Pre-existing cardiopulmonary disease was observed in 88% of the cats that had pleural effusion, pulmonary edema, or both. Pleural effusion was known to be a new development in 5 cats, and only 2 of these cats had substantial effusion that warranted treatment. Eleven of 25 (44%) cats with pleural effusion or pulmonary edema also received concurrent blood transfusions, which potentially exacerbated a rapid increase in intravascular volume. Ideally, the central venous pressure should be monitored during infusion, and the infusion rate and dose of HBOC solution should be altered if there are increases in central venous pressure. On the basis of central venous pressure and adjustments in rate of administration of HBOC solution during the canine clinical trial, it appears that the rate of administration of HBOC solution (> 10 ml/kg per hour) may have been associated with development of pulmonary edema in normovolemic dogs. A significant correlation with dose or rate of administration and development of pulmonary edema was not evident in our study; however, mean dose was greater for the group that developed pulmonary edema than for the group that did not. There was insufficient evidence to link pleural effusion or pulmonary edema after infusion with administration of the HBOC solution; however, development of pleural effusion and pulmonary edema should be considered potential complications of HBOC administration in cats.

Despite the mortality rate in this study, there was no clinical or pathologic evidence that death or euthanasia was attributable to administration of the HBOC solution. None of the cats died because of anemia. Cardiac disease, pulmonary disease, and hematopoietic disorders were the most common causes of death among cats on which a necropsy was performed.

Hepatic lesions (bile stasis, acute centrilobular necrosis, and single-cell hepatocellular necrosis) were also common in this study, but interpretation was confounded by concurrent diseases. In a previous study, infusion of polymerized Hb solution in cats was associated with hydropic degeneration of the liver,[7] but this lesion was not identified in any cats in our study. Although there have been previous concerns about nephrotoxicity caused by lysed RBC solutions, there were no renal lesions consistent with hemoglobinuric nephrosis in the cats of this study. Renal toxicosis was not detected in an experimental study of cats that received 20 ml of HBOC solution/kg.[7] Other studies in healthy rats have revealed the safe use of ultrapurified,

stroma-free HBOC solutions, with transient, reversible mild increases in serum creatinine concentration developing only at high doses (75 ml/kg [34 ml/lb])[19,20] that were much higher than typically used in clinical situations.

Administration of the HBOC solution may provide temporary oxygen-carrying support to anemic cats when compatible RBC are not available for transfusion; however, prospective controlled studies are necessary to determine the clinical efficacy and safety of the HBOC solution and the ideal dose and rate of administration in anemic cats. Response to the HBOC solution would be indicated by improved appetite, activity, and whole blood [Hb] or plasma [Hb] measured at consistent intervals after administration of the HBOC solution. Because of the volume expanding effects of the HBOC solution, caution should be exercised when administering it to cats with evidence or suspicion of cardiopulmonary disease, especially with concurrent blood transfusions or IV fluid administration, to avoid circulatory overload.

[a]Oxyglobin, Biopure Corp, Boston, Mass.
[b]Cell Dyne 3000, Abbott Laboratories, Abbott Park, Ill.
[c]HemoCue AB, Angelholm, Sweden.
[d]Jahr JS, Luri F, Xi S, et al. Measuring relative circulating blood volume: use of a hemoglobin-based oxygen carrier (HBOC) in a rabbit model (abstr). *Anesthesiology* 2000;93:A159.
[e]SAS statistical software, version 8.0, SAS Institute, Cary, NC.

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