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ORIGINAL ARTICLE

Use of Ringer Lactate in the Correction of Diabetic Ketoacidosis Depletion

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Keywords:
Diabetic ketoacidosis, Ringer's solution, Saline solution.

Abstract

Introduction: Diabetic ketoacidosis (DKA) is an emergency often associated with dehydration, and volume replacement is one of its therapeutic pillars. The best fluid for this is uncertain. This study aims to compare the use of Ringer lactate (RL) and saline0.9% (SF0.9%) in the correction of DKA depletion in pediatrics patients. **Methods:** Cross-sectional and analytical study, with ambispective data collection. The inclusion criteria were patients aged 0-14 years, diagnosed with DKA, who received a correction for depletion with SF0, 9% or RL, in the first 24 hours of treatment. The primary outcome was the resolution time of DKA. Secondary outcomes were the amount of insulin infused, volume received and changes in serum sodium, chloride, anion gap, blood glucose, and lactate levels over 24 hours. **Results:** 48 hospitalizations were included: 33 received 0.9% SF and 15 received RL. The median age was 123.5 (20.9-167.2) months and 54.2% were female. The duration of DKA was observed to be lower in the RL group (median: 18 [4-39] hours) compared to the SF0.9% group (median: 24 [6-80] hours) (p = 0.018). Regarding the rate of insulin infusion, a greater percentage change per hour was shown in the SF0,9% group than in the RL group (p<0,001). Regarding laboratory measurements, there was no statiscal difference between variables in the subgroups. **Conclusions:** The use of TL was associated with faster resolution of DKA compared to that of saline. It suggests that balanced crystalloids may be preferred in the treatment of DKA depletion corretion in pediatric patients.

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INTRODUCTION

Diabetic ketoacidosis (DKA) is the main hyperglycemic emergency in children and adolescents with type 1 diabetes mellitus (T1DM). It results from circulating insulin deficiency and increased levels of counter-regulatory hormones such as glucagon, catecholamines, and cortisol. Biochemical criteria include plasma glucose > 200mg/dL, pH < 7.3 or bicarbonate < 18 mmol/L, and ketonuria (moderate, at least ++) or ketonemia (β-hydroxybutyrate ≥3 mmol/L)[1]. The condition is categorized according to the degree of acidosis as mild (pH < 7.3 or bicarbonate < 15 mmol/L), moderate (pH < 7.2 or bicarbonate < 10 mmol/L), or severe (pH < 7.1 or bicarbonate < 5 mmol/L)[1,2].

Signs and symptoms include dehydration, electrolyte imbalance, and hyperglycemia. Intravenous fluid therapy is a crucial element in the treatment of DKA[1,2]. Treatment protocols include fluid resuscitation within the first hour of care followed by volume depletion correction in 24 to 48 hours[1].

Ample availability and affordability make 0.9% saline solution the intravenous fluid of choice in the main guidelines. However, since it contains 154 mEq/L of chloride, its use has been associated with hyperchloremic metabolic acidosis, which may impair the resolution of DKA[1,3]. Balanced solutions with electrolyte concentrations similar to plasma have been recommended in protocols to avoid the side effects of 0.9% saline solution. Ringer's Lactate is the most commonly used solution, containing approximately 111 mEq/L of 1.4 chloride.

The institution where this study was developed used 0.9% saline solution to correct volume depletion in patients with DKA. In August 2021, it changed its care protocol to use Ringer's lactate to manage volume depletion. This study compares patients treated with Ringer's lactate with patients historically treated with 0.9% saline solution, the time to resolve acidosis, and changes in laboratory tests between the two groups.

METHODOLOGY

This cross-sectional analytical ambidirectional cohort study was conducted in the Pediatric Intensive Care Unit (PICU) of the University Hospital Complex of the Federal University of Paraná (CHC-UFPR). The study period was from January 2019 to July 2021 for retrospective cases (patients given 0.9% saline solution) and from August 2021 to August 2022 for prospective cases (patients given Ringer's lactate).

The medical records of 60 patients aged 0-14 years hospitalized for DKA and treated for volume depletion with 0.9% saline solution of Ringer's lactate for 24 hours were selected. Eight medical records were incomplete; four belonged to patients treated with other solutions, such as 0.45% saline solution. The remaining 48 medical records were included in the study.

Two patients were divided into two groups, one with individuals given 0.9% saline solution (n=33) and another with prospective patients' medical records (n=15). The patients from the two groups were diagnosed with DKA based on the criteria in effect at CHC-UFPR (plasma glucose > 200 mg/dL; pH < 7.3; bicarbonate level < 15 mEq/L; ketonuria/ketonemia).

The study's primary endpoint was the time to resolve ketoacidosis, defined as the moment when pH > 7.4 and bicarbonate > 15 mEq/L. Secondary endpoints refer to the first 24 hours of treatment, including the total insulin administered in IU/kg/h, the total fluid volume given during depletion correction, and changes in serum sodium, chloride, blood glucose, anion gap, and lactate levels.

The following data were recorded: age, sex, body weight, body surface area, presence or absence of a diagnosis of DM1, and procedures performed before admission to the PICU (such as fluid replacement and administration of bicarbonate and insulin in other wards).

Arterial/venous blood gas, electrolytes, and blood glucose levels were collected at 0, 3, 6, 12, and 24 hours after admission to the PICU. The mortality rate was calculated based on the Pediatric Index of Mortality (PIM2).

The data were typed in a Microsoft Excel spreadsheet. Statistical analysis was performed on IBM SPSS Statistics v.28.0.0. The quantitative variables for the two groups (0,9% saline solution and Ringer's lactate) were described based on means and standard deviations or medians and interquartile range in asymmetry cases. The groups were compared using the Student's t-test or the nonparametric Mann-Whitney test.

Categorical variables were described based on absolute and relative frequencies, and comparisons were made using Fisher's exact test. The log-rank test was used to analyze the time to resolve ketoacidosis. Linear mixed models with random slope and intercept were used to evaluate the changes in laboratory parameters in the groups over time (0, 3, 6, 12, and 24 hours).

The Jointpoint Regression Program version 4.9.1.0 Statistical Research and Applications Branch was used to analyze the insulin doses administered over 24 hours. A p-value <0.05 was adopted to indicate statistical significance.

The Institution's Ethics Committee approved the study under opinion number 5,204,356.

RESULTS

The medical records of 48 patients were included in the study. The median age was 123.5 (20.9-167.2) months, and 54.2% were female. A diagnosis of DKA was mentioned in 45.8% of the records, and none had been diagnosed with T1DM. Twenty-one patients were admitted for severe DKA (pH < 7.1), 11 for moderate DKA (pH < 7.2), and 16 for mild DKA (pH < 7.3). Before admission to the PICU, fluid replacement was prescribed to 85.4% of the patients and insulin to 20.8%.

Volume depletion correction was prescribed to 68.7% of the patients in the 0.9% saline solution group (n=33) and 31.3% of the individuals in the ringer's lactate group (n=15) after admission to the PICU. The mean volume administered

per square meter of body surface in 24 hours was 4569 ± 1619 ml, without statistical difference between the groups. The median mortality at admission to the PICU, described based on the PIM2, was 1.7 (1-15) in the group given 0.9% saline solution and 1.7 (0-10) in the ringer's lactate group. No patient died. The general characteristics of the study population and laboratory test results at admission are presented in Table 1.

The median time to resolve ketoacidosis in both groups was 22 (4-80) hours. The duration was shorter in the ringer's lactate group (median: 18 [4-39] hours) compared to the 0.9% saline solution group (median: 24 [6-80] hours), with a significant difference between treatments (p=0.018) (Figure 1).

The analysis of the mean volumes of intravenous insulin (IU/kg/h) administered at different points (0h, 3h, 6h, 12h, and 24h) revealed a statistically significant difference between groups at 24h (p=0.011) (Table 2). Both groups had increases in insulin administration in the first two hours. In the 0.9% saline solution group, volumes stabilized from 3 to 15 hours, increased from 15 to 18 hours, and decreased from 18 to 24 hours. In the ringer's lactate group, a significant decline was

Table 1. General characteristics of the sample and laboratory data on admission

Variável	Depletion correction	n	Mean ± standard deviation	p*
General characteristics				
Age (months)	Serum	33	116,0 ± 36,6	
	Ringer	15	112,3 ± 44,6	0,768
Weight(kg)	Serum	33	31,7 ± 10,5	
	Ringer	15	34,7 ± 14,5	0,417
Length of stay (days)	Serum	33	2,5 ± 1,1	
	Ringer	15	2,2 ± 1,8	0,152
Volume/kg before ICU	Serum	27	32,4 ± 22,8	
	Ringer	12	24,2 ± 20,8	0,104
Glasgow on admission	Serum	30	14,3 ± 1,2	
	Ringer	14	14,6 ± 0,9	0,630
Admission laboratories				
Glucose mg/dL	Serum	33	394,6 ± 144,1	
	Ringer	15	382,7 ± 210,1	0,821
pH	Serum	33	7,10 ± 0,15	
	Ringer	15	7,15 ± 0,16	0,239
Bicarbonate mEq/L	Serum	33	5,7 ± 3,5	
	Ringer	15	7,5 ± 4,4	0,133
Lactate	Serum	33	2,14 ± 1,17	
	Ringer	15	1,67 ± 1,4	0,016
Anion GAP	Serum	33	26,4 ± 6,8	
	Ringer	15	23,8 ± 5,5	0,207
Sodium mEq/L	Serum	33	137,6 ± 9,4	
	Ringer	15	134,1 ± 4,7	0,207
Chloride mEq/L	Serum	33	108,1 ± 7,5	
	Ringer	15	106,3 ± 7,7	0,628
Osmolarity at admission	Serum	33	300,4 ± 22,3	
	Ringer	15	293,4 ± 9,1	0,131
Total volume administered in 24h	Serum	33	5326 ± 2148	
	Ringer	15	4580 ± 2104	0,230

*Teste t de Student para amostras independentes ou teste não-paramétrico de Mann-Whitney, p<0,05

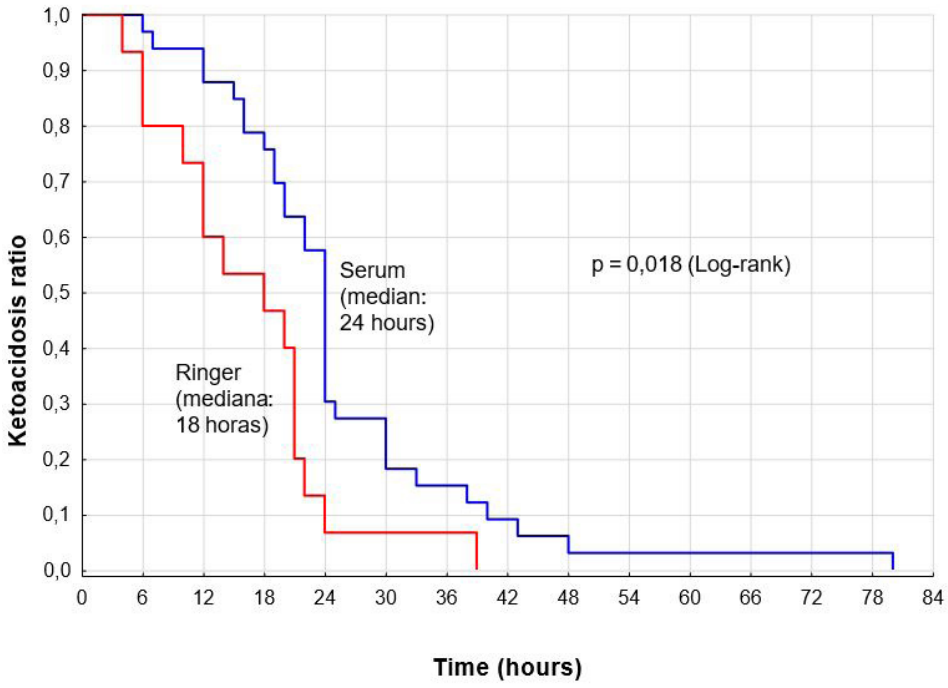


Figure 1. Time elapsed until resolution of acidosis
Caption: Episodes of resolution of diabetic ketoacidosis in each hospitalization.

Table 2. Average amount of intravenous insulin received in IU/kg/h in 24 hours

Time	Treat	n	Insulin	
			Mean ± standard dev	p*
0H	Serum	33	0,026 ± 0,044	
	Ringer	15	0,037 ± 0,048	0,410
3H	Serum	33	0,095 ± 0,029	
	Ringer	14	0,089 ± 0,035	0,584
6H	Serum	33	0,094 ± 0,025	
	Ringer	14	0,087 ± 0,029	0,551
12H	Serum	32	0,094 ± 0,049	
	Ringer	11	0,08 ± 0,029	0,363
24H	Serum	23	0,083 ± 0,051	
	Ringer	8	0,025 ± 0,046	0,011

*Mann-Whitney non-parametric test, p<0.05

seen at two hours, followed by a more accentuated decline at 22 and 24 hours. Figure 2 illustrates the significant difference between the two groups in this parameter (P<0.001).

No significant differences in anion gap, pH, bicarbonate, lactate, sodium, chloride, or glycemia were identified between the groups. A trend towards higher chloride levels was observed in the 0.9% saline solution group (p>0.05). No significant difference was found in serum sodium and lactate levels between the groups.

DISCUSSION

The CHC-UFPR PICU staff has extensive experience treating DKA. Practically all cases of DKA admitted to the service are treated in the unit. In other services, DKA is a condition frequently managed in emergency departments by healthcare personnel from different specialties, not only intensive care.

In this study, volume depletion correction performed with Ringer's lactate was associated with a faster resolution

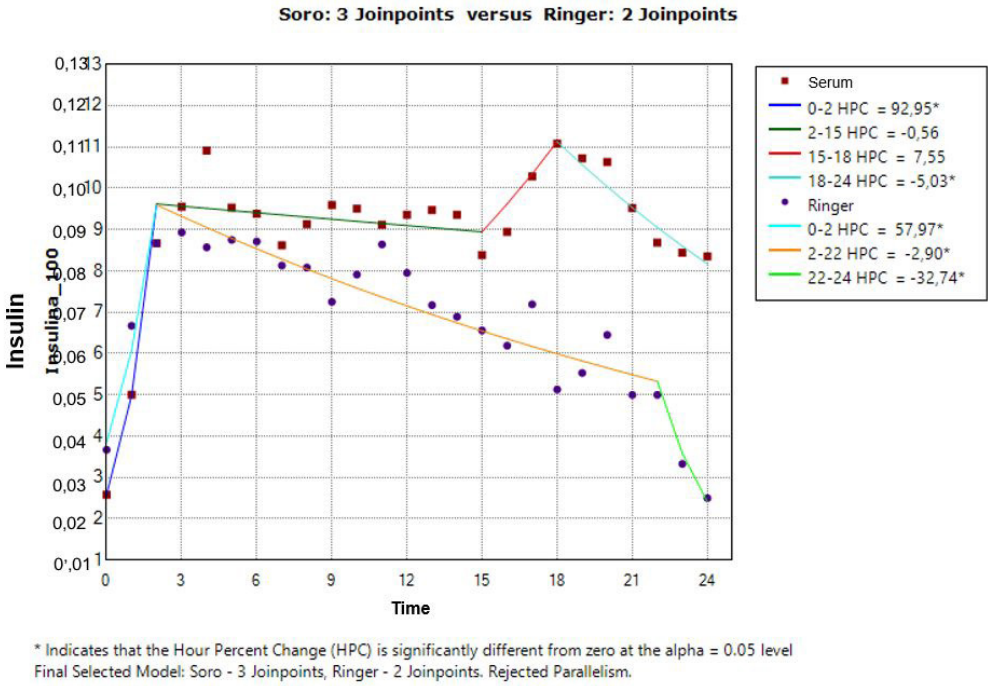


Figure 2. Amount of intravenous insulin received within 24 hours of hospitalization
Caption. Percentage changes per hour in the amount of intravenous insulin received in 24 hours. *HPC = Hour percent change

of DKA. Ringer's lactate yielded an absolute reduction of approximately six hours compared to 0.9% SF, which is consistent with what has been described in the literature.

Two randomized studies reported a time to resolve DKA approximately four hours shorter in patients given balanced solutions[5,6]. This data is essential because a faster resolution of this complication directly affects the severity of the disease, patient mortality, the number of interventions to which patients are submitted, the number of medications prescribed, and the length of hospitalization in the PICU[7]. The difference in resolution time may be related to the composition of the fluids studied.

0.9% saline solution contains 154 mmol/L of sodium and 154 mmol/L of chloride and has an osmolarity of 308 mOsm/L. For this reason, using this solution may increase serum chloride and decrease bicarbonate levels, resulting in hyperchloremic acidosis[8]. A literature review conducted in 2015 with trauma patients showed a higher incidence of hyperchloremic metabolic acidosis after infusion of 0.9% saline solution when compared to balanced solutions. Hyperchloremia resulted in the perpetuation of acidosis, acute kidney injury, and increased use of therapeutic resources[9]. As in other conditions, this alteration may act as a confounding factor and unnecessarily prolong the management of DKA[7]. We found no statistically significant difference in serum chloride levels between the groups.

Ringer's lactate is a balanced solution with sodium and chloride concentrations of 131 and 111 mEq/L, respectively, and an osmolarity of 281 mmOsm/L[8]. Although Ringer's lactate has not been associated with hyperchloremic metabolic acidosis, there is a concern that it may increase serum lactate levels, generating lactic acidosis and hampering the identification of DKA resolution[5]. A study published in 2018 demonstrated that the mean serum lactate level increased by 0.93 mmol/L in patients with septic shock given 30 mL/kg of Ringer's lactate. However, the difference was insignificant compared to 0.9% saline solution[10]. This correlation was not established in the present study, although a slight nonsignificant increase in lactate was observed at 12 hours.

Another concern regarding the use of Ringer's lactate is that studies have shown that isotonic solutions are more effective in preventing hyponatremia in critically ill children. Since it is a slightly hypotonic fluid, Ringer's lactate may be associated with hyponatremia, increasing the risk of cerebral edema and seizures[11]. A cross-sectional descriptive study conducted in 2021 with 109 children in postoperative care described a prevalence of 48.6% of hyponatremia in individuals given Ringer's lactate. None had severe hyponatremia or required correction[12]. Our study found no statistical difference between sodium levels in the two groups.

According to epidemiological data, DKA affects 10 in every 100,000 children in Brazil and is the most common cause of hospitalization in individuals with diabetes, mainly those under four years of age[13]. It often occurs at the initial diagnosis of DM1, with incidence ranging from 13% to 80%[2]. Almost half (45.8%) of our patients had DKA as the initial manifestation of DM1.

Although no deaths were described in our analysis, mortality rates due to DKA in population studies are relatively consistent: 0.15% in the United States, 0.18% to 0.25% in Canada, and 0.31% in England accounting for more than 50% of all deaths of children with DM1, with cerebral edema as the main etiology[13].

Some protocols, including that of the institution where this study was conducted, recommend that intravenous fluids not exceed 4000 ml/m² in 24 hours14,15. In our population, the average volume administered in 24 hours was 4569 ± 1619 ml. Although this information has not been thoroughly analyzed, none of the patients had symptoms of cerebral edema.

This study has some limitations. First, it is an observational analysis, in which protocol changes were reviewed, and part of the data was collected retrospectively. Second, the modest sample size and the fact that the mortality rate was calculated based on the Pediatric Index of Mortality (PIM2) limited the analysis of some variables, making it impossible, for example, to randomize participants according to severity or assess the changes in pH and acidosis in each subgroup. Third, crystalloids administered in other wards before referral to the PICU were not quantified or analyzed.

Our study found that Ringer's lactate was associated with a faster resolution of DKA than 0.9% saline solution. In addition, we did not observe complications such as clinically significant hyponatremia or hyperlactatemia. In this context, balanced crystalloids may be preferred over saline solution to treat volume depletion secondary to DKA in children. Further studies with larger populations must be conducted to confirm these findings, evaluate the cost of care and severity scores for each patient, and indicate required protocol changes.

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