Original Study

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A pilot study comparing a protocol using intermittent administration of glargine and regular insulin to a continuous rate infusion of regular insulin in cats with naturally occurring diabetic ketoacidosis

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Abstract

Objective – The goal of this pilot study was to compare regular insulin administered by continuous rate infusion (CRI) to an approach using insulin glargine and regular insulin administered intermittently.
Design – Prospective randomized clinical trial.
Setting – University teaching hospital.
Animals – Sixteen cats with diabetic ketoacidosis (DKA).
Interventions – Cats with DKA were randomized to either low-dose regular insulin CRI (CRI group; $n = 8$) or intermittent short- and long-acting insulin injections (subcutaneous [SC] glargine plus intramuscular [IM] regular insulin; SC/IM group; $n = 8$).
Measurements and Main Results – Time of normalization of pH, bicarbonate, hyperglycemia, ketonemia, and appetite, as well as duration of hospitalization were recorded. Eleven of 16 cats (59%) survived to discharge, with no difference in survival between groups ($P = 0.99$). Times of resolution of hyperglycemia ($P = 0.02$) and ketonemia ($P = 0.04$), and normalization of pH ($P = 0.04$), and bicarbonate ($P = 0.03$) were significantly shorter in the SC/IM group. Cats in the SC/IM group also had a significantly shorter duration of hospitalization (SC/IM: median = 54 hr [range, 19–118 hr]; CRI: median = 111 hr [range, 58–271 hr]; $P = 0.04$). Time of first meal was not significantly different between groups.
Conclusions – Although further research is required, an approach using intermittent short- and long-acting insulin injections appeared to be an effective option for treatment of DKA in cats.

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Keywords: diabetes, cats, diabetic ketoacidosis, insulin

Abbreviations

CRI	continuous rate infusion
DM	diabetes mellitus
DKA	diabetic ketoacidosis
IM	intramuscular
SC	subcutaneous

Introduction

Diabetic ketoacidosis (DKA) is a life threatening complication of diabetes mellitus (DM). Medical management of DKA can be challenging as cats with DKA typically present in a state of metabolic acidosis, profound volume depletion, and electrolyte imbalance.[1] In one study of

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42 cats with either diabetic ketosis or DKA, 11 cats died or were euthanized, and survivors were hospitalized for an average of 5 days.[2] Treatment for cats with DKA includes IV fluids and treatment for metabolic derangements, but insulin remains the mainstay of treatment.[3] Regular insulin typically is administered according to a sliding scale as an IV continuous rate infusion (CRI), although intramuscular (IM) or subcutaneous (SC) routes of insulin also can be used.[1,3,4] Treatment of DKA can be complicated by episodes of hypoglycemia, hypokalemia, and hypophosphatemia and requires intensive blood glucose monitoring, frequent fluid and electrolyte adjustments, and, often, prolonged hospitalization. This can represent a large financial burden on clients.

In human medicine, there has been interest in simplifying treatment for DKA. Diabetic ketoacidosis is an important cause of morbidity and mortality in people and remains the most common cause of death in children with type 1 diabetes mellitus.[5,6] Low dose regular insulin by CRI administered in an intensive care setting remains the standard of care for management of moderate to severe DKA.[7,8] However, alternative insulin protocols are being tested in people with DKA.[9–13,a] For example, a retrospective cohort study of children with moderate and severe DKA showed that SC insulin glargine in addition to a regular insulin CRI resulted in a faster resolution of acidosis and a trend toward shorter hospital stays compared to regular insulin alone.[13] A prospective study, published in abstract form only, compared people with DKA who received regular insulin by CRI to regular insulin CRI plus glargine SC and found that the addition of glargine reduced insulin requirements, duration of acidosis, and hospital stay.[a] Two protocols compared the insulins lispro or aspart administered SC to a CRI of regular insulin and found no significant difference between groups, suggesting that this approach may represent a simplified approach to the treatment of DKA.[9,12]

In dogs, one study reported their results comparing regular and lispro insulins administered by CRI for the treatment of DKA.[14] In that study, the median time to resolution of biochemical parameters associated with DKA was significantly shorter in dogs in the lispro group compared to those in the regular insulin group. Finally, a recently published study evaluated the effects of intramuscular (IM) glargine administration in cats with DKA (with or without SC glargine).[15] In that study, all 15 cats survived and were discharged from the hospital.

Glargine has shown promise as a maintenance therapy in cats with DM,[7,16,17] but has not been compared to treatment for DKA in cats using a regular insulin CRI. As a long-acting insulin, glargine administered SC may be useful in conjunction with regular insulin for the treatment of DKA in cats. Therefore, the objective of this pilot study was to compare a regular insulin CRI method of treating cats with DKA to glargine administered SC in conjunction with regular insulin administered IM.

Materials and Methods

Eligible client-owned cats presented to the Tufts Cummings School of Veterinary Medicine were recruited into the study. Inclusion criteria included cats with DKA that were newly diagnosed with DM or those with known DM. Cats with congestive heart failure, venous pH < 6.9, or those who were receiving glucocorticoid treatment were excluded. At or near the time of presentation, a complete medical history and physical examination were performed. Blood was collected by jugular venipuncture for a complete blood count, serum biochemistry profile, and venous blood gas analysis. A diagnosis of DKA was made based on documentation of venous pH < 7.35, ketonemia or ketonuria, and hyperglycemia (blood glucose concentration > 14 mmol/L [>250 mg/dL]).

Eligible cats were randomly assigned to either the low-dose regular insulin CRI (CRI group) or the intermittent SC glargine with IM regular insulin (SC/IM group). A randomization table was generated using a computer program, and as each cat enrolled in the study, it was assigned to the next group in the table. In addition to insulin, all cats received standard care for DKA, including but not limited to aggressive IV fluids to replace deficits and meet ongoing losses, potassium supplementation, phosphorous supplementation, antimicrobials, and blood transfusions, if indicated. For each cat in both groups, blood glucose was monitored every 2–4 hours using a handheld glucose and ketone meter.[c] Blood ketones were evaluated every 8 hours using the same handheld meter.[c] Venous blood gas, electrolytes, and renal values were evaluated every 8 hours using a point-of-care analyzer.[d] Cats in the CRI group received an IV CRI of regular insulin based on a modified sliding scale (Table 1).[4] A dose of 1 unit/kg/day was diluted in 240 mL of 0.9% sodium chloride and the first 50 mL was run through the line and discarded prior to connection to the cat. Blood glucose was evaluated by glucometer every 2–4 hours. The administration rate of this solution and dextrose supplementation were adjusted based on the modified sliding scale (Table 1).[4] A fresh insulin infusion was prepared q 24 hrs.

Cats in the SC/IM group received glargine at a dose of 0.25 U/kg SC every 12 hr. In addition, these cats received an additional 1 unit of regular insulin IM up to every 6 hours if the blood glucose was > 14 mmol/L

Table 1: Sliding scale for adjustment of insulin administration used for the cats with diabetic ketoacidosis randomized to the group to receive regular insulin by continuous rate infusion

If glucose is ... (mg/dL)	Fluids	Insulin – 1 U/kg regular insulin/ 240 mL 0.9% NaCl (mL/hr)
>500	0.9% NaCl	20
400–500	0.9% NaCl	15
250–399	0.9% NaCl	10
80–249	0.9% NaCl + 2.5% dextrose	0-5
<80	0.9% NaCl + 5% dextrose + bolus IV 0.5 ml/kg 50% dextrose	0

Note: Potassium phosphate and potassium chloride also were added as needed based on serum potassium and phosphorus concentrations.
NaCl, sodium chloride.

[>250 mg/dL] at those time points. Insulin was not administered at other time points regardless of blood glucose concentration. If blood glucose was below 14 mmol/L [250 mg/dL] at the time of the evaluations performed every 2–4 hr, dextrose was added to the IV fluids (2.5% dextrose if blood glucose was 4.4–13.8 mmol/L [80–249 mg/dL] and 5.0% dextrose plus a bolus of 50% dextrose [0.5 mL/kg body weight] for glucose <4.4 mmol/L [80 mg/dL]).

The primary endpoint of this study was established as the time until normalization of pH, which was defined as venous pH = 7.35–7.44. Secondary endpoints included duration of hospitalization, time until the cat's first meal (ie, any oral intake of food), time until resolution of hyperglycemia (defined as glucose < 14 mmol/L [<250 mg/dL]) and ketonemia (defined as ketones <2.55 mmol/L on the portable ketometer),[18] and time to normalization of bicarbonate (defined as bicarbonate = 18–24 mmol/L). The study was approved by the university's Institutional Animal Care and Use Committee and all owners signed an informed consent form.

Statistical analysis

Data were evaluated visually and using the Komogorov–Smirnov test. Since many of the data were not normally distributed, data are presented as median (range). Categorical variables were compared between groups (CRI vs SC/IM) using Fisher's exact tests. Continuous data were compared between groups with independent *t*-tests (normally distributed data) or Mann–Whitney U tests (skewed data). Cats that did not achieve a specific endpoint (eg, resolution of hyperglycemia) and cats that died before resolution of that endpoint were censored for the purposes of survival analysis, with the time of death used for cats that died. Kaplan–Meier curves and log-rank tests were used to compare time to endpoint between the CRI and SC/IM groups. Statistical analysis was performed using a commercial statistical software package.[e] P values <0.05 were considered statistically significant.

Results

Sixteen cats were enrolled in the study. Two cats were initially recruited and randomized but were subsequently dropped from the study due to major protocol deviations. For 1 cat, insulin treatment was switched from regular insulin CRI to SC/IM glargine insulin by the primary clinician before the cat reached any of the study endpoints. In the second cat, the clinician elected to switch the cat to SC glargine insulin only before the cat achieved any of the study endpoints. Two additional cats were enrolled to replace these 2 cats (and assigned to the same groups the 2 cats were originally randomized to) so that a total of 16 cats (CRI, $n = 8$ and SC/IM, $n = 8$) completed the study. All results are presented only for the 16 cats that completed the study (ie, achieved the primary endpoint, died or was euthanized, or was discharged). There were no significant differences between groups in age ($P = 0.34$), sex ($P = 0.52$), breed ($P = 0.49$), body weight ($P = 0.21$), or body condition score ($P = 0.55$; Table 2). There were 6 cats with newly diagnosed DM in the CRI group and 3 cats with newly diagnosed DM in the SC/IM group ($P = 0.32$). There also were no significant differences in baseline ketones, pH, bicarbonate, or biochemistry profile variables (Table 2).

Eleven of the 16 cats (69%) survived to discharge (CRI group, $n = 6$; SC/IM group, $n = 5$; $P = 0.59$). Of the 5 cats that died, 1 cat died and 4 cats were euthanized. Median time to death was 24 hours (range, 19–76 hr). For the 4 cats that were euthanized, the owners elected euthanasia for worsening condition or failure to respond to treatment for DKA. The cat that died had cardiac arrest and the owner elected to have no resuscitation efforts performed. There were no significant differences between groups for the number of cats that achieved each endpoint (Table 3), but there were significantly shorter times to normalization of pH ($P = 0.04$) and bicarbonate ($P = 0.03$), as well as times to resolution of hyperglycemia ($P = 0.02$) and ketonemia ($P = 0.04$) in the SC/IM group (Table 3). Time of first meal ($P = 0.36$) was not significantly different between groups.

Table 2: Baseline characteristics of cats with diabetic ketoacidosis randomized to receive regular insulin by continuous rate infusion (CRI) or to receive glargine insulin subcutaneously with intermittent administration of regular insulin intramuscularly (SC/IM). Data are presented as median (range)

	CRI ($n = 8$)	SC/IM ($n = 8$)	*P* value
Age (years)	11.9 (6.6–18.4)	10.1 (7.0–17.3)	0.34
Sex			0.52
Male	4 (3 castrated)	4 (4 castrated)	
Female	4 (all spayed)	4 (3 spayed)	
Breed			0.49
DSH/DLH	6	4	
Himalayan	1	1	
Abyssinian	0	1	
Maine Coon	1	0	
Ragdoll	0	1	
Siamese	0	1	
Body weight (kg)	3.5 (2.7–5.6)	4.3 (2.2–5.1)	0.21
Body condition score (1–9)	4 (3–7)	5 (3–7)	0.55
Serum glucose (mmol/L)	20.0 (13.4–54.3)	27.5 (16.9–40.8)	0.40
Serum glucose (mg/dL)	361 (259–978)	496 (305–736)	0.40
pH	7.20 (7.06–7.29)	7.26 (7.05–7.34)	0.29
Bicarbonate (units)	9.6 (6.2–15.5)	11.1 (9.0–17.3)	0.07
Blood ketones (mmol/L)	5.5 (2.9–6.8)	4.9 (1.6–8.1)	0.50
Creatinine (μmol/L)	106.1 (53.0–327.1)	1.8 (1.0–6.3)	0.17
Creatinine (mg/dL)	1.2 (0.6–3.7)	1.8 (1.0–6.3)	0.17
Total bilirubin (μmol/L)	8.6 (1.7–174.4)	23.9 (0.0–130)	0.21
Total bilirubin (mg/dL)	0.5 (0.1–10.2)	1.4 (0.0–7.6)	0.21
Gamma glutamyl transferase (U/L)	1 (1–4)	2 (2–6)	0.53
Alkaline phosphatase (U/L)	47 (24–69)	57 (35–77)	0.46
Alanine aminotransferase (U/L)	141 (60–758)	150 (35–575)	0.82
Asparate aminotransferase	139 (27–481)	151 (13–456)	0.64

DSH, domestic shorthair; DLH, domestic longhair.

Table 3: Outcomes for cats with diabetic ketoacidosis randomized to receive regular insulin by continuous rate infusion (CRI) or to receive glargine insulin subcutaneously with intermittent administration of regular insulin intramuscularly (SC/IM). Data for time to events are presented as median (range) for those cats that achieved that individual endpoint

	CRI ($n = 8$)	SC/IM ($n = 8$)	*P* value
Survived to discharge (number of cats)	6	5	0.59
Time to discharge (hr)	153 (87–271)	92 (35–118)	**0.04**
Normalization of pH (number of cats)	7	5	0.25
Time to normalization of pH (hr)	41 (14–97)	23 (6–40)	**0.04**
Normalization of bicarbonate (number of cats)	5	4	0.61
Time to normalization of bicarbonate (hr)	92 (41–137)	39 (6–69)	**0.03**
Resolution of hyperglycemia (number of cats)	6	8	0.13
Time to resolution of hyperglycemia (hr)	12 (4–48)	9 (4–20)	**0.02**
Resolution of ketonemia (number of cats)	6	6	1.00
Time to resolution of ketonemia (hr)	62 (40–118)	44 (18–71)	**0.04**
Ate during hospitalization (number of cats)	6	5	0.59
Time to first meal (hr)	29 (2–244)	20 (6–48)	0.36

Cats in the SC/IM group also had a significantly shorter duration of hospitalization ($P = 0.04$).

Discussion

Treating DKA in cats can be labor intensive and expensive. Therefore, a simplified but effective approach to management of cats with DKA would be beneficial for cats and their owners, as well as for the veterinary healthcare team. While there are no studies in people with the exact study design to the current study, a recent study comparing the use of a regular insulin CRI with or without the addition of glargine in people with diabetes showed no difference in glucose concentrations, insulin dose, or length of time in the intensive care unit between groups.[19] However, patients who received glargine in

addition to the CRI had less rebound hyperglycemia when transitioned off the CRI without increased risk of hypoglycemia.[19] This human study suggests that this new approach is at least no worse than a regular insulin CRI approach and may have some additional benefits (eg, reduction in rebound hyperglycemia when transitioning off the CRI).

Much additional research in cats with DKA is required, but in the current study the simplified approach using intermittent short- and long-acting insulin injections appeared to result in shorter times of several outcomes. This included the time to normalization of pH, as well as secondary endpoints of time to resolution of hyperglycemia and ketonemia, in which times were shorter in cats on the simplified protocol. Due to the design of the study (ie, clinicians were not blinded to the assigned study group), insulin requirements were not compared between the 2 groups but would be important data to collect in future studies. Time of first meal was not found to be significantly different between groups. This may be related to the relatively small sample size, the fact that not all cats ate during hospitalization (11 of 16 cats ate), or to lack of a difference in efficacy.

If future studies can determine that the simplified SC/IM protocol is equal or more effective than the traditional CRI approach based on further studies, it may have a number of advantages such as cost and the ability to administer insulin and perform needed monitoring without 2 IV catheters (since vascular access can be difficult in critically ill cats so that having the availability of more than 1 catheter is not always possible). Although this study is a first step in evaluating this simplified approach compared to the traditional CRI approach, additional research is needed to confirm this finding and to examine the other issues such as ease of use and treatment errors.

Cats in the simplified SC/IM group also had a significantly shorter hospitalization time, with a median hospitalization time of less than half of that of the CRI group. A limitation of this variable is that there were no specifically defined criteria for when a cat would be discharged so this could be influenced by the clinician, the owner, or both. One human study which compared subcutaneous glargine plus regular insulin CRI to regular insulin CRI alone showed a numerically but not significantly ($P = 0.10$) shorter hospitalization time in the glargine group.[13] Although cost of treatment was not assessed in the current study, this would be a useful measurement in future studies. It is anticipated that cost would likely decrease if the hospitalization time was shorter, but this would need to be measured. If cost of treatment could be decreased using this simplified approach to treating cats with DKA with no reduction in efficacy of treatment (or, potentially, an improvement in efficacy), this would be very beneficial for the cats, the cats' owners, and the veterinary healthcare team.

In addition to the numerous previously mentioned limitations (eg, small sample size, 2 cats dropped from the study for major protocol deviations, not all cats achieving the measured endpoint, methodologies), the study has a number of other important limitations that must be addressed. Because of the patient population seen in the authors' hospital and specific study inclusion and exclusion criteria, the patient population in this study may not be representative of all cats treated for DKA. Blood glucose was tested q 2–4 hr in cats so this may have introduced additional variability into the results. Finally, the study was not blinded and while difficult to design a study of this nature that was double-blinded, efforts to address this limitation would be important to consider. Despite these limitations, the results of this pilot study suggest that this approach using intermittent short- and long-acting insulin injections was useful for the treatment of cats with DKA. Further studies are needed with this, and potentially other simplified methods of treating DKA that could result in more effective treatment for cats, with lower cost and less intensive monitoring.

Footnotes

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[d] Stat Profile-M, NOVA Biochemical, Waltham, MA.
[e] Systat 13.0, SPSS, Chicago, IL.

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