Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis

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Received 30 December 2009; revised 4 February 2010; accepted 5 February 2010

Abstract

Objective: The objective of the study was to determine if balanced electrolyte solution (BES) prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis (DKA).

Methods: This is a prospective, randomized, double-blind study. A convenience sample of DKA patients aged 18 to 65 years with serum bicarbonate less than or equal to 15 and anion gap greater than or equal to 16 was enrolled at “Louisiana State University Health Sciences Center-Shreveport” an capitalize Emergency Department over a 24-month period (2006-2008). Patients were randomized to standardized resuscitation with normal saline (NS) or BES (Plasma-Lyte A pH 7.4; Baxter International, Deerfield, IL). Every 2 hours, serum chloride and bicarbonate were measured until the patient’s anion gap decreased to 12. An intention-to-treat analysis was performed on patients who met inclusion criteria and received at least 4 hours of study fluid. Chloride and bicarbonate measurements from the BES and NS groups were compared using unpaired and paired Student t tests.

Results: Of 52 patients enrolled, 45 (22 in BES group and 23 in NS group) met inclusion criteria and received 4 hours of fluid. The mean postresuscitation chloride was 111 mmol/L (95% confidence interval [CI] = 110-112) in the NS group and 105 mmol/L (95% CI = 103-108) in the BES group (P ≤ .001). The mean postresuscitation bicarbonate was 17 mmol/L (95% CI = 15-18) in the NS group and 20 mmol/L (95% CI = 18-21) in the BES group (P = .020).

Conclusions: Resuscitation of DKA patients with BES results in lower serum chloride and higher bicarbonate levels than patients receiving NS, consistent with prevention of hyperchloremic metabolic acidosis.

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1. Introduction

Diabetic ketoacidosis (DKA) is a common problem seen in emergency departments (EDs) worldwide. Annually, there are approximately 100,000 hospitalizations for DKA in the United States alone. Because of the rising incidence of obesity and diabetes in the developed world, DKA is likely to be an increasingly common problem [1].
Diabetic ketoacidosis is a life-threatening consequence of insulin resistance or deficiency resulting in accumulation of ketone bodies, severe volume depletion, and electrolyte derangements. Typical volume loss from DKA is 100 mL/kg or roughly 7 L in an average 70-kg adult [2,3]. According to the American Diabetes Association (ADA) guidelines, the first priority for treatment in DKA is to restore the volume deficit with crystalloid [2-5]. However, the optimal type of crystalloid has yet to be determined. Despite its frequent use, normal saline (NS) has potential drawbacks, including a pH of 5.5 and high chloride content. Studies on postoperative and pediatric patients suggest that large volume resuscitation with NS is associated with hyperchloremic metabolic acidosis (HMA) [6-10]. Hyperchloremic metabolic acidosis has also been reported in DKA patients resuscitated with NS [11-13]. Unlike NS, a balanced electrolyte solution (BES) is similar to serum in chloride concentration and pH. However, BESs have yet to be studied in DKA. The objective of this study is to determine if BES prevents HMA in patients with DKA.

2. Methods

2.1. Study design and selection of participants

This was a prospective, randomized, double-blind study comparing resuscitation with BES and NS in patients with DKA. This study was approved by the institutional review board of the sponsoring organization. A convenience sample of patients, aged 18 to 65 years, with moderate to severe DKA were enrolled over a 24-month period (2006-2008) at “Louisiana State University Health Sciences Center-Shreveport” ED. Moderate to severe DKA was defined by a serum glucose greater than 200 mg/dL, serum bicarbonate less than or equal to 15 mmol/L, and anion gap greater than or equal to 16 mmol/L. Patients with hyperosmotic hyperglycemic nonketotic syndrome, hyperglycemia without signs of DKA, mild DKA, and patients receiving greater than 500 mL of crystalloid or an insulin bolus before enrollment in the study were excluded. Additional exclusion criteria included evidence of myocardial infarction, sepsis, respiratory failure, cerebral edema, and age less than 18 or greater than 65 years. Randomization was achieved by block randomization of 8 consecutive subjects, and the investigators were blinded to the randomization schedule.

2.2. Study intervention

Patients were randomized 1:1 to a standardized resuscitation protocol with 0.9% NS or BES (Plasma-Lyte A pH 7.4; Baxter International, Deerfield, IL). The institution’s research pharmacy provided blinded study fluids according to the randomization schedule. Before fluid administration, the patient’s percentage dehydration, volume deficit, and maintenance fluid requirement were calculated. Each subject received a 20-mL/kg bolus of study fluid. The remaining volume deficit was replaced over 24 hours, with the first half given over the first 8 hours and the rest over the remaining 16 hours. Hourly maintenance fluids were added to the hourly volume replacement rate. Calculations were based on ideal body weight, and fluids were capped at 700 mL/h. See Table 1 for a summary of the protocol calculations.

All subjects received a regular insulin drip, with no bolus, at 0.1 U/(kg h). When blood sugars dropped to 250 mg/dL or less, patients were started on dextrose containing study fluids. The hourly fluid rate remained the same, with half of the hourly volume as dextrose containing study fluid and half as nondextrose study fluid. Treating physicians were instructed to avoid the use of insulin boluses or sodium bicarbonate. Study subjects completed the resuscitation, which was targeted at an anion gap of 12 or less, in the ED or medical intensive care unit.

2.3. Data collection

Each subject had a baseline chemistry panel that included a serum sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, and glucose measurement. The patient’s anion gap was calculated and recorded along with chloride and bicarbonate levels. After initiation of the fluid resuscitation, a chemistry panel was measured every 2 hours for the duration of the study. Subjects were monitored for adverse events, such as cerebral edema and hypoglycemia.

2.4. Statistical analysis

An intention-to-treat analysis was performed on patients meeting inclusion criteria and receiving at least 4 hours of study fluid. Chloride and bicarbonate measurements from the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of study calculations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study parameter</td>
<td>Calculation</td>
</tr>
<tr>
<td>Volume deficit (L)</td>
<td>Weight (kg) × percentage dehydration</td>
</tr>
<tr>
<td>Fluid bolus (mL)</td>
<td>Weight (kg) × 20 mL</td>
</tr>
<tr>
<td>Remaining volume deficit (mL)</td>
<td>Volume deficit − fluid bolus</td>
</tr>
<tr>
<td>1st 8-h replacement rate (mL/h)</td>
<td>(Remaining volume deficit/2)/8 h</td>
</tr>
<tr>
<td>Next 16-h replacement rate (mL/h)</td>
<td>(Remaining volume deficit/2)/16 h</td>
</tr>
<tr>
<td>Total fluid rate 1st 8 h</td>
<td>8-h replacement rate + maintenance (4, 2, 1 rule)</td>
</tr>
<tr>
<td>Total fluid rate next 16 h</td>
<td>16-h replacement rate + maintenance (4, 2, 1 rule)</td>
</tr>
<tr>
<td>Insulin drip (U/h)</td>
<td>Weight (kg) × 0.1 unit regular insulin</td>
</tr>
</tbody>
</table>
BES and NS groups were compared using unpaired \( t \) tests for between-group comparisons and paired \( t \) tests for inter-subject comparisons. Statistical analysis was performed with SPSS 11.0 (Chicago, IL) for Windows.

3. Results

Over the 24-month study period during 2006-2008, 52 patients were enrolled. A total of 45 patients, 22 in the BES group and 23 in the NS group, met inclusion criteria and received a minimum of 4 hours of study fluid. Of the 7 patients excluded from data analysis, 4 did not meet inclusion criteria and 3 did not receive at least 4 hours of study fluid. See Fig. 1 for study flow diagram. Demographic characteristics of subjects are summarized in Table 2.

Subjects randomized to the NS group had a mean baseline serum chloride of 94 mmol/L (95% confidence interval [CI] = 92-96) compared with 98 mmol/L (95% CI = 96-100) for the patients randomized to the BES group (\( P = .027 \)). The mean postresuscitation chloride was 111 mmol/L (95% CI = 110-112) in the NS group and 105 mmol/L (95% CI = 103-108) in the BES group (\( P \leq .001 \)). Mean increase in serum chloride in the NS group was 16.5 mmol/L (95% CI = 14-19) compared with 8 mmol/L (95% CI = 6-9) in the BES group (\( P \leq .001 \)).

Patients randomized to the NS group had a mean serum bicarbonate of 10 mmol/L (95% CI = 8-12) vs 10.5 mmol/L (95% CI = 9-12) for the BES group (\( P = .67 \)). The mean postresuscitation bicarbonate was 17 mmol/L (95% CI = 15-18) in the NS and 20 mmol/L (95% CI = 18-21) in the BES group (\( P = .02 \)). Mean increase in serum bicarbonate was 7 mmol/L (95% CI = 5-8) in the NS group compared with 9 mmol/L (95% CI = 8-11) in the BES group (\( P = .023 \)).

Results are summarized in Table 3 and Fig. 2. No subjects developed cerebral edema or hypoglycemia.

4. Discussion

Patients resuscitated with BES had lower postresuscitation serum chloride concentrations and higher postresuscitation serum bicarbonate concentrations consistent with prevention of HMA. Lower postresuscitation serum chloride in the BES group occurred despite the group having a significantly higher baseline chloride concentration compared with the NS group. High postresuscitation serum chloride concentrations in the NS group were consistent with the previously reported literature suggesting that NS causes HMA in patients with DKA [11-13].

The ability of BES to prevent HMA can be explained by examining the chemistry of NS relative to serum and BES. Important differences between NS and serum or BES are pH and chloride content. Normal saline has a pH of 5.5 and a chloride content of 154 mmol/L. Plasma-Lyte A pH 7.4 is

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**Table 2** Demographic characteristics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>NS group (n = 23)</th>
<th>BES group (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>38 (±14)</td>
<td>33 (±11)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>11 (48)</td>
<td>10 (45)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (52)</td>
<td>12 (55)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, n (%)</td>
<td>4 (17)</td>
<td>7 (32)</td>
</tr>
<tr>
<td>African American, n (%)</td>
<td>19 (83)</td>
<td>16 (68)</td>
</tr>
</tbody>
</table>

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Fig. 1 Study flow diagram.
similar to serum, with a pH of 7.4 and a chloride of 98 mmol/L [14]. Serum conforms to the principle of electrical neutrality, containing an equivalent number of positively and negatively charged ions. Therefore, to maintain electrical neutrality in the face of rising serum chloride anions from NS resuscitation, the serum loses an equal amount of bicarbonate anions resulting in HMA. Balanced electrolyte solution does not lower bicarbonate because of its normal chloride content [15,16].

Although this study suggests that BES prevents HMA in patients with DKA, the clinical significance of HMA has yet to be determined. A review of the literature suggests that HMA causes derangements that may negatively impact patient outcome. Animal models of sepsis have demonstrated less metabolic acidosis, less inflammatory cytokines, and longer survival with BES resuscitation compared with NS [17,18]. Hyperchloremic metabolic acidosis has also been associated with more blood product transfusion in postoperative patients and impaired renal function [19,20]. However, the impact of HMA on mortality remains unknown. Future comparison studies between NS and BES in DKA patients should be adequately powered to detect differences in patient outcomes.

### 5. Limitations

This study enrolled a small number of subjects at a single institution. Therefore, the results of this study may not be generalizable to patient populations at other hospitals. In addition, a convenience sample was used, which could have produced selection bias. Another limitation is the significantly lower baseline serum chloride level in the NS group compared with the BES group. This occurred by chance because of the small sample size. Although a difference in baseline chloride was an unexpected limitation, it strengthens the conclusions of the study. Despite significantly lower serum chloride in the NS group, the postresuscitation chloride levels were still significantly higher in the NS group compared with the BES group.

Definitions of moderate and severe DKA used in this study differ from the ADA guidelines [2-5]. Physicians from

<table>
<thead>
<tr>
<th>Mean electrolyte concentration</th>
<th>NS (mmol/L)</th>
<th>95% CI</th>
<th>BES (mmol/L)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline chloride</td>
<td>94</td>
<td>92-96</td>
<td>98</td>
<td>96-100</td>
<td>.027</td>
</tr>
<tr>
<td>Postresuscitation chloride</td>
<td>111</td>
<td>110-112</td>
<td>105</td>
<td>103-108</td>
<td>≤.001</td>
</tr>
<tr>
<td>Change in chloride</td>
<td>16.5</td>
<td>14-19</td>
<td>8</td>
<td>6-9</td>
<td>≤.001</td>
</tr>
<tr>
<td>Baseline bicarbonate</td>
<td>10</td>
<td>8-12</td>
<td>10.5</td>
<td>9-12</td>
<td>.667</td>
</tr>
<tr>
<td>Postresuscitation bicarbonate</td>
<td>17</td>
<td>15-18</td>
<td>20</td>
<td>18-21</td>
<td>.020</td>
</tr>
<tr>
<td>Change in bicarbonate</td>
<td>7</td>
<td>5-8</td>
<td>9</td>
<td>8-11</td>
<td>.023</td>
</tr>
</tbody>
</table>

**Table 3** Summary of mean serum chloride and bicarbonate concentrations in the NS and BES groups.

**Fig. 2** Comparison of baseline and postresuscitation chloride and bicarbonate concentrations.
the Emergency Medicine, Internal Medicine, and Adult and Pediatric Critical Care Departments were involved in the development of the study. The available medical literature and institutional practices were considered in the formulation of study definitions and the treatment algorithm. The major difference between our protocol and the ADA guidelines is use of arterial pH as diagnostic criteria for mild, moderate, and severe DKA. Blood gases were not required in our study because of institutional practices and feasibility. In addition, arterial pH has been deemphasized as a criteria for DKA in other guidelines [5,21]. However, by using an institutional definition of moderate to severe DKA, the results of this study may not be generalizable to patients in institutions strictly adhering to ADA guidelines or with differing institutional definitions.

6. Conclusions

Resuscitation of DKA patients with BES results in lower serum chloride and higher bicarbonate levels compared with patients receiving NS. This suggests that BES prevents HMA in patients with DKA. Although prevention of HMA by BES is statistically significant, clinical significance has yet to be determined.

References