Comparison of Plasma-Lyte A and Sodium Chloride 0.9% for Fluid Resuscitation of Patients With Diabetic Ketoacidosis

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Abstract

Purpose: The aim of this study was to compare Plasma-Lyte A (PL) and sodium chloride 0.9% (NS) in regard to time to resolution of diabetic ketoacidosis (DKA) when one fluid was used predominantly over the other for resuscitation. **Methods:** We performed a retrospective analysis of the records of patients treated for DKA at a large, academic medical center between July 1, 2013, and July 1, 2015. Patients were placed into the PL or NS group based on the predominant fluid they received during fluid resuscitation. Serum biochemistry variables were categorized as follows: initial, 2 to 4 hours, 4 to 6 hours, 6 to 12 hours, and 12 to 24 hours. The primary outcome was mean time to resolution of DKA. **Results:** Eighty-four patients were included in the study. The primary outcome of mean time to resolution of DKA was similar between the PL (19.74 hours) and NS (18.05 hours) groups ($P = .5080$). Patients treated with PL had a significantly greater rise in pH within the 4- to 6-hour and 6- to 12-hour periods. The chloride level was significantly higher and the anion gap was significantly lower for the NS group in the 6- to 12-hour period. **Conclusion:** These data suggest that the use of PL for fluid resuscitation in DKA may confer certain advantages over NS.

Keywords

diabetic ketoacidosis, normal saline, Plasma-Lyte A

Introduction

Diabetic ketoacidosis (DKA) is a serious metabolic manifestation of diabetes mellitus, with the symptoms of nausea, vomiting, excessive thirst, and frequent urination. The resulting dehydration necessitates initial fluid resuscitation aimed at the repletion of intravascular, interstitial, and intracellular volumes. Current guidelines recommend sodium chloride 0.9% (NS) as the fluid of choice for initial resuscitation, but there are no data supporting its use over other fluids for this indication.¹

Studies in surgical patients and children have demonstrated that the administration of large volumes of NS is associated with the development of hyperchloremic metabolic acidosis.^{2–6} This consequence could affect outcomes in DKA patients—In fact, 2 studies associated the development of hyperchloremic metabolic acidosis with a delay in the resolution of DKA.^{7,8} Given that Plasma-Lyte A (PL) has been shown to prevent the development of hyperchloremic metabolic acidosis in DKA patients compared with NS, the choice of PL as the predominant fluid for resuscitation may lead to quicker resolution of DKA.⁹

Only 1 previous study evaluated the question of fluid choice and its effects on the outcomes of patients with

DKA.¹⁰ The 9 patients in this study who received PL showed a faster resolution of metabolic acidosis and a smaller increase in serum chloride compared with the 14 patients who received NS. The duration of insulin infusion and intensive care unit (ICU) length of stay were similar in the PL and NS groups.

The primary objective of our study was to determine the difference in time to resolution of DKA among patients given PL versus NS for fluid resuscitation in an emergency department (ED). We hypothesized that DKA would resolve faster in the group that received PL predominantly than in the group that received NS.

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Materials and Methods

Study Design and Setting

This was a retrospective cohort study of patients treated for DKA at a large, urban, academic medical center ED between July 1, 2013, and July 1, 2015. The authors' institutional review board approved this study.

Selection of Participants

Patients were identified via International Classification of Diseases, Ninth Revision (ICD-9) codes for DKA, that is, 250.1, 250.12, and 250.13. The resuscitation fluid(s) used for each patient was identified through pharmacy charge reports. Patients were included in the study if they had been diagnosed with DKA in the ED, were between the ages of 18 and 89, and met the following criteria: serum bicarbonate, ≤ 18 mEq/L; a calculated anion gap (AG) > 10 ; plasma glucose concentration, > 250 mg/dL; and ketonemia and/or ketonuria. Patients with DKA were categorized as mild (serum bicarbonate, 15–18 mEq/L; AG > 10 ; plasma glucose concentration, > 250 mg/dL), moderate (serum bicarbonate, 10– < 15 mEq/L; AG > 12 ; plasma glucose concentration, > 250 mg/dL), or severe (serum bicarbonate, < 10 mEq/L; AG > 12 ; plasma glucose concentration, > 250 mg/dL). Patients were excluded if they received equal amounts of the 2 study fluids or more than 1 L of the other study fluid from their assigned group.

Interventions

Patients received PL, NS, or a combination of the 2 for resuscitation. They were assigned to groups according to the volume of fluid they received: Those who received predominantly PL were called the PL group, and those who received predominantly NS were assigned to the NS group. They could receive up to 1 L of the other fluid and remain in their assigned group.

PL has the following composition: sodium, 140 mEq/L; potassium, 5 mEq/L; magnesium, 3 mEq/L; chloride, 98 mEq/L; acetate, 27 mEq/L; and gluconate, 23 mEq/L. Its osmolality is 294 mOsm/L, and its pH is 7.4. NS has the following composition: sodium, 154 mEq/L and chloride, 154 mEq/L. Its osmolality is 308 mOsm/L and its pH is 5.5.

Insulin is administered by infusion and subcutaneous injection in accordance with hospital guidelines, which recommend initiation of infusion at 0.1 units/kg/h with a maximum initial rate of 10 units/h. The rate is adjusted based on hourly blood glucose readings, and the infusion is stopped when the calculated AG and serum bicarbonate normalize. Long-acting insulin is injected subcutaneously 2 to 3 hours before the anticipated cessation of intravenous (IV) administration.

Measurements

Data were abstracted retrospectively from medical records. Serum biochemistry variables were placed into the following ordinal groups: initial, 2 to 4 hours, 4 to 6 hours, 6 to 12 hours, and 12 to 24 hours. Time to resolution of acidemia, time to resolution of DKA, duration of hospital stay, duration of IV insulin, and cumulative insulin requirement were calculated in relation to the time of initial presentation. Changes in serum biochemistry variables were measured in relation to the initial serum biochemistry measurement. The AG was calculated with the following formula: $AG = [Na^+] - ([Cl^-] + [HCO_3^-])$.

Outcomes

The primary outcome was time to resolution of DKA, which was defined according to the criteria set forth in current guidelines¹: blood glucose concentration < 200 mg/dL and 2 of the following: serum bicarbonate level ≥ 15 mEq/L, venous pH > 7.3 , and a calculated AG ≤ 12 mEq/L.

Secondary outcomes were cumulative volumes of PL or NS infused, cumulative insulin requirement at 24 hours, duration of IV insulin infusion, cumulative dose of subcutaneous plus IV insulin for 48 hours from study baseline, potassium balance up until 24 hours from baseline, change in serum biochemistry values up until 24 hours from baseline, and duration of hospital stay in hours.

Analysis

Descriptive statistics were used for the demographic data and comparison of means for the primary objective and secondary objectives. Means were compared using a *t* test for independent samples. Categorical variables were compared using a chi-square test. We used a null hypothesis of no difference between treatment groups. An a priori level of significance of 0.05 was used for all analyses.

Results

Eighty-four patients with mild, moderate, and severe DKA were determined to be eligible for the study. Of these patients, 23 were assigned to the PL group and 61 to the NS group (Figure 1).

The baseline characteristics of the 2 study groups were similar (Table 1). The mean bicarbonate was 14.83 mEq/L in the PL group compared with 14.34 mEq/L in the NS group ($P = .7184$). The mean pH in the PL group was 7.21 compared with 7.25 in the NS group ($P = .1322$). The AG was also similar between the PL and NS groups (23.52 and 23.30 mEq/L, respectively, $P = .8723$).

The cumulative volume of all fluids infused was similar between the groups for all time periods (Table 2). During the initial 12 hours after baseline, the PL group received a mean of 2826 mL of PL and the NS group received a mean of 3111 mL of

Figure 1. Flow diagram for patient selection.

Table 1. Baseline Characteristics.

Variables	Predominant fluid 12 h from baseline	
	PL (n = 23)	NS (n = 61)
Age, mean	40.78	43.13
Gender, n (%)		
Male	12 (52)	28 (46)
Female	11 (48)	33 (54)
Race, n (%)		
White	3 (13)	10 (16)
Black	20 (87)	49 (80)
Other	0	2 (4)
Reason for DKA, n (%)		
New onset	1 (5)	6 (10)
Infection	4 (17)	5 (8)
Noncompliance	15 (65)	33 (54)
Unknown	3 (13)	17 (28)
Severity of DKA, n (%)		
Mild	13 (56)	28 (46)
Moderate	5 (22)	22 (36)
Severe	5 (22)	11 (18)
Initial lab values, mean		
Sodium (mEq/L)	135.22	133.44
Potassium (mEq/L)	5.11	4.98
Chloride (mEq/L)	96.87	95.80
Bicarbonate (mEq/L)	14.83	14.34
Blood urea nitrogen (mEq/L)	25.17	27.44
Serum creatinine (mg/dL)	1.10	1.61
pH	7.21	7.25
Anion gap (mEq/L)	23.52	23.30
Glucose (mg/dL)	565.27	618.56

Note. PL = Plasma-Lyte A; NS = sodium chloride 0.9%; DKA = diabetic ketoacidosis.

Table 2. Cumulative Volumes Infused, Mean.

Total volume infused, mL ± SD	PL (n = 23)	NS (n = 61)	P
2-4 h	2358.70 ± 710.42	2357.38 ± 819.29	.9946
4-6 h	2823.91 ± 863.64	2891.80 ± 1042.36	.7816
6-12 h	3995.65 ± 1330.83	3846.72 ± 1469.61	.6723
12-24 h	5143.48 ± 1663.46	4948.36 ± 1989.87	.6771

Note. PL = Plasma-Lyte A; NS = sodium chloride 0.9%.

Table 3. DKA Resolution at Specific Time Intervals.

DKA resolution, n (%)	PL (n = 23)	NS (n = 61)
2-4 h	0 (0)	0 (0)
4-6 h	0 (0)	5 (8)
6-12 h	3 (13)	22 (36)
12-24 h	18 (78)	26 (43)
>24 h	2 (9)	8 (13)

Note. PL = Plasma-Lyte A; NS = sodium chloride 0.9%; DKA = diabetic ketoacidosis.

NS ($P = .3535$). The PL group received a mean of 874 mL of NS, and the NS group received a mean of 295 mL of PL ($P = .0001$).

The primary outcome of mean time to resolution of DKA was similar between the PL and NS groups (19.74 vs 18.05 hour, respectively, $P = .5080$). Table 3 indicates the percentage of patients achieving DKA resolution at the specific time intervals in this study. The 2 groups were also similar regarding the secondary outcomes of duration of IV insulin infusion, total dose of insulin at 24 hours, total dose of insulin at 48 hours, and duration of hospital stay.

Table 4. Electrolyte and Acid-Base Balance, Mean.

Potassium level (mEq/L)	PL	n	NS	n	Mean difference [95% CI]
2-4 h	4.48	17	4.52	32	0.04 [-0.51, 0.60]
4-6 h	4.23	18	4.11	40	-0.12 [-0.45, 0.21]
6-12 h	4.22	20	3.90	49	-0.320 [-0.58, -0.06]
12-24 h	3.86	23	3.93	56	0.07 [-0.20, 0.34]
Change in chloride (mEq/L)	PL	n	NS	n	Mean difference [95% CI]
2-4 h	4.28	18	6.77	35	2.49 [-0.18, 5.16]
4-6 h	7.22	18	9.28	40	2.06 [-1.17, 5.29]
6-12 h	7.25	20	11.40	53	4.15 [1.02, 7.28]
12-24 h	7.91	23	10.28	57	2.37 [-1.09, 5.83]
Change in bicarbonate (mEq/L)	PL	n	NS	n	Mean difference [95% CI]
2-4 h	-0.33	18	1.09	35	1.42 [-0.50, 3.34]
4-6 h	2.33	18	2.10	40	-0.23 [-2.27, 1.81]
6-12 h	4.00	20	5.87	53	1.87 [-0.70, 4.44]
12-24 h	8.22	23	6.72	57	-1.50 [-4.11, 1.11]
Change in pH	PL	n	NS	n	Mean difference [95% CI]
2-4 h	-0.03	2	0.04	2	NA
4-6 h	0.27	2	0.07	7	-0.20 [-0.32, -0.08]
6-12 h	0.25	5	0.08	8	-0.17 [-0.32, -0.02]
12-24 h	0.16	3	0.06	3	-0.10 [-0.55, 0.35]
Anion gap (mEq/L)	PL	n	NS	n	Mean difference [95% CI]
2-4 h	22.94	18	19.31	35	-3.63 [-7.65, 0.39]
4-6 h	19.28	18	17.88	40	-1.4 [-5.12, 2.32]
6-12 h	17.00	20	13.58	53	-3.42 [-5.55, -1.29]
12-24 h	11.57	23	11.39	57	-0.18 [-1.58, 1.22]
Change in anion gap (mEq/L)	PL	n	NS	n	Mean difference [95% CI]
2-4 h	-0.61	18	-3.94	35	-3.33 [-7.46, 0.80]
4-6 h	-5.06	18	-5.30	40	-0.24 [-4.12, 3.64]
6-12 h	-7.20	20	-10.36	53	-3.16 [-6.57, 0.25]
12-24 h	-11.96	23	-11.95	57	0.01 [-3.28, 3.30]

Note. PL = Plasma-Lyte A; NS = sodium chloride 0.9%; CI = confidence interval.

In regard to serum biochemistry measurements, the PL group had a significantly greater rise in pH for the 4- to 6-hour and 6- to 12-hour periods. The NS group had a significantly higher chloride concentration, a significantly lower potassium concentration, and a significantly lower AG at the 6- to 12-hour period. The change in serum bicarbonate concentration and change in AG were not significantly different (Table 4).

Discussion

Our study was designed to assess the effect of using a balanced electrolyte solution for resuscitation or NS on the time to resolution of DKA. We found no statistical difference. In addition, we observed no differences in duration of insulin infusion, cumulative insulin dose administered at 24 and 48 hours, or duration of hospital stay. Those secondary

findings coincide with the observations reported by Chua and colleagues,¹⁰ who detected a trend toward faster resolution of DKA in their patients treated with PL than in those treated with NS.

The reason we did not see a difference in our primary outcome (mean time to resolution of DKA) is likely multifactorial. Initial or sequential venous blood gas measurements were not obtained in most of the patients identified in our retrospective review; thus, we had to rely on AG and the serum bicarbonate concentration to determine the resolution of DKA. Given that the administration of substantial volumes of NS causes hyperchloremia,²⁻⁶ the elevated chloride level could cause the calculated AG to close faster and create the appearance that DKA had resolved prior to true correction of metabolic derangements. Also, the timing of specimen acquisition was not standardized, creating variations in

the intervals of blood draws and potentially affecting the primary and some of the secondary study endpoints.

Our study included patients with mild, moderate, and severe DKA. The previous comparable study, by Mahler et al, looked only at patients with moderate and severe DKA and found more profound differences in serum biochemistry values and time to resolution of DKA.⁹ Our inclusion of patients with mild metabolic imbalance could make it more difficult to discern a difference in the time until resolution of DKA.

Despite not finding a time difference in resolution of DKA, we did observe serum biochemistry changes that could indicate its faster resolution. Patients in the PL group had a significantly greater rise in pH for the 4- to 6-hour and 6-to 12-hour periods when compared with the patients' initial pH measurement; however, venous blood gases were only measured on a small portion of the study population making this result difficult to interpret. In addition, the NS group experienced a greater increase in serum chloride concentration.

The PL group received a mean of 874 mL of NS, and the NS group received a mean of 295 mL of PL, which was a statistically significant difference. This difference is likely due to NS being the only fluid included in the DKA order set at our institution. Thus, most patients probably received an initial liter of NS because that is how the order set is structured. Although the volume difference was significant, it probably did not have a major effect on our findings.

The major limitation for this study is its retrospective review of medical records, which makes determining causation/correlation more difficult. The study also included a small number of subjects which could limit the applicability of our findings to larger populations. Use of a combination of NS and balanced electrolyte solutions, while reflecting clinical practice, additionally complicates the interpretation of our results. In addition, the time to resolution of DKA is difficult to calculate because specimens for laboratory tests were obtained at the discretion of the managing team. Also, although titration of the insulin infusion is covered in institutional guidelines, it is possible that some care providers deviated from the protocol.

Conclusion

In summary, many factors likely contributed to our observation of similar times to resolution of DKA; however, these data suggest that the use of PL for fluid resuscitation in DKA may confer certain advantages over NS. Given that only 2 small retrospective studies have been conducted, a larger randomized controlled trial is needed to further assess differences in the effectiveness of the 2 fluids for DKA.

Authors' Note

Bryan D. Hayes was at the University of Maryland at the time of the study.

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