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Effects of Hydroxyethyl Starch 130/0.4 on Serum Creatinine Concentration and Development of Acute Kidney Injury in Nonazotemic Cats

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Background: Hydroxyethyl-starch (HES) solutions might have renal adverse effects in humans and dogs.

Objective: To determine if administration of 6% HES-130/0.4 is associated with an increase in serum creatinine concentration and development of acute kidney injury (AKI) in nonazotemic cats.

Animals: A total of 62 critically ill cats; 26 HES exposed and 36 unexposed.

Methods: Retrospective cohort study (2012–2015). Serum creatinine concentrations were recorded and changes in serum creatinine concentrations before exposure (baseline) and 2–10 and 11–90 days, respectively, were determined. Development of AKI was defined as *a* > 150% increase or >26 μmol/L increase in serum creatinine concentration from baseline. Risk factors, such as HES administration, cumulative volume of HES (mL/kg) and number of days of HES administration leading to development of AKI, and change in serum creatinine were analyzed.

Results: Cats in the HES cohort received a mean volume of 98.5 ± 76.2 mL/kg (range, 8–278 mL/kg) HES over a median of 4 (range, 1–11) days, resulting in a median dose of 20.1 (range, 8–40.5) mL/kg per day. Short-term %change in serum creatinine concentration ($P = 0.40$) and development of AKI ($P = 0.32$) were not significantly different between cohorts. Multivariable logistic regression did not identify HES dose in mL/kg ($P = 0.33$) and number of days of HES application ($P = 0.49$) as a risk factor for development of AKI.

Conclusion and Clinical Importance: Hydroxyethyl-starch administration to critically ill nonazotemic cats seems to be safe. A larger prospective study is required to determine the effect of HES administration at higher dosages and for prolonged time periods.

Key words: Acute kidney injury; Feline; Hydroxyethyl-starch; Renal injury.

Hydroxyethyl starch (HES) is an artificial colloid solution used in both human and veterinary medicine for resuscitation of emergency and critically ill animals during the past 30 years. Beneficial effects of HES administration, such as an increase in colloid osmotic pressure[1,2] and blood volume,[3,4] are well documented in dogs. Indications for HES administration in cats are not well documented. One abstract presented over 10 years ago showed an increase in blood pressure after HES administration to cats,[5] otherwise no clinical studies evaluating benefits of HES administration in cats were performed. Nevertheless, HES solutions are widely used in feline patients for the treatment of hypovolemia, hypotension, and low colloid osmotic pressure.[6–8]

Abbreviations:

AKI	acute kidney injury
HES	hydroxyethyl starch
ICD	International Statistical Classification of Diseases and Related Health Problems
ICU	intensive care unit
Lrm	logistic regression model
Mlrm	multivariable linear regression model
PRAC	Pharmacovigilance Risk Assessment Committee of the European Medicine Agency
pRBC	packed red blood cells
VAKI	veterinary acute kidney injury

Hydroxyethyl-starch administration has been associated with renal injury in humans.[9–13] In veterinary medicine, studies investigating potential renal adverse effects of HES solutions are limited. In dogs, conflicting results were found regarding the incidence of acute kidney injury (AKI) after HES administration in hospitalized dogs.[14–16] A single study investigated the effect of HES on renal function in cats and did not identify an increase in plasma creatinine concentration in cats exposed to HES-130/0.4.[17]

The goal of this historical cohort study was to determine if administration of 6% HES-130/0.4 solution[a] is associated with an increase in serum creatinine concentration and development of AKI in critically ill, nonazotemic cats. We distinguished between a short-term HES effect [increase in serum creatinine concentration from the last value before exposure (baseline) to the last recorded value between 2 and 10 days after exposure] and a long-term effect (increase in serum creatinine concentration from baseline to the

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last recorded value between 11 and 90 days after exposure).

Our null hypothesis was that HES exposure did not effect changes in serum creatinine concentration and development of AKI in cats being treated with 6% HES-130/0.4 in an intensive care unit (ICU).

Material and Methods

The computer database of the Vetsuisse Faculty of the University of Zurich was searched for billing of HES and ICU hospitalization between January 2012 and December 2015. Cats which received 6% HES-130/0.4[a] and had at least 1 serum creatinine concentration determined before the start of HES administration as well as at least 48 hours after the start of HES administration, were eligible to enter the study as exposed cats. Exclusion criteria consisted of the following: cats with a baseline serum creatinine concentration above the reference interval (>163 μmol/L; >1.84 mg/dL), cats which received less than 5 mL/kg HES, administration of another synthetic colloid besides HES-130/0.4, and substantial missing data.

All cats, which were hospitalized in the ICU between January 2014 and December 2015, received IV isotonic crystalloid fluids, and which had at least 2 serum creatinine concentrations measured >48 hours apart but within 10 days, served as the unexposed cohort. The same exclusion criteria as above were applied for the unexposed cats.

Age, sex, breed, and weight were recorded for all cats. The database and feline records were further evaluated for the cumulative volume (mL) of HES administered and the number of days of HES administration. Day 0 (baseline) was defined as the first day of HES administration. Total volume of HES per kg body weight (mL/kg) and corresponding daily dose (mL/kg per day) were calculated for each cat. In addition, the number of crystalloid fluid days before the first serum creatinine concentration measurement, concurrent blood product administration, diagnosis, duration of hospital stay, and hospital discharge were extracted.

The diagnosis identified in the record was further classified into one of the 21 groups of the International Statistical Classification of Diseases and Related Health Problems (ICD) System (http://apps.who.int/classifications/icd10/browse/2016/en). If >1 diagnosis was present in a cat, the primary presenting problem (the complaint responsible for the cat being in the ICU) was used for the classification. For statistical analysis, the ICD classification was further narrowed into the following groups: abdominal disease (ICD XI, including parvovirus infection from ICD I and gastrointestinal neoplasia from ICD II), urogenital disease (ICD XIV), trauma (ICD XIX), and other diagnoses (all other ICD classifications including infectious disease, respiratory, neurologic, and endocrinologic problems).

Serum creatinine concentrations were extracted from the hospital database. Some baseline values were measured in the stat laboratory,[b] all others in the hospital's laboratory,[c] with both machines having comparable upper reference intervals (160 and 163 μmol/L, respectively). The baseline serum creatinine concentration of the exposed group was defined as the last concentration available before HES administration. In the unexposed cohort, the first available serum creatinine concentration measured after admission to the ICU was used as baseline serum creatinine concentration. Serum creatinine concentrations were then recorded each available day until day 90. During the time period of days 2–10, the highest and the last serum creatinine concentration was determined and used for statistical analysis of the short-term effect. Additionally, the last serum creatinine concentration between days 11 and 90 was determined for analysis of the long-term influence. Serum creatinine changes were calculated as absolute change in serum creatinine concentration (delta creatinine) from baseline to the last and highest concentration within 2–10 days. Additionally, the change in percent (%change) from baseline to the last and highest serum creatinine concentration within 2–10 days and from baseline to the last serum creatinine concentration within 11–90 days was calculated. Based on the veterinary acute kidney injury (VAKI) scoring system,[18] development of AKI was defined as an absolute increase in serum creatinine concentration >26 μmol/L (0.3 mg/dL) or increase of >150% in serum creatinine concentration from baseline.

Data Analysis

The data were entered into a spreadsheet and were double-checked by 2 of the authors. Statistical analyses were performed by SPSS[d] and Stata 10.[c] Normality was tested for continuous data with Shapiro-Wilk. Fisher's exact test or Chi-square test was used for determination of an association between categorical variables, whereas a Mann–Whitney or independent *t*-test was used for continuous data.

The primary outcomes were %change in serum creatinine concentration (%change) and development of AKI (as defined above) from baseline to the last serum creatinine concentration within 2–10 days of HES administration (short-term effect). The secondary outcome was %change in serum creatinine concentration from baseline to the last serum creatinine concentration within 11–21 days of HES administration (long-term effect).

Potential risk factors including the following main exposure variables (a) HES administration (yes/no), (b) cumulative volume of HES per kg body weight (mL/kg), (c) mL/kg per day, or (d) number of days HES was administered, and age, sex, ICD score, duration of hospital stay, red blood cell, and plasma transfusion are listed in Table 1. The association between the outcomes "%changelast" (%change in serum creatinine concentration from baseline to the last recorded concentration within 2–10 days) and "AKI" (development of AKI) with exposure variables listed in Table 1 was analyzed in two steps. First, bivariably by univariable linear regression analysis and secondly, by multivariable linear regression (mlrm) and logistic regression (lrm) modeling. We built four mlrm and lrm, assessing the association between the outcome "%changelast" and "AKI", respectively, and the following main exposure variables (a) HES administration (yes/no), (b) cumulative volume of HES per kg body weight (mL/kg), (c) mL/kg per day, or (d) number of days HES (Table 1), by a manual stepwise forwards and backwards procedure. Other exposure variables and potential confounders listed in Table 1 were included in the model if they improved the model fit assessed by adjusted *r*-squared (mlrm) and likelihood ratio test (lrm). To identify observations with potential influence on regression coefficient estimates, we performed linear regression diagnostics, assessing studentized residuals and leverage, and for overall measures of influence, we assessed Cook's D. We tested for a normal distribution and homoscedasticity of residuals and whether there was a linear relationship between the outcome and exposure variables. The tested null hypotheses were that HES administration in cats was not associated with the %change in serum creatinine concentration and with development of AKI, when adjusting for potential confounding factors.

Statistical significance was set at $P < 0.05$ for all analyses.

Results

A total of 62 cats met the inclusion criteria. The exposed cohort (HES-exposed cohort) included 26 (42%) cats with a median age of 38 months (range, 3–217 months) and a median weight of 3.9 kg (range,

Table 1. Frequencies of predictor variables in cats exposed and unexposed to 6% HES-130/0.4.

		Unexposed (n = 36)		HES Exposed (n = 26)		
Parameter (Exposure/Risk Factor)	Categories	n	Median (Min–Max) Mean ± SD	n	Median (Min–Max) Mean ± SD	*P*-Value
Age (month)	Continuous	36	108 (11–218)	25	38 (3–217)	0.030
Weight (kg)	Continuous	36	4.3 (3–10)	26	3.9 (2–7)	0.15
HES cumulative dose (mL/kg)	Continuous	0	0	26	98.5 ± 76.2	
HES number of days (d)	Continuous	0	0	26	4 (1–11)	
HES dose per day (mL/kg per day)	Continuous	0	0	26	20.1 ± 8.2	
Hospital stay (days)	Continuous	36	9 (3–37)	26	8.5 (1–45)	0.89
Crystalloid fluid days before HES start/first crea in ICU	Continuous	36	1 (0–5)	26	1 (0–2)	0.19

Parameter (Exposure/Risk Factor)	Categories	n/N	%	n/N	%	*P*-Value
Sex	Male	20/36	56	14/26	54	0.55
	Female	16/36	44	12/26	46	
Diagnosis	ICD 19 (Trauma)	15/36	42	12/26	46.2	0.015
	ICD 11 (abdominal)	4/36	11	10/26	38.5	
	ICD 14 (urogenital)	1/36	3	1/26	3.8	
	ICD (others)	16/36	44	3/26	11.5	
Red blood cell transfusion	Yes/no	4/36	11	9/26	34.6	0.027
Plasma transfusion	Yes/no	2/36	6	9/26	34.6	0.004
HES application	Yes/no	0/36	0	26/26	100	

Crea, serum creatinine concentration; ICD, International Statistical Classification of Diseases and Related Health Problems; ICU, intensive care unit.

2–7 kg). Twelve (46%) cats were female and 14 cats (54%) were male. The European Shorthair cat was most prevalent (65%), followed by Main Coon, Persian, and Norwegian forest cat (8%, each). The HES cohort received a mean total cumulative volume of 98.5 ± 76.2 mL/kg (range, 8–278 mL/kg) HES-130/0.4 over a median of 4 days (range, 1–11 days). This resulted in a mean dose of 20.1 ± 8.2 mL/kg per day (range, 8–40.5 mL/kg per day).

The unexposed cohort included 36 (58%) cats with a median age of 108 months (range, 11–218 months) and a median weight of 4.3 kg (range, 3–10 kg). Sixteen (44%) cats were female and 20 cats (56%) were male. Several breeds were identified including 81% European Shorthair cats and 6% Birman being the most common.

The 2 cohorts were similar in terms of sex, breed, weight, days of fluid treatment before the first serum creatinine measurement, number of hospital days, and day of last serum creatinine concentration measurement, but differed significantly in age ($P = 0.030$) and diagnosis ($P = 0.015$) (Table 1). The HES cohort received significantly more red blood cell transfusions ($P = 0.027$), plasma transfusions ($P = 0.004$) and presented with a significantly lower serum albumin (20.4 ± 6 g/L versus 27.7 ± 6 g/L; $P < 0.001$). Hospital discharge was not significantly different between cohorts (33/36 in the HES unexposed; 19/26 in the exposed cohort; $P = 0.054$).

Serum creatinine concentrations at the evaluated time points are summarized in Table 2. The unexposed cohort showed significantly higher mean serum creatinine concentrations at baseline and last measurement within 2–10 days. The change in serum creatinine concentration (%changelast) from baseline to last serum creatinine concentration within 2–10 days as well as from baseline to last serum creatinine measurement within 11–90 days was not significantly different between the two cohorts (Table 2).

Based on the above AKI definition (increase in serum creatinine concentration >26 μmol/L (0.3 mg/dL) or increase from baseline >150%), 11/36 unexposed cats (31%) and 5/26 (19%) HES-exposed cats developed AKI within 2–10 days ($P = 0.24$). There was no difference in AKI development using highest versus last serum creatinine concentration within 2–10 days (data not shown).

The univariable analysis did not identify a significant association between HES administration and short-term %change in serum creatinine concentration ($P = 0.395$) and development of AKI ($P = 0.32$) (Tables 2 and 4).

The long-term change in serum creatinine concentration (baseline to last value within 11–90 days) did not differ statistically between HES exposed and unexposed cats ($P = 0.57$) (Table 2). Four of 17 (24%) unexposed and 1/9 (11%) HES-exposed cats showed an increase >150% from baseline to the last serum creatinine concentration within 11–90 days ($P = 0.42$).

Multivariable Analysis

Multivariable analysis was performed for the outcomes % increase in serum creatinine concentration from baseline to the last measurement within 2–10 days (%changelast) and development of AKI. None of the four multivariable linear regression models revealed a statistically significant association between the outcome

Table 2. Serum creatinine concentrations (crea) in cats exposed and unexposed to 6% HES-130/0.4.

	Unexposed (n = 36)				HES Exposed (n = 26)				
Variable	n	Mean ± SD or Median	Min	Max	n	Mean ± SD or Median	Min	Max	*P*-Value
Crea day 0 (μmol/L)	36	113.5 ± 36	39	163	26	84.3 ± 35	21	143	0.001
(mg/dL)		1.28 ± 0.4	0.44	1.84		0.95 ± 0.4	0.24	1.62	
Last crea within days 2–10 (μmol/L)	36	111.9 ± 53	25	246	26	73.8 ± 32	18	140	0.001
(mg/dL)		1.27 ± 0.6	0.28	2.78		0.84 ± 0.4	0.2	1.58	
% change between day 0 and last Crea day within days 2–10 (%)	36	103.8 ± 45	17	194	26	94.5 ± 38	40	167	0.40
Day last crea for long-term evaluation (day)	17	13.0	11	62	9	17.5	11	76	0.19
Last crea within days 11–90 (μmol/L)	17	123.7 ± 45	42	229	9	100.8 ± 21	58	133	0.16
(mg/dL)		1.4 ± 0.5	0.48	2.59		1.14 ± 0.2	0.66	1.50	
% change between day 0 and last Crea within days 11–90 (%)	17	115.3 ± 48	35	209	9	104.4 ± 40	41	182	0.57

Crea, serum creatinine concentration.

"%changelast" and one of the four main exposure variables (a) HES administration yes/no ($P = 0.38$), (b) total HES volume in mL/kg ($P = 0.24$), (c) HES days ($P = 0.13$), and (d) HES mL/kg per day ($P = 0.51$), once adjusted for potential confounding variables. We adjusted for the following exposure variables (potential confounders): red blood cell transfusion, plasma transfusion, age, sex, duration of hospital stay, and ICD score. However, only the duration of hospital stay improved the model fit and remained in the final model (Table 3). All 4 tested HES exposure variables revealed a negative coefficient, meaning that HES administration was associated with a reduction in serum creatinine concentration. However, this association was not statistically significant (Table 3).

In the multivariable logistic regression model, the simple model had the best fit and did not identify HES administration, cumulative HES dose in mL/kg and mL/kg per day and number of days of HES application as a risk factor for development of AKI ($P = 0.32$, $P = 0.33$, $P = 0.19$ and $P = 0.49$, respectively) (Table 4).

Multivariable analysis revealed that the administration of HES did not show a statistically significant effect on the change of serum creatinine concentration and AKI.

Linear and logistic regression diagnostics revealed a few outliers and residuals. Their removal did not have an effect on the coefficients of the regression models and was therefore kept in the models.

Discussion

Our study investigating the effect of HES 130/0.4 administered to nonazotemic cats did not identify an increase in serum creatinine concentration both within 10 (short-term) and within 90 days (long-term) when compared to unexposed cats. Development of AKI was further not statistically significantly different between HES exposed and unexposed cats.

Table 3. Multivariable linear regression analysis on the effect of exposure variables on change of serum creatinine concentrations in cats (n = 62) exposed and unexposed to 6% HES-130/0.4.

Model	Effect on Change of Creatinine (% changelast)	Coefficient	*P*-Value	95% CI	Adjusted r^2
1	HES yes/no	−9.55[a]	0.38	−31.0–11.87	0.032
	Number of hospital days	−1.21	0.076	−2.56–0.13	
	Intercept	117.44	0	97.0–138.0	
2	HES mL/kg	−0.09	0.24	−0.25–0.06	0.042
	Number of hospital days	−1.05	0.13	−2.41–0.32	
	Intercept	115.38	0	97.0–134.0	
3	Number of days of HES administration	−3.05	0.13	−7.02–0.93	0.057
	Number of hospital days	−0.99	0.15	−2.35–0.36	
	Intercept	116.56	0	98.0–135.15	
4	HES mL/kg per day	−0.31	0.51	−1.26–0.63	0.054
	Number of hospital days	−1.20	0.079	−2.55–0.14	
	Intercept	115.94	0	95.95–135.94	

[a]Meaning: The change in serum creatinine concentration was reduced by 9.55 units with the administration of HES, assuming all other variables were held constant. In simple words: HES administration is associated with a reduction in serum creatinine concentration. However, this association is not statistically significant, as *P*-value is >0.05.

Table 4. Multivariable logistic regression analysis on the effect of exposure variables on development of AKI within 2–10 days after exposure in cats (n = 62) exposed and unexposed to 6% HES-130/0.4.

Effect on Development of AKI[a]	Odds Ratio	*P*-Value	95% CI
HES administration yes/no	0.54	0.32	0.16–1.81
Total HES dose (mL/kg)	0.99	0.33	0.98–1.01
Number of days of HES administration	0.84	0.19	0.64–1.09
HES mL/kg per day	0.98	0.49	0.93–1.04

[a]The simple model had the best fit.

Our findings are in accordance with the canine studies and the single feline study that have investigated the effect of the same tetrastarch (6% HES-130/0.4) solution.[15–17] The feline study evaluated the increase in plasma creatinine concentration between admission and highest creatinine concentration during hospitalization.[17] Our study protocol was slightly different, as we chose the last serum creatinine concentration before HES administration as the baseline serum creatinine concentration and follow-up serum creatinine concentrations had to be measured at least 48 hours after baseline measurement. With this approach, we decreased the possibility of falsely higher admission serum creatinine concentrations due to hemoconcentration, which can hide an increase in serum creatinine concentration after HES exposure in combination with volume expansion. We further decided to analyze the association between HES administration and the last rather than the highest serum creatinine concentration within 2–10 days. While the increase from baseline to the highest serum creatinine concentration can better reflect a potential adverse effect of HES administration, we believe the last serum creatinine concentration to be more relevant for the cat's clinical condition. However, the last serum creatinine concentration was very similar to the highest and did not change the study results when used as the outcome (data not shown).

Our study is the first investigating the relationship of dose and time of HES administration on changes in serum creatinine concentrations in cats. In contrast to a recent canine study evaluating the same HES solution,[16] we did not identify the number of days of HES administration as a risk factor of AKI development within 10 days of HES exposure.

In human studies and in 1 canine study, a dose-response relationship of HES administration has been proposed.[14,19] The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency therefore recommends using HES solutions at the lowest effective dose, generally for a maximum of 24 hours and avoiding administration as a constant rate infusion (CRI)[20]. In our study, the volume of HES administration was kept wide on purpose, as HES volume per kg body weight was analyzed as possible risk factor for an increase in serum creatinine concentration. A higher HES dose per kg body weight and per kg body weight per day was not associated with an increase in serum creatinine concentration. This is in accordance with our study in dogs[15] and the last Cochrane review[21] that did not find an association between the HES dose and development of AKI or need for renal replacement therapy. In humans, cumulative HES dosages as low as 39 mL/kg have been shown to induce AKI.[22] In contrast, dosages of up to 86 and 94 mL/kg HES-130/0.4 did not induce AKI in dogs and cats, respectively.[15–17] The cats in our study received a median cumulative HES dose of 99 mL/kg, resulting in a median daily dose of 20 mL/kg per day. While the total cumulative HES dose is comparable or even higher to other studies, the daily dose administered was below the maximal dose recommended by the manufacturer[a] (30 mL/kg per day). The given sample size of 62 cats was sufficient for the detection of a significant difference between the 2 cohorts if the incidence in the unexposed cohort was 0.3, assuming a relative risk of 2.2, with the desired confidence level of 0.95 and a power of 0.85. However, to detect a significant difference between the two cohorts for a smaller relative risk as in this study, the sample size would have had to be larger. For example, to detect a relative risk of 1.1, the sample size would have had to be 8602 cats (4301 in each cohort; http://epitools.ausvet.com.au/content.php?page=cohortSS). Therefore, we conclude that a daily dose of 20 mL/kg per day in nonazotemic cats seems to be safe; however, a larger sample size is needed to confirm our results.

As serum creatinine lags behind renal injury[23], we only included cats with follow-up serum creatinine concentrations >48 hours after exposure. Serum creatinine concentration could also be an insufficient marker of renal function.[23] However, histologic changes have been described in the kidneys within 24 hour of HES administration[24] and an increase in serum creatinine concentration after a decrease in glomerular filtration rate is expected after 24–48 hours.[10,25] The mechanism of action of renal impairment with HES administration in humans is not fully understood. High concentrations of HES molecules have been identified in the proximal renal tubular cells of various species.[26] Cellular uptake of HES leads to osmotic nephrosis, characterized by accumulation of intracellular water, cytoplasmic swelling, and cellular disruption.[27,28] No histopathologic studies showing HES accumulation in feline renal tubular cells could be identified; however, there is no reason to believe that HES does not accumulate in feline renal tubular cells as it accumulates in many other species.[26,28]

Several studies indicated an increased risk of renal injury in human patients exposed to HES.[9–13] An increase in the need for renal replacement therapy (RRT) and development of AKI is predominantly documented in humans with sepsis that was exposed to HES solutions.[9–11] We did not analyze the effect of HES in subgroups of cats with sepsis. Several studies in trauma and surgical patients do not support the increased need for RRT as seen in septic patients[13,29–31] implying either variable effects of HES or different predispositions in different patient populations.[15,16,19,32] Given the most

common ICD classifications of our study population, our findings are better compared to studies focusing on trauma and surgical human patients. Regarding the difference between septicemic patients and other populations, the renal impairment seems to occur independent of inflammation even though changes are pronounced with concurrent sepsis in a rat model of septic AKI.[24] Renal injury induced by HES treatment therefore might be more severe and clinically important in septic patients, requiring further studies in both septicemic dogs and cats.

The different findings in our study compared to the human studies might also be caused by different HES solutions investigated. In a porcine renal perfusion model, HES administration leads to impairment of renal function and induction of interstitial proliferation and macrophage infiltration within 6 hours. The effect was significantly more pronounced with HES 200/0.5 compared to the tetrastarch HES 130/0.42.[33] On the other hand, in an in vitro model of human proximal tubular cells, it was concluded that not the type or size of the HES molecule but rather the number of molecules or cumulative dose was responsible for proximal tubular cell harm.[34] In dogs, the type of HES might influence renal injury, as administration of 10% HES 250/0.5 leads to an increase in AKI[14] while 6% HES 130/0.4 did not.[15,16] The 2 available studies in cats examined the same tetrastarch; therefore, conclusions regarding the type (pentastarch versus tetrastarch) or concentration (10% versus 6%) remain unanswered. The available data in cats treated with 6% HES 130/0.4 imply that this tetrastarch is safe when administered to nonazotemic cats.

Long-term effects on survival caused by tissue accumulation of HES are expected 20 days after initial exposure in humans.[11] The PRAC recommends monitoring of serum creatinine concentrations for 90 days after exposure[d]. Therefore, long-term monitoring of renal function in cats is as important as short-term evaluation. As discussed above, increases in serum creatinine concentrations are expected within 2–4 days after renal injury and renal injury by HES has been identified histologically after 24 hours of HES administration.[10,23–25] We therefore defined short-term evaluation as changes between baseline and 2–10 days and long-term evaluation as changes between baseline and 11–90 days. The low number of animals available for long-term analysis and median days of last creatinine determination being <20 days limits our findings regarding long-term evaluation and linear regression analysis investigating potential risk factors for a long-term effect of HES therefore was not performed. Further prospective studies investigating long-term effects of HES administration are needed.

As does any retrospective study, our study has several limitations. First, the exposed and unexposed cohorts differed at baseline in terms of age, baseline serum albumin, and transfusion requirements. As these factors also are indications for HES administration being required, it would be difficult to find a matching control group. Transfusion requirements and age were not significant risk factors in the linear regression models and did not improve model fit. Therefore, we assume that our study results were not strongly biased by these differences between the exposed and unexposed cohorts. Second, the diagnosis in cats in the two cohorts was different, with more cats in the HES group presenting with an abdominal problem and fewer cats presenting with endocrinologic problems and heart disease. This could account for the significantly lower baseline and follow-up serum creatinine concentration in the HES cohort. Again, diagnosis was not a significant risk factor in the linear regression models and did not improve model fit. Illness severity scores were not performed due to incomplete data and reasons for HES administration, such as hypotension and hypoalbuminemia, are part of the illness severity score parameters and eventually lead to different scores between HES exposed and unexposed cats as seen in previous studies.[14,17] Therefore, we do not believe that description of illness severity scores are beneficial in describing the patient population. Third, the volume of crystalloid fluid administration before determination of baseline serum creatinine concentration might have an effect on changes in serum creatinine concentration. We did not determine the cumulative dose of crystalloids before or after exposure. However, the number of days of crystalloid fluid treatment before exposure was not statistically different between exposed and unexposed cats, and therefore, we believe that cats received comparable volumes of crystalloid fluids before the first serum creatinine measurement and hydration status therefore can be assumed to be comparable. After inclusion, cats in both cohorts received at least maintenance crystalloid requirements independently of HES administration. Fourth, data were collected retrospectively and serum creatinine concentrations were not available at multiple, predefined time points. Some cats had serum creatinine concentrations measured several times, while in others, only a single postexposure value was available. However, all other available studies investigating HES administration in veterinary patients also did not serially measure serum creatinine concentrations; therefore, our results are comparable to those results.[14–17] Further prospective studies with a higher number of cats, specifically septic cats, and investigating the effect of higher and longer HES administration on serial serum creatinine concentrations or renal histopathology results are required to investigate the safety of HES administration in cats.

In conclusion, 6% HES-130/0.4 administration to critically ill nonazotemic cats was not associated with an increase in serum creatinine concentration both short- and long-term or development of AKI within 10 days. We conclude that 6% HES-130/0.4 administration in moderate dosages seems to be safe in nonazotemic cats.

Footnotes

[a] Voluven (HES 130/0.4) 6% solution, http://compendium.ch/mpro/mnr/15871/html/de Accessed November 22, 2016.

[b] Fujifilm Dri-Chem 3500i; Polymed Medical Center, Rümlang, Switzerland.
[c] Cobas Integra 800, Roche Diagnostics, Rotkreuz, Switzerland.
[d] IBM SPSS v.21 for Mac OS X; IBM Corporation, New York, NY.
[e] StataCorp, Data Analysis and Statistical Software, College Station, TX, FDA inlet: http://www.fda.gov/downloads/.../UCM083138.pdf.

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Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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