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Research Article

Prospective Review of Clinical Hypersensitivity Reactions After Administration of 5% Human Serum Albumin in 40 Critically Ill Cats

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A B S T R A C T

This prospective study assesses the presence of immediate and delayed clinical hypersensitivity reactions in 40 hypoalbuminemic critically ill cats during and after an intravenous administration of 5% human serum albumin (HSA). Twenty hypoalbuminemic critically ill cats with no known exposure to HSA (control group) were also checked in order to highlight any clinical signs related to the underlying disease which could mimic hypersensitivity reactions. The administration of 10-20 mL/kg of 5% HSA at 2 mL/kg/h in critically ill cats did not lead to clinical signs of types I and III hypersensitivity reactions at days 0, 7, 14, 21, and 28, unlike previous findings with 25% HSA in this species.

Introduction

Hypoalbuminemia in animals is a common consequence of many critical illnesses, including sepsis, inflammation, heatstroke, burns, end-stage hepatic failure, protein-losing enteropathy, pancreatitis, trauma, and nephrotic syndrome.[1] The ensuing hypoalbuminemia can result in severe complications such as hypovolemia, interstitial edema, and fluid losses into the body cavities (e.g., pleural space, abdominal cavity) and gastrointestinal tract.[1]

Albumin can be used to treat hypoalbuminemia[2-7] and to maintain colloid oncotic pressure (COP)[7-11] in small hypoalbuminemic animal patients. The advent of a commercially available canine lyophilized albumin product has provided an avenue for albumin replacement in dogs.[3] However, no feline-specific albumin is currently available, thus HSA remains an option in cats. In veterinary medicine type I hypersensitivity immune reactions and type III hypersensitivity to HSA infusion in dogs and cats have been reported.[5,6,12-14]

Type I hypersensitivity is a protective immune response to agents that cross mucosal sites, the skin, airways, or the gastrointestinal tract. When allergens cross these sites, mast cells degranulate and release a potent combination of preformed inflammatory mediators including histamine, heparin, serotonin, kininogenase, tryptase, chymase, exoglycosidases, eosinophils as well as neutrophil chemotactic factors and platelet activating factors. The vasoactive effect of mast cell degranulation is rapid and the process is described as immediate hypersensitivity.[15] Clinical signs of hypersensitivity type I are: hypotension, bronchospasm, angioedema, urticaria, erythema, pruritus, laryngeal edema, vomiting, abdominal pain, and anaphylactic shock.[15] Immediate hypersensitivity type I to HSA typically occurs within 1-15 minutes, but may occur at any time during a transfusion.[5,12-14]

The third type of hypersensitivity involves the formation or deposition of immune complexes of soluble antigens and antibodies (generally IgG) within tissue, with subsequent complement fixation, and localized inflammation. In sensitized individuals, exposed to high levels of circulating antigens, immune complexes form within the bloodstream, activated complement leading to the release of vasoactive amines from basophils and platelets.[15] Clinical signs of type III hypersensitivity are: fever, vesicular and ulcerative dermatitis, lethargy, inappetence, signs of depression, generalized lymphadenopathy, diarrhea with hematochezia, melena, and atrophy of the temporalis and masseter muscles.[12] This type of hypersensitivity has been observed 5-16 days after albumin administration.[12,13]

In the veterinary literature only 1 study[5] has described hypersensitivity reactions in cats during and after HSA infusion. In that study, 25% HSA was administered to 66 critically ill pets (64 dogs and 2 cats). Several adverse effects were reported including the death of some of the animals, one of which was a cat. In 2010, a retrospective study[2] described the infusion of a less concentrated HSA solution (5%) in critically ill patients using a particular protocol: 10-20 mL/kg IV in 24 hours at the rate of 2.0 mL/kg/h IV were administered to 418 dogs and 170 cats, without reporting any hypersensitivity reaction. The main limitation of the study was the absence of a control group and follow-up.

The aim of this prospective study was to observe the clinical signs of immediate and delayed hypersensitivity reactions (types I and III) following the administration of 5% HSA in critically ill cats, compared with a control group. HSA was administered at the same total dose, concentration, and rate as the largest study[2] performed on cats. To the best of our knowledge, this is the first prospective study carried out on cats.

Materials and Methods

This study was carried out in a private veterinary clinic over a 7-year period (from November 2010 to January 2018), in accordance with good clinical practice (Federation of Veterinarians of Europe, FVE, Code of Good Veterinary Practice, 2003). Protocols of animal husbandry and experimentation were reviewed in accordance with the Directive 2010/63/EU for animal experiments. Informed client consent was obtained from all animal owners prior to enrollment in the study.

Inclusion criteria were: (1) life-threating pathologies that lead to serum albumin less than 2.0 g/dL (diagnosed with serum biochemical analysis[1]), such as peritonitis, nephropathies, protein losing enteropathies, liver diseases, burns, injuries, and sepsis; (2) being able to check the clinical perfusion parameters and specific signs of hypersensitivity reaction for a 28-day follow-up period.

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Table 1
Demographic Data and Type of Fluid Used in Cats Treated With Human Serum Albumin (HSA Group) vs. control (Ctrl Group)

	Breed					Sex		Age (years)	Weight (kg)	Type of Solution		
Group	DSH	DLH	Main Coon	Persian	Siamese	M	F	Mean± SD	Mean± SD	NaCl	Normosol R	LRS
HSA ($n = 40$)	35	1	1	3	1	20	20	7.31 3.99	3.86 1.33	4	11	25
Ctrl ($n = 20$)	18	0	0	2	0	12	8	7.25 3.70	4.26 1.32	5	6	9

Exclusion criteria were: (1) exposure to blood transfusion and/or colloids prior to or during hospitalization, and use of vaccines in the previous month; (2) the administration of antihistamines, glucocorticoid, or immunosuppressive drugs (e.g., cyclosporine), prior to or during hospitalization; (3) death or abandonment of follow-up.

A peripheral venous (cephalic or saphenous vein) access was achieved in all the animals and a blood sample was drawn in order to determine the levels of albumin. When possible, acid base status and electrolyte measurements were performed[2] to guide the choice of isotonic crystalloid solution. Animals were hospitalized and additional investigations, supportive care, and treatment were at the discretion of the veterinarian responsible for the treatment.

The protocol consisted of the intravenous administration of 5% HSA (HSA group) or isotonic crystalloids (control group). Animals were randomly assigned to the 2 groups based on the medical record number (even or odd).

In the HSA group, a commercial solution of 25% HSA[3] was diluted to 5% in an isotonic crystalloid solution. In both groups, crystalloids were chosen on the basis of the acid base status and serum electrolyte levels of the cats: .9% saline,[4] Normosol R[5] or lactate's Ringer solution (RLS),[6] in the case of metabolic alkalosis and/or hyponatriemia, in the case of metabolic acidosis or when it was not possible to know the acid base status, respectively.

In the HSA group, the solutions were infused, according to the largest study done on cats,[2] at a constant rate of 2 mL/kg/h with up to 10-20 mL/kg/day, for at least 5 up to 10 hours, until desirable serum albumin levels (≥ 2.0 g/dL) were obtained. During the following days, if the value was less than 2.0 g/dL, additional HSA infusions (1 or more) were administered at 2 mL/kg/h with up to 10-20 mL/kg/day. In the control group, crystalloids were infused with the same rate for 3 days. No other colloids or transfusion products were administrated in the 2 groups.

In the HSA group, during hospitalization, serum albumin levels were measured at least once per day, at the end of 5-hour HSA infusion and when hemodynamic stabilization was reached.

Each animal from both groups was monitored strictly during hospitalization (day 0) and weekly for a 1-month follow-up period (at days 7, 14, 21, and 28 after the first infusion of HSA or crystalloids). Clinical perfusion parameters and any signs of hypersensitivity reactions were reported on a specific sheet. These data were collected every 15 minutes in the first hour of infusion, and every 60 minutes in the following hours.

The clinical perfusion parameters considered[16] were: level of consciousness, heart rate, mucous color membrane, capillary refill time, peripheral pulse quality, respiratory rate, rectal temperature, and noninvasive blood pressure.[7] Signs of hypersensitivity reactions consisted in: respiratory distress (e.g., bronchial constriction or laryngeal edema), abdominal pain, vomiting, diarrhea with hematochezia and melena, skin lesions (particularly pruritus, signs of angioedema, facial or peripheral edema, urticaria or erythema, vesicular and ulcerative dermatitis), fever, lameness, generalized lymphadenopathy, lethargy, and anaphylactic shock (e.g., hypotension, weakness, weak pulse, and pale mucous membranes).

On each check-up, the owners were asked for a recent history of the occurrence of clinical signs on the days in between the weekly physical examinations.

Statistical Analysis

Data were analysed using specific software.[8] The Kolmogorov-Smirnov test was used for normality of data distribution. Because normally distributed ($P > .05$), all data are reported as mean ± standard deviation and percentage change (Δ%). A t test was used to compare differences in albumin levels between-groups and within-groups. For comparisons, P values of less than .05 were considered significant.

Results

Eighty-six cats, 43 per group, met the inclusion criteria during the study period. Three cats from the HSA group were excluded from the study because they died during hospitalization, due to the worsening of the underlying disease: 2 cats suffering from peritonitis died because of the severe hypoxia caused by massive pleural effusion and because of the onset of an arrhythmia due to a hypertrophic cardiomyopathy; the other cat, with multiple traumas, died of a massive hemorrhage caused by a liver injury. Twenty-three cats in the control group were excluded from the study: 22 due to lack of follow-up; the other cat died due to the worsening of the underlying disease. Demographic data of the remaining 60 cats (40 in the HSA group and 20 in the control group) are reported in Table 1.

The diseases responsible for hypoalbuminemia were: peritonitis [12/40 cats (30%) in the HSA group; 8/20 (40%) in the control group], nephropathy [11/40 (27.5%) in the HSA group; 4/20 (20%) in the control group], protein losing enteropathy [6/40 (15%) in the HSA group; 4/20 (20%) in the control group], liver disease [4/40 (10%) in the HSA group; 3/20 (15%) in the control group], triaditis [2/40 (5%) in the HSA group; 1/20 (5%) in the control group], hit by a car [2/40 (5%) in the HSA group], burns [1/40 (2.5%) in the HSA group], feline infectious peritonitis [1/40 (2,5%) in the HSA group], and sepsis [1/40 (2.5%) in the HSA group].

In relation to the type of crystalloid solution used for the dilution of HSA, the results were as follows: 4 cats received HSA diluted in .9% saline solution, 11 cats in multiple electrolyte injection type 1, and 25 cats in LRS. In the control group, 5 cats received .9% saline, 6 cats received multiple electrolyte injection type 1, and 9 cats received LRS (Table 1).

The total mean HSA volume administered was 14.4 ± 3.9 (from 10 to 20) mL/kg in a mean infusion time of 7 hours and 11 minutes ± 1 hour and 58 minutes (from 5 to 10 h). Each control animal received 20 mL/kg/day of isotonic solution (60 mL/kg overall) (Table 2).

In the HSA group, the desirable serum albumin level (≥ 2.0 g/dL) was achieved in half of the cats (20/40; 50%): in 11 of them (27.5%) after only 1 cycle of HSA and in 9 (22.5%) after another cycle. In the

[2] i-ISTAT 1 Abbot Point of Care inc. USA.
[3] Uman Albumin 250 g/l; Kedrion S.p.A., Barga (Lucca), IT.
[4] Sodium Chloride 0,9 g/100 ml; Piramal, Verona, IT.
[5] Normosol-R; Buxter, Roma, IT.
[6] Lactated Ringer's solution; Pierrel, Potenza, IT.
[7] VET HDO Monitor Pro, S+B medVET Gmbh, Babenhausen, Germany.
[8] Statistica 7, Stat Soft Inc, OK, USA, 2003.

Table 2
Mean (± standard deviation) Values of: Albuminemia Before (Preinfusion) and After (Postinfusion) Administration of 5% Human Serum Albumin (HSA group) or Isotonic Crystalloid Solutions (Ctrl Group) and Their Differences (Δ, Δ%) and Comparison (*t* Test); Total Fluid Administered in 60 Hypoalbuminemic Cats and the Time of Infusion at a Constant Rate of 2 mL/kg/h

		Albumin Levels (g/dL)					
Group		Preinfusion	Postinfusion	Δ	Δ%	Total Fluid Volume Administered (mL/kg)	Time of Infusion at 2 mL/kg/h
HSA	Mean	1.52*	2.00**	.48	34.95	14.39	7 h 11 min
	±SD	.33	.35	.28	24.81	3.93	1 h 58 min
Ctrl (crystalloids)	Mean	1.61	1.58	−.04	−.91	60	10 h/day
	±SD	.26	.32	.23	13.92	0	0

t test.
* Significantly lower than post-HSA infusion ($P < .001$).
** Significantly higher than control group postinfusion ($P < .001$).

other 20 cats, although the albumin level remained below the threshold, it was not possible to administer more than 1 (12 cats, 30%) or 2 (8 cats, 20%) cycles of HSA, because of the owners' financial restrictions. All the animals, however, showed an improvement in the clinical conditions.

A statistical comparison of mean serum albumin concentrations between-groups and within-groups is shown in Table 2. Albumin levels between cats that received HSA transfusion and those that received crystalloid fluid therapy (control group) at the time of enrolment did not show significant differences, demonstrating the homogeneity of the 2 groups.

The mean serum albumin levels were: 1.5 ± .3) g/dL and 2.0 ± .3 g/dL before and after HSA infusion respectively, showing a significant increase ($P < .001$) due to treatment; 1.6 ± .3 g/dL before and after crystalloid infusion with no significant difference ($P > .05$) in the control group. The mean increase in albumin recorded at the end of the total volume of HSA administered was .5 ± .3 g/dL, with an average percentage increase of 35 ± 25%; in the control group the albumin remained low (1.58 ± .32 g/dL; Δ%: −1%) (Table 2).

None of the animals (HSA and control group) showed any clinical signs of types I and III hypersensitivity reactions during and after infusion of the various solutions at any time (day 0, 7, 14, 21, 28). The owners also reported no adverse signs during the observation time.

Discussion

In the present study, human albumin was used because feline albumin is not available in the market. The administration of 5% HSA at 2.0 mL/kg/h in critically ill cats did not lead to clinical signs of types I and III hypersensitivity reactions at days 0, 7, 14, 21, and 28, unlike previous findings with 25% HSA in this species.[5] No cat included in the study developed clinical signs of immediate and delayed hypersensitivity reactions during HSA infusion nor in the following observational period (4-week follow-up). The clinical examinations did not show alteration that could be correlated with hypersensitivity reactions types I and III, such as pruritus, urticaria, erythema, ecchymosis, vomiting, muscle tremors, lameness, bronchospasm, laryngeal edema, anaphylactic shock, facial or peripheral edema, fever, vesicular and ulcerative dermatitis lethargy, inappetence, signs of depression, generalized lymphadenopathy, diarrhea with hematochezia or melena.

In the veterinary literature, and particularly as regards cats, there are insufficient studies concerning adverse reactions to HSA in ill cats. In 2005, 1 study[5] described the reactions to 25% HSA in 66 animals (64 dogs and 2 cats). In that study several adverse effects were reported including the death of some of the animals. Two animals had facial edema during the infusion, 47 (71%) survived infusion, 11 (16%) were euthanized, and 8 (12%) died. Five animals died during or within 18 hours of HSA administration. One of these was a cat with severe hepatic lipidosis, which had received blood products (whole blood and plasma) during a 10-day stay in an intensive care unit; its clinical condition also rapidly deteriorated, requiring vasopressor support prior to HSA administration. The opinion of the authors of that study was that since HSA is a heterologous protein, it could potentially cause immune-mediated reactions in dogs and cats. Thus its use was only recommended when the benefits outweigh the potential risks of adverse events.[6]

A subsequent retrospective study[2] described the infusion of 5% HSA in critically ill dogs and cats (418 and 170, respectively). A volume of 10-20 mL/kg was administered intravenously in 24 hours at the rate of 2 mL/kg/h, which was the same protocol used in the present study. During the infusion, no hypersensitivity reactions were observed. The limitations of the study were the retrospective and descriptive nature of the study, the absence of a control group and the lack of follow-up data.

The reasons for the lack of hypersensitivity reactions mentioned above could include the lower HSA concentration (5% rather than 25%), the administration rate (2 mL/kg/h) and the total dose infused, which did not exceed the maximum daily volume for colloids.[17] However, in feline medicine there are insufficient studies to correlate the absence of hypersensitivity reactions and the HSA infusion protocol used in this study. On the other hand, the concentration, rate and total dose adopted in our study were chosen based on the largest study carried out on cats.[2] The concentration of HSA was chosen in order to be closer to the physiological COP exerted by the albumin in the vascular compartment, and to avoid an excess of albumin concentration in the fenestrated capillaries in the liver where a high concentration of albumin can produce an inhibition in its synthesis.[1] In fact, a 5% HSA solution has a COP value of about 20 mmHg, which is close to the blood COP (25 mmHg), while a 25% solution has a COP value of about 200 mmHg.[18] At the infusion rate of 2 mL/kg/h, the COP of the animal does not suddenly change but is maintained for a period of time that can vary from 5 to 10 hours based on the total amount administered (10-20 mL/kg).

Another possible reason for the absence of hypersensitivity reactions observed in our study is the variability in the HSA composition. This blood product is created from a pool of donors, which may therefore contain different quantities and types of immunoglobulin which could change from unit to unit, and in addition the protein conformation of albumin in some samples, could be modified under oxidative stress conditions. The HSA is not standardized with regards to the presence of possible proteins or other molecules that can produce immune reactions. The product we used may therefore have been less immunogenic than others.

In our study, the control group was included to highlight any clinical signs related to the evolution of the underlying disease which could mimic hypersensitivity reactions or due to other drugs used to treat the disease itself (e.g., antibiotics). The use of other drugs was an obligatory clinical choice and could have been a confounding factor because of the potential sensitization. In all the patients (HSA and

control group) no drugs were administered that could have depressed the immune system (e.g., corticosteroids or cyclosporine), because the use of drugs known to interfere with the immune system was considered as an exclusion criterion at all time-points during the study.

This is a preliminary study, which has some limitations: (1) the relatively small size and the heterogeneity of the sample (cats varying in age, weight, and cause of hypoalbuminemia); (2) the lack of a scoring system to evaluate the severity of disease; (3) the lack of histopathological and laboratory investigations for the detection of hypersensitivity reactions (e.g., specific anti-HSA antibody tests), not performed for financial reasons; (4) fewer animals (20/42) remained in the control group, due to abandonment of follow-up, with loss of information about any hypersensitivities reactions or death.

Although the evaluation of HSA effectiveness was not the target of our study the significant increase in albumin levels in hypoalbuminemic cats may further support the use of 5% HSA in this species. We did not have data regarding the survival rate because it was beyond the scope of the study. Given that there have been few veterinary studies on this matter, further investigations are required to evaluate the risks and benefits of HSA infusion in cats. Larger cross-sectional and prospective studies are needed to confirm these findings and to establish the safety of HSA.

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