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ORIGINAL STUDY

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Comparison of insulin infusion protocols for management of canine and feline diabetic ketoacidosis

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Abstract

Objective: Describe the use of fixed-rate intravenous insulin infusions (FRIs) in cats and dogs with diabetic ketoacidosis (DKA) and determine if this is associated with faster resolution of ketosis compared to variable-rate intravenous insulin infusions (VRIs). Secondary objectives were to evaluate complication rates, length of hospitalization (LOH), and survival to discharge (STD).

Design: Randomized clinical trial (January 2019 to July 2020).

Setting: University veterinary teaching hospital and private referral hospital.

Animals: Dogs and cats with DKA and venous pH <7.3, blood glucose concentration >11 mmol/L (198 mg/dL), and β-hydroxybutyrate (BHB) concentration >3 mmol/L were eligible for inclusion. Patients were randomly assigned to receive either FRI or VRI.

Interventions: Neutral (regular) insulin was administered IV as an FRI or VRI. For FRI, the rate was maintained at 0.01 IU/kg/h. For VRI, the dose was adjusted according to blood glucose concentration.

Measurements and Results: Sixteen cats and 20 dogs were enrolled. Population characteristics, mean insulin infusion rate, time to resolution of ketosis (BHB <0.6 mmol/L), complications, LOH, and STD were evaluated. In cats, overall resolution of ketosis was low (9/16 [56.3%]), limiting comparison of protocols. In dogs, resolution of ketosis was high (19/20 dogs [95.0%]) but the time to resolution in the FRI group was not different than that in the VRI group ($P = 0.89$), despite a 25% higher average insulin infusion rate in the FRI group ($P = 0.04$). The incidence of complications was low and did not differ between protocols. In cats, LOH and STD did not differ between protocols. All cats that died (5/16) did so within 78 hours and none had resolution of ketosis. Dogs receiving FRI had a shorter LOH ($P = 0.01$) but STD did not differ between protocols. Six dogs (30.0%) did not survive to hospital discharge but all had resolution of ketosis.

Conclusions: FRIs can be used in veterinary species but may not hasten resolution of ketosis.

Abbreviations: APPLE, Acute Patient Physiologic and Laboratory Evaluation; BG, blood glucose; BHB, β-hydroxybutyrate; DKA, diabetic ketoacidosis; FRI, fixed-rate intravenous insulin infusion; LOH, length of hospitalization; STD, survival to discharge; VRI, variable-rate intravenous insulin infusion.

KEYWORDS
constant rate infusion, diabetes mellitus, glucose, ketosis, veterinary

1 | INTRODUCTION

Diabetic ketoacidosis (DKA) is a severe complication of diabetes mellitus. It develops secondary to insulin deficiency or defective insulin-mediated signaling and glucose transport (insulin resistance), resulting in inadequate glucose uptake into cells.[1,2] Hepatic ketone production is a normal physiologic mechanism to provide an alternative energy source from glucose; however, excessive ketone production can lead to dehydration and acidemia.[3,4]

In patients with DKA, insulin administration is necessary to stop production of ketones, reduce lipolysis, and encourage cellular uptake of glucose.[5,6] Many published protocols in veterinary medicine recommend the use of an intravenous variable-rate intravenous insulin infusion (VRI), whereby a short-acting insulin is infused IV and the rate is altered based on blood glucose (BG) concentration.[7–9] The use of VRI protocols can increase the risk of human error, and in cats they have been reported to result in only 24%–35% of the daily prescribed insulin dose being administered.[10] In people, despite a lack of randomized controlled trials, there has been a consensus shift to treatment of DKA using a fixed-rate intravenous insulin infusion (FRI). An FRI maintains a higher initial insulin infusion rate and utilizes a dextrose infusion to ensure that BG concentration remains between 10 and 15 mmol/L (180–270 mg/dL). The FRI is suggested to improve ketone clearance. Once ketosis has resolved (blood β-hydroxybutyrate [BHB] concentration <0.6 mmol/L) using the FRI, the patient may be switched to a subcutaneous insulin or a VRI if not tolerating enteral nutrition.[11] In veterinary medicine, reduced time to resolution of ketosis and commencement of subcutaneous insulin therapy could translate to reduced hospitalization time and reduced cost to owners.

This prospective randomized study aimed to compare an FRI protocol to a VRI protocol in dogs and cats with DKA. We hypothesized that use of an FRI protocol would result in faster resolution of ketosis compared to a VRI protocol. Secondary objectives were to compare differences in complication rates, length of hospitalization (LOH), or mortality rate between protocols.

2 | MATERIAL AND METHODS

Client-owned dogs and cats with DKA presenting to a university teaching hospital or a private referral practice between January 2019 and July 2020 were eligible for inclusion. DKA was defined based on published human guidelines: venous blood pH <7.3, BG concentration >11 mmol/L (198 mg/dL), and ketonemia >3 mmol/L.[11] Resolution of ketosis was defined as serum BHB concentration <0.6 mmol/L measured on a ketometer.[a,11] Patients were excluded if signed owner consent for study participation was not obtained or if the patient had received any form of long-acting insulin within the previous 12 hours.

Previously reported mean times for resolution of ketosis were 49 hours in cats[10] and 26 hours in dogs.[7] We considered that a difference of >14 hours for ketone resolution between protocols would reflect a clinically significant difference and avoid the need for more than twice daily blood ketone measurement. A sample size calculation[b] indicated that 14 cats and 22 dogs (7 cats and 11 dogs in each VRI and FRI group) would provide 80% power to detect this difference (alpha 0.05).

Written study information was provided and signed informed consent was obtained from all owners prior to inclusion. Patients were assigned to receive either an FRI or VRI protocol by randomized blocking in a 1:1 ratio using a random number generator.[c] The protocol was concealed in an opaque envelope, which was opened by the duty clinician when a case was deemed eligible for inclusion. Once enrolled and randomized for treatment, the patient was managed as per the FRI or VRI protocols described in Appendices S1a and S1b, respectively. Insulin infusions were started as soon as the patient was normokalemic and no longer deemed to be hypovolemic by clinical assessment by the attending clinician. This study was approved by the university's Clinical Research Ethical Review Board (URN 1745-3). An Animal Test Certificate (ATC) was obtained from the Veterinary Medicine Directorate (VMD) for both cats and dogs (ATC-S-096/7) to allow randomization of insulin protocols.

Briefly, the FRI protocol (Appendix S1a) required 50 IU of neutral (regular) insulin[d] to be added to a 500-mL bag of 0.9% sodium chloride. This solution was then administered IV at a rate of 1 mL/kg/h. When BG concentration was <15 mmol/L (270 mg/dL), the insulin infusion rate was maintained but 5% dextrose was added to the isotonic crystalloid maintenance fluids, with the rate of administration adjusted to maintain a BG concentration between 10 and 15 mmol/L (180–270 mg/dL). The VRI protocol required 2.2 IU/kg of neutral (regular) insulin[e] to be added to a 250-mL bag of 0.9% sodium chloride. A sliding scale was then used to adjust the insulin infusion based on BG concentration (Appendix S1b). Insulin infusion bags and lines were changed every 24 hours and lines primed with 50 mL of insulin solution to allow for insulin adsorption to plastic. Intravenous 5% dextrose supplementation was added to the maintenance isotonic crystalloid fluids when BG concentration was <15 mmol/L (<270 mg/dL), and the rate was adjusted to maintain a BG concentration between 10 and 15 mmol/L (180–270 mg/dL). The duty clinician could increase the insulin infusion rate in the presence of persistent hyperglycemia or ketonemia; however, this was not protocolized. Hourly insulin infusion rate and any times when insulin was disconnected for >5 minutes were recorded and used to calculate the average rate of insulin administration in IU/kg/h until ketosis resolved (blood BHB <0.6 mmol/L) and the insulin

infusion was stopped. Patients were then released from the study protocol (see Appendix S2). Patients who died or were discharged before resolution of ketosis were excluded from statistical comparison of protocols for time to resolution of ketosis. Transition to subcutaneous insulin injections was at the discretion of the attending clinician.

All cats and dogs received intravenous fluids in addition to the insulin protocol but this was prescribed as deemed clinically necessary by the attending clinician. Requirement for administration of norepinephrine, sodium bicarbonate, phosphate, or magnesium, as well as feeding tube placement or blood transfusion, was documented but was also at the discretion of the attending clinician.

Data prospectively collected during the course of the study included signalment, previous diabetic status, Acute Patient Physiologic and Laboratory Evaluation (APPLE) severity score,[12,13] serial venous blood gas[f] results, whole BG[e] and blood BHB concentrations, and results of urinalysis and urine bacteriologic culture. Where available, species-specific serum pancreatic lipase activity[g] and thoracic and abdominal imaging were documented. Pancreatitis was diagnosed based on consistent ultrasonographic findings with or without quantitative species-specific pancreatic lipase measurement. Presence of cardiac disease was diagnosed by echocardiography. Hepatobiliary disease was diagnosed based on consistent biochemical changes with or without consistent ultrasonographic findings. Urinary disease was diagnosed based on serum creatinine or bacteriologic culture of urine. Neurologic disease was diagnosed based on physical examination. All ketone measurements were made on the same make and model of point of care ketometer[a] across both enrolling sites. Additionally, the mortality probability for each animal was calculated based on baseline physical examination, comorbidities on presentation, APPLE score, and components of the complete blood count and biochemistry in dogs[12] and cats.[13]

Data were collected regarding time to the start of insulin infusion, average dose of insulin given per hour, and time until the resolution of ketosis. Medical records were also reviewed to identify any deviations in study protocol and complications during therapy, including changes in BG concentration >5 mmol/L/h (90 mg/dL/h), instances of BG concentration <7 mmol/L (126 mg/dL) and <4.5 mmol/L (81 mg/dL), rapid decrease in corrected sodium (>5 mmol/L [5 mEq/L] change over 12 h) or development of hyponatremia (defined as sodium <135 mmol/L [<135 mEq/L]), occurrence of anemia (defined as PCV <30% in cats and <35% in dogs), and serum potassium or phosphorus concentrations outside of reference intervals. LOH and outcome (defined as survival to discharge [STD], euthanasia, or cardiopulmonary arrest) were recorded.

2.1 | Statistical methods

Data were analyzed using commercial statistical software.[h] Continuous variables were assessed for normality using the Shapiro–Wilk test. For descriptive purposes, normally distributed variables were described using mean (± standard deviation) and nonnormally distributed variables were described as median (interquartile range). Categorical data were described using frequencies or percentages. Student's *t*-test and Mann–Whitney *U* test were used to compare groups for continuous parametric and nonparametric variables, respectively. Chi-square and Fisher's exact tests were used to compare categorical variables between groups. Correlation between calculated mortality probability at presentation and LOH (cats and dogs) and correlation between resolution of ketosis and LOH (dogs) were assessed using Spearman rank correlation.

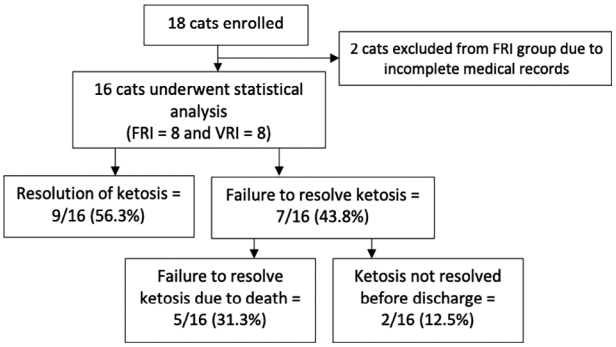

FIGURE 1 Outcome of cats with diabetic ketoacidosis (DKA) enrolled into study.

3 | RESULTS

3.1 | Cats

Eighteen cats were enrolled. All cats were recruited from the university teaching hospital population. Two cats, both from the FRI randomized group, were later excluded from statistical analysis because of incomplete medical records. Eight cats therefore received the FRI and 8 cats received the VRI protocol (Figure 1). Baseline characteristics are presented in Table 1. Comorbidities are reported in Table 2. Data averages for all cats are summarized in Table 3.

Ketosis resolved in 9 of 16 cats (56.3%) with an overall median time to resolution of 72 hours (13.5–73 h). All cats that died (5/16 [31.3%]) failed to achieve resolution of ketosis. A further 2 cats (12.5%) failed to achieve resolution of ketosis before discharge (Figure 1). There was no difference between FRI and VRI groups for baseline BHB concentration, baseline blood pH, time to initiation of insulin therapy, or the rate of insulin infusion until resolution of ketosis (Table 5). In cats without resolution of ketosis, the minimum blood BHB concentration ranged from 0.8 to 6.8 mmol/L in the FRI group and from 1.9 to 3.2 mmol/L in the VRI group. Of the 8 cats assigned to the VRI, 4 (50%) had persistent hyperglycemia (>15 mmol/L [>270 mg/dL]) and consequently insulin infusion rates were never varied. Of these cats, 3 (75%) never had resolution of ketosis and received the insulin infusion until death. In the FRI group, 4 of 8 cats (50%) never achieved BHB concentration <0.6 mmol/L and of these, 2 were still receiving insulin infusion at the time of death.

Complications are described in Table 4. No cats had a decrease in BG concentration below 4.5 mmol/L (81 mg/dL), but 6 of 16 cats (37.5%; 4

TABLE 1 Baseline characteristics of cats and dogs with diabetic ketoacidosis (DKA) enrolled in the current investigation.

		Cat			Dog		
		FRI ($n = 8$)	VRI ($n = 8$)	*P*-value	FRI ($n = 10$)	VRI ($n = 10$)	*P*-value
Age (months)		115 (54.3)	130 (52.0)	0.54	82 (39.8)	94 (13.3)	0.44
Sex	Neutered	8 (100%)	7 (87.5%)	1	7 (70.0%)	8/10 (80.0%)	–
	Male	3 (37.5%)	6 (75%)	0.31	6 (60.0%)	3 (30.0%)	–
	Female	5 (62.5%)	2 (25%)	–	4 (40.0%)	7 (70.0%)	–
Weight (kg)		4.5 ± 1.45	4.1 ± 1.17	0.8	8.3 ± 1.34	11.7 ± 3.9	0.82
Breeds		6 DSH, 1 Siamese, 1 Burmese	7 DSH, 1 Cornish Rex	n/a	3 terrier, 3 mixed-breed, 1 poodle, 1 chihuahua, 1 border collie, 1 schnauzer	4 terrier, 4 mixed-breed, 1 Cavalier King Charles spaniel, 1 schnauzer,	n/a
Previous diagnosis of diabetes mellitus		2 (25%)	3 (37.5%)	1	3/8 (37.5%)	2/8 (25%)	1
Mortality probability based on APPLE score (%)[12,13]		40 (22.3)	73 (43.0)	0.11	13.0 ± 27.4	42.0 ± 29.9	0.32

Note: Normally distributed data are expressed as mean ± standard deviation. Data with nonnormal distributions are expressed as median (interquartile range). Proportions are expressed with the total number of animals and the percentage in parentheses.
Abbreviations: FRI, fixed-rate insulin infusion protocol; n/a, not applicable; VRI, variable-rate insulin infusion protocol.

TABLE 2 Absolute number of cats and dogs with concurrent diseases amongst the study population.

	Cat		Dogs	
Concurrent disease	FRI ($n = 8$)	VRI ($n = 8$)	FRI ($n = 10$)	VRI ($n = 10$)
Pancreatitis	3	2	4	2
Urinary system (acute kidney injury/acute on chronic kidney disease/urinary tract infection)	4	3	2	2
Hepatobiliary disease	1	2	0	1
Cardiac disease	0	1	0	0
Neurologic disease	0	0	1	0

Abbreviations: FRI, fixed-rate insulin infusion protocol; VRI, variable-rate insulin infusion protocol.

on FRI and 2 on VRI protocols) had BG concentration measured below 7 mmol/L (126 mg/dL), necessitating temporary cessation of insulin administration. Two of 16 cats (12.5%), both from the VRI group, had a decrease in corrected sodium >5 mmol/L (90 mg/dL) over a 12-hour period, but this was not associated with clinical signs. One cat required a blood transfusion due to anemia attributed in the clinical notes as secondary to gastrointestinal hemorrhage.

Length of hospitalization and STD for cats receiving FRI and VRI protocols are summarized in Table 5. Eleven of 16 (68.8%) cats survived to discharge. Mean LOH for cats that survived was 178 ± 28.2 hours. Calculated mortality probability based on APPLE score at presentation was not correlated with LOH ($r^2 = -0.1$, $P = 0.74$) and was not different between survivors and nonsurvivors. All cats that died did so within 78 hours of admission. Four of the 5 (80%) nonsurvivors died from cardiopulmonary arrest and the other was euthanized. No cat that died achieved resolution of ketosis.

3.2 | Dogs

Twenty-three dogs were enrolled. Two dogs were treated at the private referral center and the remainder at the university teaching hospital. Three dogs were excluded from statistical analysis—1 due to an incomplete medical record (FRI group) and 2 because review of the medical history showed that long-acting insulin had been administered within 12 hours of presentation (1 each from VRI and FRI groups). Baseline characteristics and comorbidities are presented in Tables 1 and 2, respectively. There were no significant differences in any of the baseline characteristics or incidence of comorbidities between dogs that received either insulin protocol. Data averages for all dogs are summarized in Table 3.

There was no significant difference between protocol groups for baseline blood BHB concentration, baseline blood pH, or time to initiation of insulin therapy (Table 5). Ketosis resolved in 19 of 20 (95%) dogs with an overall mean time to resolution of 27.8 ± 13.1 hours. Only 1 dog (5%) did not achieve resolution of ketosis (lowest blood BHB concentration was 1 mmol/L); however, this dog was still discharged from the hospital.

For the remaining 19 of 20 dogs (95%), there was no difference in time to resolution of ketosis between protocols, although the insulin rate was 25% higher in the FRI group compared with the VRI group (Table 5). All dogs had resolution of hyperglycemia.

All observed complications are recorded in Table 4. No dogs had a decrease in BG concentration below 4.5 mmol/L (81 mg/dL). However, 5 of 20 dogs (25%; 3 on FRI and 2 on VRI protocols) had a

TABLE 3 Summary of insulin, ketone, and hospitalization data for dogs and cats with diabetic ketoacidosis (DKA) receiving either fixed-rate (FRI) or variable-rate (VRI) insulin infusions.

	Cats	Dogs
Time to starting insulin infusion (h)	5.8 ± 3.9	4.7 ± 2.3
Baseline ketones (mmol/L)	5.8 ± 1.2	5.4 ± 2.2
Number of animals achieving resolution of ketonemia (serum ketones <0.6 mmol/L)	9/16 (56.3%)	19/20 (95%)
Survival to discharge	11/16 (69%)	14/20 (70%)
Time to ketones <0.6 mmol/L if did resolve (h)	72 (61.5)	27.8 ± 13.1
Time to death (h)	58 (38.3)	72 (68)
Baseline blood glucose mmol/L / (mg/dL)	24.4 ± 6.9 [439.2 ± 124.2]	31.2 ± 6.3 [561.6 ± 113.4]
Baseline pH	7.09 ± 0.04	7.15 ± 0.03

TABLE 4 Incidence of complications and interventions in dogs and cats with diabetic ketoacidosis (DKA) receiving either fixed-rate (FRI) or variable-rate (VRI) insulin infusions.

	Cat		Dog	
	FRI	VRI	FRI	VRI
β-hydroxybutyrate never <0.6 mmol/L	4	4	1	0
Change in BG concentration >5 mmol/L/h (90 mg/dL)	0	0	0	0
BG concentration <7 mmol/L (126 mg/dL)	4	2	3	2
BG concentration <4.5 mmol/L (81 mg/dL)	0	0	0	0
Change in corrected sodium >5 mmol/L/h (5 mEq/L/h)	0	2	0	0
Development of hyponatremia	2	1	0	0
Worsening anemia	1	0	2	3
Blood transfusion	1	0	0	0
Worsening of hypokalemia	1	0	0	0
Worsening of hypophosphatemia	0	0	1	0
Phosphate supplementation	2	5	2	0
Magnesium supplementation	1	2	0	0
Norepinephrine administration	0	3	0	1
Sodium bicarbonate administration	2	1	0	0
Feeding tube placement	1	1	3	1

decrease in BG concentration below 7 mmol/L (126 mg/dL). Five of 20 dogs (25%) became anemic but only 1 (5%) received a blood transfusion. This anemia was recorded in the clinical notes to be secondary to gastrointestinal bleeding.

LOH and STD for dogs receiving FRI and VRI protocols are reported in Table 5. Fourteen of 20 (70%) dogs survived to discharge. Mean LOH for all dogs was 159 ± 33.4 hours. Dogs on the FRI protocol had a significantly shorter LOH but this was only moderately correlated with time to resolution of ketosis ($r_s = 0.32$, $P = 0.02$). Calculated mortality probability was not different between survivors and nonsurvivors and was not correlated with LOH ($r_s = -0.38$, $P = 0.27$).

All 6 dogs that died did so after resolution of ketosis with a median time to death of 96 hours (6–108 h) postadmission. Of these, 4 of 6 (66.6%) deaths were associated with respiratory deterioration secondary to suspected aspiration pneumonia, 1 had an inoperable pancreatic abscess, and 1 was euthanized due to persistent anorexia and gastrointestinal signs.

4 | DISCUSSION

In this patient population, there was not a clinically significant difference in time to resolution of ketosis in cats and dogs with DKA receiving insulin by an FRI or a VRI. In the feline group, statistical comparison of efficacy was limited due to 7 of 16 (43.8%) cats failing to achieve resolution of ketosis before death or discharge. As all cats that died did so within 78 hours of study enrollment, their STD would have likely increased the time to ketone resolution in their respective groups.

The failure to achieve resolution of ketosis was higher than previously reported (ranging from 0% to 25%),[8,10,14,15] which may reflect

TABLE 5 Comparison of insulin, ketone, creatinine, and hospitalization parameters for cats and dogs with diabetic ketoacidosis (DKA) receiving either fixed-rate (FRI) or variable-rate (VRI) insulin infusion protocols.

	Cat			Dog		
	FRI	VRI	*P*-value	FRI	VRI	*P*-value
Time to starting Insulin (h)	3.3 ± 1.1	5.0 ± 2.6	0.13	4.29 ± 2.5	5.1 ± 2.45	0.63
Baseline ketones (mmol/L) [mg/dL]	5.9 ± 1.2 [34.3 ± 6.9]	5.0 ± 1.4 [29.1 ± 8.1]	0.26	5.9 ± 1.6 [34.3 ± 9.3]	5.1 ± 2.3 [26.6 ± 13.4]	0.55
Baseline blood glucose (mmol/L)	23 .5 ± 7.1 [423 ± 127.8]	27.7 ± 4.5 [498.6 ± 81.0]	0.28	31.5 ± 3.5 [567.0 ± 63.0]	30.5 ± 8.5 [549.0 ± 153.0]	0.98
Baseline pH	7.08 ± 0.09	7.07 ± 0.09	0.89	7.14 ± 0.07	7.16 ± 0.13	0.71
Baseline creatinine (μmol/L) [mg/dL]	89 (49) [1.01 (0.55)]	113 (275) [1.28 (3.11)]	0.25	83 (58) [0.94 (0.66)]	150 (262) [1.7 (2.96)]	0.11
Resolution of ketonemia	5/8	4/8	1.00	9/10	10/10	1.00
Insulin rate until resolution of ketonemia (IU/kg/h)	0.1 (0.04)	0.09 (0.17)	n/a	0.1 (0.09)	0.08 (0.03)	0.04*
Time to β-hydroxybutyrate <0.6 mmol/L [<3.5 mg/dL] if achieved (h)	48 (38.25)	37 (40)	n/a	31.8 ± 16.1	25.1 ± 9.8	0.89
Hospitalization time for patients discharged (h)	165.2 ± 27.4	120.3 ± 34.6	n/a	129.3 ± 32.2	200.3 ± 47.5	0.005*
Survival to discharge	6/8	5/8	1	8/10	6/10	0.63

Note: An asterisk represents a *P*-value of <0.05 and statistical significance.
Abbreviation: n/a, not applicable.

either a more severely affected population, increased frequency and severity of comorbidities, or more stringent criteria for resolution of ketosis in the current study. The lack of severity scoring in other studies of cats with DKA limited the ability to make comparisons to the current population and would be beneficial to include in future studies of patients with DKA. The lack of significant difference between admission severity scores for survivors and nonsurvivors may also reflect the need for a different scoring system in this patient population.

In this study, resolution of ketosis was defined as blood BHB concentration <0.6 mmol/L. In other studies, resolution criteria have included undetectable urine or serum acetoacetate[10] or serum BHB concentration <2.55[14] or <1 mmol/L.[15] Semiquantitative urine test strips only measure acetoacetate, the serum concentrations of which are relatively lower than BHB in DKA. As such, these should no longer be considered appropriate for determining resolution of ketosis.[16] We chose a lower blood BHB concentration than other studies to ensure a complete resolution of ketosis. However, a more lenient criteria could be considered for future studies, particularly for cats in which basal serum ketone concentration in "healthy" diabetic patients could be higher than 0.6 mmol/L. Standardized consensus veterinary definitions for diagnosis of DKA and resolution of ketosis in both dogs and cats would be beneficial for comparing protocols in future studies.

In dogs, resolution of ketosis and average time to resolution of ketosis were similar to previously reported studies.[7,18] In our study, overall resolution was 95% as opposed to 100% in others.[7,17] Average time to resolution of ketosis in the current study was 27.8 hours, while other studies have reported times to resolution of 26–43.5 hours (using undetectable urine acetoacetate[7] or <2 mmol/L serum BHB[17] as measures of resolution). The time to resolution of ketosis was not different between dogs who received either fixed or variable insulin infusions despite a 25% higher mean insulin rate in the dogs receiving FRI. Given the overlap of standard deviations between the groups, this may reflect the small sample size. Although not prospectively recorded in this study, the impact of body condition on the dose–response of insulin infusions may also have further limited our ability to see a difference in ketosis resolution.

In retrospect, protocolizing changes in insulin rate should also have been included in the study design, as in human guidelines, due to the initial insulin resistance that can occur with severe hyperglycemia.[20] High rates of persistent hyperglycemia, in the feline group particularly, resulted in similar insulin infusion rates in the VRI and FRI groups.

Neither species had significantly increased rates of complications with the FRI, although the overall incidence of complications was low and this study should not be considered sufficiently powered to confirm this finding. More cats and dogs receiving the FRI did require their insulin infusion to be temporarily stopped due to BG concentration <7 mmol/L (126 mg/dL), and with a larger population this subset of patients might have been larger. Close BG concentration monitoring should be used in animals receiving FRI or VRI, with a greater emphasis on delivering higher dosages (rates or concentrations) of dextrose when using an FRI protocol. Higher rates of fluid delivery may be problematic in cats unable to tolerate high volumes of IV fluids, particularly if no central venous access is present to facilitate the administration of higher concentrations of dextrose. Ideally all patients receiving an FRI would have central venous access to facilitate administration of up to 10% dextrose.

Although comparisons of illness severity and conclusions regarding LOH and STD have a risk of type II error due to the small sample size, the insulin protocol did not appear to influence LOH and STD in cats or dogs with DKA. However, irrespective of protocol, all cats that died (only 1 due to euthanasia) did so within 78 hours without resolution of ketosis, suggesting that severity of comorbidities in cats (rather than owner factors such as motivation or finances) should be considered in relation to outcome. All dogs that died did so following resolution of ketosis, suggesting that the development of complications was more relevant to outcome in this population.

In dogs, randomization to an FRI protocol resulted in a shorter LOH, but the fact that resolution of ketosis was not significantly faster compared to the VRI group suggests other factors may be more important for LOH. Given that all dogs that died in this study already had resolution of ketosis, the development of complications, particularly aspiration pneumonia, seemed more relevant to outcome. However, it should be noted that a larger sample size may have resulted in a different spectrum and frequency of complications. Variable mortality rates have been reported for DKA in cats (0%–41.9%[8,10,14,15]) and dogs (8.3%–30%[7,18,21]), and further prospective investigation clearly documenting the time and reason for death or euthanasia in DKA patients is warranted.

There are several limitations to this study. Regarding design, our study was only powered to detect whether time to resolution of ketosis differed by more than 14 hours between protocols. Smaller differences may therefore not have been detected. However, a difference of 14 hours was deemed to be a clinically relevant time frame. This sample size calculation was also based on both groups being relatively similar but the population was still small and therefore prone to heterogenicity. For example, despite there being no significance difference in baseline creatinine between groups (Table 5), difference and changes in renal ketone clearance could have impacted the time to resolution of ketosis. Other comorbidities were common (Table 2) and could have led to variable insulin resistance, but incomplete quantifiable diagnostic testing (e.g., species-specific pancreatic lipase measurements) across the groups limited further statistical analysis. Future studies could also try to take into the consideration the impact of individual hormonal counterregulatory responses that would impact an individual patient's response to insulin. This population also consisted mainly of secondary or tertiary referral cases, limiting the applicability to practices where illness severity might be lower. Lower levels of insulin resistance in a less severely affected population may have improved the ability to document a difference between the protocols.

Although this study was only designed to investigate whether insulin protocol alone could make a significant difference in time to resolution of ketosis, future studies could investigate the impact of confounding factors such as renal impairment and counterregulatory responses. Standardization of a greater component of patient care (e.g., volume resuscitation, acid base and electrolyte correction, and provision of nutrition) could reduce the impact of heterogenicity and may help to focus conclusions about the correlation between LOH and STD on the resolution of ketosis.

The average rate of the insulin infusion and many clinical parameters were collected from medical records and relied on accurate recording. This study also utilized point-of-care ketometers. These have been tested in dogs and cats with DKA and correlate well with the enzymatic laboratory method,[22] but even the use of the same brand of ketometer[a] across sites might be associated with higher error than submitting all samples to 1 laboratory for enzymatic ketone measurement. Given the multicenter aspect of this study, this was not feasible but it was considered unlikely to dramatically impact the results.

In summary, an FRI may be used to treat dogs and cats with DKA; however, in a referral population with high illness severity, this is unlikely to significantly hasten resolution of ketosis. However, in this population, an FRI is also unlikely to result in an increased incidence of complications unless a high rate or concentration of dextrose supplementation cannot be maintained or frequent monitoring of BG concentration is not possible. The insulin infusion protocol appears unlikely to influence LOH or STD, but the impact of comorbid disease severity, insulin resistance, and the development of complications not directly related to DKA warrants further investigation. Further prospective studies with greater standardization and larger cohorts are needed to verify that insulin protocol has minimal impact on outcome.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

OFFPRINTS

Offprints will not be available from the authors

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ENDNOTES

[a] FreeStyle Optium Neo H-ketone meter, Abbott Laboratories, Abbott Park, UK.
[b] https://clincalc.com/stats/samplesize.aspx; ClinCalc LLC, Arlington Heights, IL.
[c] https://www.random.org/; RANDOM.ORG, Chesterfield, VA.
[d] Actrapid, Novo Nordisk, Denmark.
[e] Alphatrak, Zoetis, Parsippany-Troy Hills, NJ.
[f] ABL800 FLEX analyser, Radiometer and ABL80 Flex analyser, Radiometer, Sussex, UK.
[g] SNAP cPL and Spec cPL, IDEXX, Westbrook, ME.
[h] SPSS Software, IBM, New York, NY.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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