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Clinical Investigation

Evaluation of the Two-Bag System for Fluid Management in Pediatric Patients with Diabetic Ketoacidosis

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OBJECTIVES A one-bag and a two-bag system have both been used to manage intravenous fluid administration in pediatric patients with diabetic ketoacidosis (DKA). The one-bag system, however, has been noted to have limitations, such as slow response time. This study evaluates whether the two-bag system provides any clinical benefit in pediatric DKA patients as compared to the one-bag system.
METHODS This was a retrospective, non-blinded chart review. Inclusion criteria were patients ≤ 18 years old and whose admission had the code of DKA as the diagnosis. Baseline clinical and demographic data were collected. Descriptive statistics were used in the data analysis.
RESULTS A total of 31 patients were included, 9 (29%) in the one-bag group and 22 (71%) in the two-bag group. Baseline characteristics were similar between the two groups. Mean (SD) rate of complete blood glucose (CBG) correction was 31.04 mg/dL/hr (20.61) in the two-bag group and 21.04 mg/dL/hr (16.26) in the one-bag group ($p = 0.297$). The rate of bicarbonate correction, however, was faster with the two-bag system than the one-bag system (0.949 ± 0.553 mEq/L/hr and 0.606 ± 0.297 mEq/L/hr, respectively) ($p = 0.047$). The two-bag system also had a faster time to ketone ($p = 0.04$), but not pH ($p = 0.172$), correction.
CONCLUSIONS The two-bag system provided a faster rate of bicarbonate and ketone correction compared to the one-bag system. The two-bag system also provided a trend towards a faster rate of blood glucose and pH correction.

KEYWORDS bicarbonate, blood glucose, diabetic ketoacidosis, pediatric, two-bag

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INTRODUCTION

In the United States, diabetic ketoacidosis (DKA) accounts for nearly 15% of all pediatric admissions each year.[1] It also accounts for approximately 20% of all mortality in children due to diabetes mellitus (DM).[2] Some factors that need to be considered when managing children with DKA include electrolyte imbalance, fluid loss, and hyperglycemia.[3] One of the immediate and vital interventions initiated is fluid replacement therapy. The purpose of this therapy is to replace fluid loss and correct electrolyte imbalances.

Frequent intravenous (IV) fluid modification is necessary to adapt to ongoing changes in fluid balance, serum glucose, and electrolytes.[1] A one-bag and a two-bag system have been used for fluid management of pediatric DKA patients. The one-bag system, however, has been noted to have limitations, such as slow response time and increase in hospital cost.[4] The two-bag system uses two bags of fluids containing the same amount of electrolytes but different concentrations of dextrose. By adjusting the rates of each bag, clinicians can immediately provide a customized glucose infusion rate while keeping the fluid delivery constant (Figure).[1] The two-bag system has been utilized since the 1990s.[4] Over the years, small clinical studies have shown few advantages to using the two-bag system, such as faster fluid exchange rate, less IV fluid bags used and reduced

ABBREVIATIONS CGB, complete blood glucose; DKA, diabetic ketoacidosis; DM, diabetes mellitus; IV, intravenous

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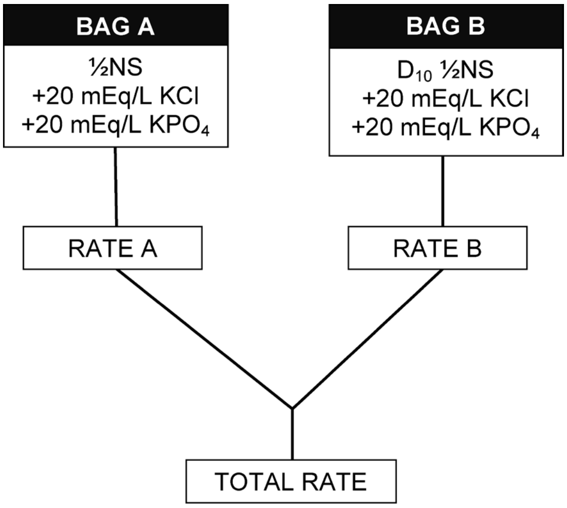

Figure. The two-bag system. The two bags of fluids contain the same amount of electrolytes but different concentrations of dextrose. Choice of electrolytes can vary based on physician's preference, but it usually contains potassium chloride. By adjusting the rate of each bag, varying rates of dextrose administration can be achieved.

cost of IV fluid therapy.[1,4] None of the studies, however, have shown any clinical benefit in terms of rate of glucose or bicarbonate correction.

The purpose of our study was to assess whether the two-bag system conveys any clinical benefit compared to the one-bag system. We also assessed what fluids were used at Moses Cone Hospital for fluid management in pediatric DKA patients.

MATERIALS AND METHODS

Patients and Study Design

This was a retrospective, non-blinded chart review. All subjects in this study were patients at Moses H. Cone Memorial Hospital from January 1, 2006 to December 31, 2006. This site is located in Greensboro, North Carolina.

Patients were included in this study if they were ≤ 18 years old with an admission diagnosis code of DKA. Patients were excluded if they had a complete blood glucose (CBG) < 200 mg/dL, venous pH >7.3, arterial pH >7.45, or a bicarbonate > 24mEq/L. Patients were also excluded if they were pregnant.

The primary objective of this study was to assess whether the two-bag system provides any benefit in pediatric patients with DKA in terms of rate of glucose or bicarbonate correction. Other objectives of this study were to determine what fluids were used for initial management of DKA in the pediatric unit at Moses Cone Hospital and to evaluate other potential benefits of using the two-bag system. This study was approved by the Committee for Human Research Protection of the Institutional Review Board at the Moses H. Cone Health System.

Data Collection

All the data used in this study were obtained from electronic and hard-copy medical records. All patients were selected in a non-randomized fashion. Once inclusion criteria were met, various information was obtained from the medical record. This information included medical record number, age, sex, weight, duration of hospitalization, past medical history of DKA and DM, prior insulin or other oral diabetes medications used, IV fluids used, initial insulin drip rate, and all pertinent labs that are usually gathered in pediatric patients with DKA (e.g., CBG, bicarbonate, pH, ketones).

Statistical Analysis

SPSS for Unix, Release 6.14 (SunOS), was the statistical software used in the data analysis of this study. Three different statistical tests were performed on the baseline characteristics to assess potential differences between the two-bag and the one-bag system group. Student's *t*-test was used for continuous variables and Fisher's exact or Chi-square test was performed on categorical variables.

RESULTS

Thirty-one pediatric patients were included in this study. The one-bag system was used in 9 patients (29%) and the two-bag system was used in 22 patients (71%). Baseline characteristics were similar between the two groups, with the exception of baseline serum creatinine (SCr) and initial insulin drip rate (Table 1). The patients in the one-bag system group had a higher baseline SCr ($p < 0.001$), while the patients in the two-bag system group had a higher initial insulin drip rate ($p < 0.001$). The mean age of the two groups was 13.5 years ($p = 0.384$). The mean weight was also similar between groups (two-bag: 49.5 ± 16.4 kg; one-bag: 55.4 ± 17.7 kg; $p = 0.475$). The majority

Table 1. Baseline Characteristics of Study Population

Characteristics	Two-Bag System	One-Bag System	p value
Demographic			
Patients, n (%)	22 (71.0)	9 (29.0)	
Male, n (%)	10 (45.5)	2 (22.2)	0.418
Age (yrs)	13.0 ± 4.3	13.9 ± 3.0	0.384
Weight (kg)	49.5 ± 16.4	55.4 ± 17.7	0.475
Duration of hospital stay (days)	3.8 ± 1.4	3.9 ± 1.8	0.747
Past Medical History			
DKA, n (%)	10 (45.5)	2 (22.2)	0.418
Diabetes mellitus, n (%)	16 (72.7)	6 (66.7)	1.000
Insulin use, n (%)	16 (72.7)	6 (66.7)	1.000
Other diabetes medications, n (%)	2 (9.1)	1 (11.1)	1.000
Initial Laboratory Values			
Hemoglobin A1c (%)	12.4 ± 1.9	10.7 ± 2.4	0.753
Na (mEq/L)	133.7 ± 4.1	132.3 ± 3.4	0.394
Cl (mEq/L)	105.1 ± 5.6	104.9 ± 4.5	0.509
CO_2 (mEq/L)	10.3 ± 3.7	10.8 ± 3.5	0.953
Bicarbonate (mEq/L)	10.0 ± 4.3	10.0 ± 5.1	0.609
Glucose (mg/dL)	489.5 ± 134.4	435.2 ± 205.8	0.171
BUN (mg/dL)	17.7 ± 7.6	16.9 ± 8.1	0.718
Serum creatinine (mg/dL)	1.1 ± 0.3	1.2 ± 0.5	0.001
Anion gap	18.0 ± 4.8	16.6 ± 6.7	0.121
pH	7.166 ± 0.096	7.186 ± 0.128	0.344
Severity of DKA			
Mild, n (%)	8 (36.4)	5 (55.6)	0.55 †
Moderate, n (%)	9 (40.9)	2 (22.2)	
Severe, n (%)	5 (22.7)	2 (22.2)	
DKA Management in the Hospital			
Duration of fluid infused (hr)	31.5 ± 18.6	31.7 ± 17.4	0.845
Duration of insulin drip used (hr)	16.6 ± 10.3	15.0 ± 5.6	0.106
Initial insulin drip rate (units/kg/hr)	0.07 ± 0.02	0.05 ± 0.00	0.001

BUN, blood urea nitrogen; Cl, chloride; CO_2, carbon dioxide; DKA, Diabetic Ketoacidosis; Na, sodium; SD, Standard Deviation;
† Chi-square test was used

of the patients were female (61%).

On admission, the mean hemoglobin A_{1c} of the subjects in the two-bag system group was 12.4 ± 1.9% and that in the one-bag system group was 10.7 ± 2.4% (p = 0.753). Thirty-nine percent (n = 12) of the population had a history of DKA and 71% (n = 22) had a history of DM. Of the 22 patients who had a history of DM, all were receiving insulin therapy prior to admission. Only 3 patients (10%) were taking oral diabetes medications, with metformin being the most common.

The mean initial glucose level in the two-bag group was 489.5 ± 134.4 mg/dL; and in the one-bag group, 435.2 ± 205.8 mg/dL (p = 0.171). The patients in the two-bag group presented with an anion gap of 18.0 ± 4.8; the anion gap in the one-bag group was 16.6 ± 6.7 (p = 0.121). The mean initial pH in the two-bag group was 7.166 ± 0.096 and that in the one-bag group was 7.186 ± 0.128 (p = 0.344). Other initial laboratories were similar between groups.

The severity of DKA was similar between groups (p = 0.55). DKA is usually classified into three major categories: mild (venous pH < 7.3

Table 2. Types of Potassium Used

Types	Two-Bag System (%)	One-Bag System (%)
KPO_4	17 (77)	5 (56)
KCl	15 (68)	7 (78)
KAcetate	4 (18)	2 (22)

KAcetate, Potassium Acetate; KCl, Potassium Chloride; KPO_4, Potassium Phosphate

or bicarbonate < 15 mEq/L), moderate (venous pH < 7.2 or bicarbonate < 10 mEq/L), and severe (venous pH < 7.1 or bicarbonate < 5 mEq/L).[5] In this study, the majority of the patients (n=13) fell into the mild category; 11 (35%) were in the moderate category.

The mean duration of fluids infused was similar between groups (two-bag, 31.5 ± 18.6 hour; one-bag, 31.7 ± 17.4 hour; p = 0.845). The majority of the patients received an insulin drip. The mean duration of insulin drip in the two-bag group was 16.6 ± 10.3 hour and in the one-bag group was 15.0 ± 5.6 hour (p = 0.106).

IV Fluids Used

No particular pattern was observed in the choice of IV fluids used in the one-bag system group. The following is a list of fluids used for the first bag: NS (33%), LR (22%), ½ NS (11%), D_5LR (11%), and D_5½NS (11%). In the two-bag system group, the majority of the fluids contained D_{10}1/2NS (55%) or D_{10}NS (36%) for one of the bags and NS (50%) or LR (41%) for the other bag.

Types of Potassium Used

The IV fluids used in both the two-bag and one-bag group contained potassium phosphate or potassium chloride or both (Table 2). Potassium acetate was used only 18% of the time in the two-bag group and 22% in the one-bag group.

Rate of CBG and Bicarbonate Correction

The mean ± SD rate of CBG correction was 31.04 ± 20.61 mg/dL/hr in the two-bag group and 21.04 ± 16.26 mg/dL/hr in the one-bag group. This difference was not significant (p = 0.297). The two-bag group had a faster rate of bicarbonate correction as compared to the one-bag group (0.949 ± 0.553 mEq/L/hr and 0.606 ± 0.297 mEq/L/hr, respectively; p = 0.047) (Table 3).

Time to pH and Ketone Correction

The time to pH correction was not different between groups (p = 0.172). Time to pH correction was 9.1 ± 7.4 hour in the two-bag group, and 9.7 ± 4.3 hour in the one-bag group. The two-bag group had a faster time to ketone correction (p = 0.04) (Table 3).

DISCUSSIONS

Despite the small sample size, our results suggest that the two-bag system can provide a faster rate of bicarbonate and ketone correction in pediatric patients with diabetic ketoacidosis. We also found a trend towards a faster rate of CBG and pH correction with the two-bag system. The latter endpoints were not significant probably due to the small sample size and the retrospective nature of this study. The rate of CBG and bicarbonate correction were used as the primary endpoints in this study because these two parameters were also used in a previous study to assess the efficacy of the two-bag system.[1] The time to pH and ketone correction were used as secondary endpoints because they potentially can serve as indicators of metabolic acidosis resolution and lipolysis cessation, which are big components in the pathophysiology of diabetic ketoacidosis.[5]

The mean rate of CBG correction with the two-bag system in this study was similar to that reported in the prospective study published by Poirier and colleagues.[1] In their study, the mean (95% CI) rate of CBG correction with the two-bag system was 33.1 mg/dL/hr (95% CI, 22-44 mg/dL/hr) compared to 31.04 mg/dL/hr in our study. The mean rate of CBG correction with the one-bag system was quite different (current study: 21.04 vs Poirier: 30.2 mg/dL/hr). This difference may be explained by the small sample size of the one-bag group in our study (n = 9) as compared to the study by Poirier and colleagues (n = 16). Also, their study was randomized and prospective.[1] According to the literature,[1,3] the goal rate of CBG decline with insulin drip should not be faster than 100 mg/dL/hr due to the concern of hypoglycemia. This concern is another reason that dextrose is administered to the

Table 3. Clinical Results of Using Two-Bag vs. One-Bag System

Clinical Observations	Two-Bag System	One-Bag System	p value
Rate of CBG correction (mg/dL/hr)	31.04 ± 20.61	21.04 ± 16.26	0.297
Rate of bicarbonate correction (mEq/L/hr)	0.949 ± 0.553	0.606 ± 0.297	0.047
Time to pH correction (hr)	9.1 ± 7.4	9.7 ± 4.3	0.172
Time to ketone correction (hr)	34.2 ± 14.7	53.9 ± 34.5	0.04

CBG, Complete Blood Glucose
All data presented as mean ± SD

patients once their CBG reaches 250-300 mg/dL.[5] A rapid glucose correction can theoretically cause a sudden shift in serum osmolarity, which may lead to extrapontine myelinolysis.[6] However, the rate of glucose correction has not been found to increase the risk of cerebral edema or brainstem herniation.[7,8]

Since both continued ketone production and reduced bicarbonate concentration can lead to elevated anion gap, more rapid bicarbonate and ketone correction achieved by the two-bag system can potentially resolve the metabolic acidosis faster.[3] These endpoints, in turn, may decrease days of pediatric intensive care and total hospital stay; however, these potential benefits have not been proven in clinical studies.

Correcting acidosis faster can ultimately prevent the use of bicarbonate therapy. Bicarbonate therapy in DKA patients may increase hepatic ketone production and lead to paradoxical acidosis of the cerebrospinal fluid and serum hypertonicity (due to hypokalemia and hypernatremia).[3,5] Correcting acidosis with bicarbonate therapy has also been associated with an increased risk of cerebral edema.[7]

Even though the patients in the one-bag system group had a higher baseline SCr, this observation is probably not clinically significant in this particular study. However, the difference in the initial insulin drip rate between the two groups may be clinically significant because insulin resistance can be offset by an insulin concentration of around 100-200 μU/mL, which can induce cessation of lipolysis and ketogenesis. This concentration can usually be achieved by an insulin drip rate of around 0.1 units/kg/hr.[5] Thus, the higher initial rate of the insulin drip in the two-bag group may have influenced some of the study endpoints.

No particular pattern was observed in the choice of IV fluids and electrolytes used in both the two-bag and the one-bag group. This inconsistency of fluid prescribing may indicate that more education for the house staff would be beneficial. Guidelines to help standardize the prescribing of IV fluid therapy for pediatric patients with DKA may also be valuable.

The two-bag system, as indicated by previously published studies, provides easier management of DKA patients by nursing staff. It provides a faster fluid exchange rate, fewer IV fluid bags used, and reduced cost of IV fluid therapy.[1,4] Using one standard method of managing pediatric DKA patients within an institution could help reduce the potential for errors.

A limitation to this study is that the size of the two groups was not equal. This discrepancy is probably due to the fact that at our institution, most of the pediatric intensive care attending physicians prefer using the two-bag system for DKA fluid management.

In conclusion, using the two-bag system to manage pediatric patients with DKA in our institution appeared to provide a faster rate of bicarbonate and ketone correction. A larger, randomized prospective study to further look into this issue would be beneficial.

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REFERENCES

1. Poirier MP, Greer D, Satin-Smith M. A prospective study of the "Two-Bag System" in diabetic ketoacidosis management. Clin Pediatr 2004;43:809-813.
2. Felner EI, White PC. Improving management of diabetic ketoacidosis in children. Pediatrics 2001;108:735-740.
3. Glaser N, Kuppermann N. The evaluation and management of children with diabetic ketoacidosis in the emergency department. Pediatr Emerg Care 2004;20:477-481.
4. Grimberg A, Cerri RW, Satin-Smith M, et al. The "two bag system" for variable intravenous dextrose and fluid administration: Benefits in diabetic ketoacidosis management. J Pediatr 1999;134:376-378.
5. Dunger DB, Sperling MA, Acerini CL, et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child 2004;89:188-194.
6. Bonkowsky JL, Filloux FM. Extrapontine myelinolysis in a pediatric case of diabetic ketoacidosis and cerebral edema. J Child Neurol 2003;18:144-147.
7. Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. N Engl J Med 2001;344:264-269.
8. Mahoney CP, Vlcek BW, DelAguila M. Risk factors for developing brain herniation during diabetic ketoacidosis. Pediatr Neurol 1999;21:721-727.