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Potential clinical benefits of a two-bag system for fluid management in pediatric intensive care unit patients with diabetic ketoacidosis

Potencjalne korzyści kliniczne „dwupojemnikowego systemu" gospodarki płynami na oddziale intensywnej terapii u pacjentów z cukrzycową kwiasicą ketanową

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Abstract
Introduction. Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus (DM) that requires appropriate treatment with insulin and intravenous fluids. Both one-bag and two-bag systems of fluid management are used to treat pediatric diabetic ketoacidosis. **Aim of the Study.** We compare the one-bag and two-bag systems of fluid managementwith regard to incidence of hypoglycemia, serum bicarbonate correction, pH correction and discharge from the pediatric intensive care unit (PICU). **Method.** This was a retrospective study of 61 patients less than 21 years old admitted to the PICU with a diagnosis of DKA. Of the 61 patients, 38 were treated with the one-bag system and 23 treated with the two-bag system. **Results.** The two-bag system had significantly (p=0.03) lower incidence of hypoglycemia (n=2, 8.7%) compared to the one-bag system (n=13, 34.2%). The two-bag system had significantly (p=0.001) fewer hours of PICU stay (M=29.6, SD=15.23) than the one-bag system (M=47.9, SD=22.32). However, there were no significant differences between the bag systems for hours for pH and bicarbonate correction. **Conclusion.** The two-bag system is associated with lower incidence of hypoglycemia and faster discharge from the PICU. We recommend that clinicians consider using the two-bag system for fluid management in pediatric patients with diabetic ketoacidosis.
Key words
diabetic ketoacidosis, insulin, hypoglycemia, diabetes mellitus type 1

Streszczenie
Wstęp. Kwasica ketonowa (DKA, ang. *diabetic ketoacidosis*) jest zagrażającym życiu powikłaniem cukrzycy, i wymaga odpowiedniego leczenia za pomocą insuliny i dożylnych płynów. W leczeniu kwasicy ketonowej u dzieci terapia płynowa odbywać się może za pomocą jednego lub równocześnie dwóch płynów nawadniających. **Cel badania.** Porównaliśmy dwa systemy nawadniania: za pomocą jednego i dwóch płynów nawadniających w odniesieniu do występowania hipoglikemii, korekty stężenia wodorowęglanów, pH i czasu wypisania pacjenta z oddziału intensywnej terapii (ang. *PICU-pediatric instensive care unit*). **Metody.** Retrospektywnym badaniem objęto 61 pacjentów w wieku poniżej 21 lat przyjętych na oddział intensywnej terapii z diagnozą kwasicy ketonowej. Wśród 61 pacjentów 38 leczonych było za pomocą jednego płynu nawadniającego, a u 23 pacjentów stosowano system dwóch płynów nawadaniających równocześnie. **Wyniki.** Użycie podwójnego systemu nawadniania wiązało się z istotnie mniejszym występowaniem hipoglikemii (p=0,003): (n=2, 8,7%) w porównaniu do jednego systemu nawadniania (n=13, 34,2%). Stosowanie podwójnego systemu nawadniania wiązało się również (p=0,001) z mniejszą ilością godzin spędzoną w oddziale PICU (M=29,6, SD=15,23) w porównaniu z systemem jednego płynu nawadniającego (M=47,9, SD=22,32). Nie zaobserwowano różnic pomiędzy oboma systemami w zakresie czasu potrzebnego do korekty pH i wodorowęglanów. **Wnioski.** System nawadniania za pomocą dwóch płynów równocześnie wiąże się z mniejszą częstością występowania hipoglikemii oraz szybszym wypisaniem pacjenta z oddziału intensywnej terapii. Używanie podwójnego systemu nawaniania w terapii płynowej kwasicy ketonowej u pediatrycznych pacjentów z cukrzycą powinno być rekomendowane.
Słowa kluczowe
kwasica ketonowa, insulina, hipoglikemia, cukrzyca typu 1

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Introduction

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus (DM) that requires prompt recognition and appropriate treatment [1]. In the United States, the overall rates of DKA at diagnosis in infants and children with diabetes is about 25% [2]. It also accounts for approximately 20% of all mortality in children due to DM [3]. Management of DKA includes correcting hyperglycemia, dehydration, electrolyte disturbances and acidosis using intravenous fluids (IV) and insulin [2, 3]. Frequent IV fluid modification is necessary to adapt to ongoing changes in fluid balance, serum glucose and electrolytes [4]. One-bag and two-bag systems have been used for fluid management in pediatric DKA patients [4].

There are two different approaches to fluid management. Traditionally, one bag of IV fluid with electrolytes is used. As blood glucose falls, a new bag with an appropriate glucose content is ordered from the pharmacy and when available, it replaces the previous bag even if the bag is not yet completely depleted [5]. The two-bag system consists of two bags of identical electrolyte content but with different dextrose concentrations that are administered simultaneously into a single IV line [5]. A benefit of the two-bag system is that it allows for faster response time for IV fluid changes [5, 6]. By adjusting the rate of each bag, clinicians can immediately provide a customized glucose infusion rate while keeping the fluid delivery constant [4]. We are aware of only 3 studies comparing one- and two-bag systems for DKA management in pediatric patients. A retrospective study with 20 patients found that the two-bag system had a faster response time for IV fluid change and improved cost-effectiveness as compared to the one-bag system [5]. Another retrospective study with 31 patients showed that the two-bag system had a faster rate of bicarbonate correction and faster rate of ketone correction as compared to the one-bag system but no difference for pH correction or serum glucose decline [4]. A prospective study with 33 patients found that there was a faster response time for IV fluid change with the two-bag system as compared to the one-bag system. However, there were no differences for the rate of serum glucose decline or rate of serum bicarbonate correction [6].

While these studies show a faster response time for IV fluid change for the two-bag system, none of the studies compared time to discharge or incidence of hypoglycemia. Our retrospective study comparing the one-bag to the two-bag systems for pediatric DKA management has a larger sample size of 61 patients. Our primary outcome is incidence of hypoglycemia (glucose $\leq$ 70mg/dl) in the first 24 hours of treatment initiation. Our secondary outcomes are the number of hours for serum bicarbonate correction to >15 meq/L, pH correction to >7.3, and discharge from the pediatric intensive care unit (PICU).

Aim of the study

This study aims to evaluate the potential clinical benefits of the two-bag versus a one bag system in the fluid management of pediatric intensive care unit patients with DKA.

Methods

Participants and Setting

This was a retrospective study of 61 patients less than 21 years old admitted to the PICU with a diagnosis of DKA from November 1, 2007 through July 31, 2013. This study was conducted in a public community hospital located in a suburb of New York City mostly serving patients from low- to middle-income families. Institutional Review Board approval was received to conduct this study.

Types of insulin used by patients on multiple daily injections (MDI) were a long-acting insulin (Lantus or Levemir) as a basal insulin plus a rapid-acting insulin (Novolog or Humalog) formeal boluses. Patients on continuous subcutaneous insulin infusion (CSII) were using rapid-acting insulin alone (Novolog or Humalog). The type of insulin was largely determined by insurance coverage.

Inclusion and Exclusion Criteria

Inclusion criteria: patients with type 1 diabetes mellitus (DM) <21 years old admitted to the PICU with a diagnosis of DKA (i.e., hyperglycemia >200 mg/dl, metabolic acidosis defined as venous pH <7.3, and/or plasma bicarbonate level <15 meq/L) [7]. Exclusion criteria: patients who were pregnant or who were transferred to another hospital.

One-bag System

Intravenous fluid administration was started in the emergency department (ED). The normal saline (NS) bolus was initially given in the ED and varied from 10 ml/kg to 20 ml/kg. There was no consensus in the number of fluid boluses in the ED and the number administered was based on the judgment of the clinician present. After bolus administration, IV fluid used was ½ NS+ 20 meq/L KCl + 20 mmol/L KPhos. The IV fluid rate was calculated based on the fluid deficit plus maintenance to run over 48 hours. The IV fluid deficit was calculated based on 10% dehydration (weight x 100ml/kg). Maintenance IV fluidrate was calculated based on the Holliday-Segar method [8]. Any NS bolus given in the ED was subtracted from the fluid deficit. The dose of insulin (50 units of regular insulin in 50 ml of 0.9% NS) started was 0.05 units/kg/hour regardless of age. IV fluid was changed to D5 ½ NS with 20 meq/L KCl + 20mmol/L KPhos at the same rate once blood glucose level fell below 300 mg/dl.

Two-bag System

Please refer to the appendix provided for details. The two-bag protocol was implemented in 2010. All patients who had DKA were admitted to the PICU and started on the new two-bag system. Prior to 2010, all patients admitted with DKA were admitted to the PICU and treated with the one-bag system. The one-bag and two-bag systems were all administered bya single PICU provider.

Criteria for PICU Discharge

Criteria for PICU discharge included resolution of DKA (pH>7.3 and/or HCO3 >15 meq/L) and tolerating oral intake.

Variables

Variables include bag type (one versus two), demographics of age (years), sex (male/female), race/ethnicity (white, black, Hispanic), history of previous DKA, insulin delivery (new-onset diabetes, injection, pump), initial serum pH, initial serum bicarbonate (meq/L), initial serum glucose (mg/dl) and serum hemoglobin A1c (%). Outcome variables were hypoglycemia, as defined by both the American Diabetes Association and the Endocrine Society (glucose $\leq$ 70 mg/dl) (9), in the first 24 hours of treatment with insulin, time (hours) to correction of serum bicarbonate to $>$15 meq/L, time (hours) to pH correction to $\geq$7.3, and time (hours) to discharge from the PICU.

Statistical Analyses

Mean and standard deviation were used to describe the continuous variables. Frequency and percentage were used to describe the categorical variables. Analysis of variance (ANOVA) compared bag type to the continuous variables. As appropriate, either the Pearson chi-square test or the Fisher's exact test (when any cell was $<$5) compared bag type to the categorical variables. Continuous variables with a skewed distribution were logarithmic transformed for the inferential analyses. All outcome variable comparisons with statistical significance between bag types were repeated with univariate regression analyses that included potentially relevant covariates as predictors to determine the independent relationship of each of these potentially relevant covariates with the outcome variable. Any variable statistically significant in the univariate analysis was included in a multivariate analysis. Linear regression was performed for the continuous outcome variables and logistic regression was performed for the categorical outcome variable. All p-values were two-sided. SPSS Version 22 was used for all analyses.

Table I. Sample characteristics of 61 patients with diabetic ketoacidosis
Tabela I. *Charakterystyka 61 pacjentów z cukrzycową kwasicą ketonową*

Variable	Whole Sample Mean (SD) or # (Percent)	One-bag Mean (SD) or # (Percent)	Two-bag Mean (SD) or # (Percent)	p-value
Age (years)	15.6 (3.79)	15.2 (3.94)	16.2 (3.50)	0.31
Sex (female) (%)	28 (45.9)	16 (42.1)	12 (52.2)	0.44
Race/ethnicity (%)				0.15
White	10 (16.4)	8 (21.1)	2 (8.7)	
Black	26 (42.6)	18 (47.4)	8 (34.8)	
Hispanic	25 (41.0)	12 (31.6)	13 (56.5)	
Previous DKA (%)	46 (75.4)	28 (80.0)	18 (78.3)	0.87
Insulin Delivery (%)				0.58
New-onset Diabetes	5 (8.2)	4 (11.4)	1 (4.3)	
Injection	45 (73.8)	27 (77.1)	18 (78.3)	
Pump	8 (13.1)	4 (11.4)	4 (17.4)	
Missing	3 (4.9)	---	---	
Initial pH	7.2 (0.11)	7.2 (0.11)	7.13 (0.10)	0.24
Initial serum bicarbonate (meq/L)	10.2 (4.38)	10.1 (4.17)	10.6 (4.80)	0.66
Initial serum glucose (mg/dl)	556.4 (218.08)	537.3(206.70)	587.8 (237.06)	0.50
Hemoglobin A1c (%)	12.2 (2.99)	12.3 (2.68)	12.0 (3.56)	0.68

Note: SD=standard deviation, DKA=diabetic ketoacidosis, Sample size can slightly vary due to omissions by participants.

Results

The general characteristics of subjects are shown in Table I. Mean age was almost 16 years. Females were almost half of the sample. More than 83% were minorities (Black or Hispanic) and 16% were white. More than 75% had previous DKA. Nearly 74% used injections and 13% were using an insulin pump to deliver insulin. Eight percent were new-onset diabetes presenting with DKA. Mean initial pH (7.2) and mean initial serum bicarbonate (10.2 meq/L) indicated mild to moderate severity of DKA. Mean hemoglobin A1c (12.2%) indicated long standing, poor glycemic control. None of the sample characteristics statistically differed between the bag types.

Table II shows Fisher's exact test comparisons for the bag types. The one-bag group showed a greater frequency of hypoglycemic episodes than the two-bag group (p=0.03). In the two-bag group there were 2 individuals each with 1 episode of hypoglycemia, whereas in the one-bag group, there were 8 individuals each with 1 episode of hypoglycemia, 4 individuals each with 2 episodes of hypoglycemia, and 1 individual with 5 episodes of hypoglycemia. Logistic regression analysis did not find any significantly relevant covariates (data not shown). The one-bag group showed an increased risk for hypoglycemia (p=0.04) as compared to the two-bag group (OR=5.46, 95% CI: 1.11, 26.98).

ANOVA comparison of bag types showed the two-bag group had a faster mean time to discharge from the PICU than the one-bag group (p=0.001) (Table II). There were no statistically significant differences between the bag groups for either time to serum bicarbonate correction to above 15 meq/L or time to pH correction to be $\geq$ 7.3.

Table III shows linear regression analysis for discharge from the PICU. In univariate analyses, both the two-bag group (p=0.001) and injection insulin delivery (p=0.003) were each statistically significantly associated with fewer hours until discharge. Initial glucose was statistically significantly associated with more time until discharge (p=0.01). In the multivariate analyses, the same pattern occurred that the two-bag group and injection insulin delivery were each statistically significantly associated with faster discharge from the PICU. However, initial glucose was no longer statistically significantly associated with discharge.

Discussion

In our study, we found that DKA patients who received IV fluids using the two-bag system had significantly less hypoglycemia in the first 24 hours after initiation of treatment as compared to the one-bag system. We also found that patients using the two-bag system spent less time in the PICU than the one-bag system. There were no significant differences for pH or bicarbonate correction between the bag systems. Logistic regression analysis did not reveal any relevant covariate significantly associated with hypoglycemia. In multivariate analysis, the two-bag system and patients' insulin delivery method at home were associated with a quicker discharge from the PICU.

DKA results from severe insulin deficiency and increased concentrations of counter regulatory hormones (catecholamines, cortisol, glucagon, and growth hormone) leading to hyperglycemia and ketosis [10,11]. Hyperglycemia develops as a result of increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues [11]. The inability of tissues to utilize glucose causes lipolysis with production of ketones which are responsible for metabolic acidosis, ketonemia and ketonuria [12].

DKA is characterized by severe depletion of water and electrolytes from both the intra- and extracellular fluid (ECF) compartments [13].The optimal fluid treatment regimen for pediatric DKA has been controversial. Most of the concern is centered on its role in the development of cerebral edema [14]. Despite advances in the management of Type 1DM, the Type 1DM exchange clinic registry data indicate that the frequency of having at least one DKA even within 12 months was 9.9% overall. DKA was more common in adolescents and young adults with higher HbA1c levels [15] which is similar to our study population.

Table II. Outcome comparisons between bag types
Tabela II. *Porównanie 2 typów nawadniania*

Variable	One-bag Mean or Frequency (n=38)	SD or Percent	Two-bag Mean or Frequency (n=23)	SD or Percent	p-value
Hypoglycemia (%)	13	34.2%	2	8.7%	0.03
Serum bicarbonate correction (hours)	9.1	4.97	9.8	5.67	0.62
pH correction (hours)	10.2	6.03	10.0	5.36	0.91
Discharge (hours)	47.9	22.32	29.6	15.23	0.001

Note: SD=standard deviation

Table III. Linear regression analyses for discharge from the Pediatric Intensive Care Unit
Tabela III. *Analiza regresji liniowej wypisania z oddziału intensywnej terapii*

Variable	Univariate B	SE	p-value	Multivariate B	SE	p-value
Bag Type						
One-bag	Reference			Reference		
Two-bag	-18.26	5.28	0.001	-18.27	4.86	<0.001
Age	-0.77	0.74	0.30	---	---	---
Sex (female)	4.99	5.59	0.38	---	---	---
Race/ethnicity						
White	Reference					
Black	-0.90	8.12	0.91	---	---	---
Hispanic	-7.40	8.17	0.37	---	---	---
Previous DKA	-9.92	6.89	0.16	---	---	---
Insulin Delivery						
New-onset Diabetes (None)	Reference			Reference		
Injection	-28.44	9.31	0.003	-20.29	8.92	0.03
Pump	-12.70	11.26	0.26	-6.46	10.23	0.53
Initial pH	-27.03	26.44	0.31	---	---	---
Initial serum bicarbonate	-0.93	0.63	0.15	---	---	---
Initial serum glucose	40.49	15.89	0.01	24.54	15.41	0.12
Hemoglobin A1c	0.58	1.03	0.58	---	---	---
Intercept	---	---	---	16.06	44.21	0.72

Note: B=beta, SE=standard error, DKA=diabetic ketoacidosis

Hypoglycemia

We found that the two-bag system had a lower incidence of hypoglycemia in the first 24 hours of initiation of treatment as compared to the one-bag system. A study reported 2 children with serum glucose <80 mg/dl on the insulin drip and both children were managed with the one-bag system [6]. We suggest that this reduced hypoglycemia occurs because the two-bag system allows for faster IV fluid change adjustment in response to falling blood glucose because of ongoing insulin action. Glucose titration aims to control glucose decline. A rapid glucose correction may result in a rapid decrease in osmolality, thus, a theoretical risk in the development of cerebral edema [16,17].

Cerebral edema occurs in 0.5-1% of all episodes of DKA in children and is the most common cause of mortality in these children [2]. The pathophysiologic mechanism underlying the development of cerebral edema associated with DKA is controversial. Low partial pressures of arterial carbon dioxide, higher serum urea nitrogen concentrations, and treatment with bicarbonate has been found to increase the risk of cerebral edema [18]. Recent data suggests that cerebral hypoperfusion and the effects of reperfusion during DKA treatment may also play a role in the development of this complication [14].

The two-bag system is especially important for younger patients that are more vulnerable to the consequences of hypoglycemia. The ongoing maturation of the central nervous system places children at greater risk for cognitive deficits [9] compared to adults. This consequence of hypoglycemia was not seen in our sample since the mean age that we studied were 15.2 years and 16.2 years for the one-bag and two-bag systems.

Discharge from PICU

We found that patients that used the two-bag system spent less time in the PICU compared to the one-bag system. Another study found that with the two-bag system, there is a significantly faster rate of bicarbonate and ketone correction with a trend towards a faster rate of pH correction. These authors suggest that the two-bag system may imply faster resolution of metabolic acidosis and thus may decrease length of stay in the PICU and total time hospitalized; however, this was not proven in that study [5]. Our study with 61 patients was almost twice as large as that previous study. We report a finding of shorter stay in PICU for the two-bag system yet no impact on acidosis.

Criteria for PICU discharge includes resolution of DKA and tolerating oral intake. Although patients may have resolution of DKA, hypoglycemic episodesin the first 24 hours of treatment lead to delayed discharge from PICU for the purpose of blood sugar monitoring. A study looking at hospitalized patients with diabetes showed an association between hypoglycemia and prolonged hospital stay [19]. Thus, by minimizing hypoglycemic episodes, the two-bag system may in general reduce hospital stay. Another study did not find any difference in length of hospital stay with the use of the two-bag system of IV fluid therapy as compared with the one-bag system [20]. However, their study reported number of days and did not specify length of stay in PICU or when patients were transferred to the general floor or step-down unit once DKA had resolved. Mean length of stay was 2 days in the protocol group (two-bag system) and 3 days in the non-protocol group, duration that was longer relative to our reported PICU length of stay.

In our multivariate analysis, we found that patients that used syringes to inject insulin but not continuous subcutaneous insulin infusion (CSII) pump therapy was associated with quicker discharge from PICU. There are a few possible explanations. First, we suggest that patients with known type I diabetes on multiple daily injections may be more comfortable making adjustments to their insulin regimen immediately, thus requiring less time for re-education and training. Second, it is possible that this finding is particular to our institution where a majority of patients use injection as a method for insulin delivery, as we had a much smaller number of patients using continuous subcutaneous insulin infusion (CSII) pump therapy.

Bicarbonate correction

We did not find any significant difference for bicarbonate correction between the one-bag and two-bag systems. Previous research shows conflicting findings. One study of 33 patients reported no difference in bicarbonate correction between the bag systems [6] whereas another study of 31 patients reported faster bicarbonate correction for the two-bag system as compared to the one-bag system [4]. A newer study supports our results which showed thatthe two-bag system did not show any difference with median bicarbonate correctionas compared to the one-bag system [20].

The hallmark of DKA is acidosis and the serum bicarbonate concentration is usually less than 10 meq/L. The acidosis is caused by production and accumulation of ketones in the serum. Three ketones are produced in DKA: beta-hydroxybutyrate, acetoacetate and acetone [10]. Patients with DKA have large amounts of ketones in their urine.

The mainstay of treatment for DKA is insulin because DKA is essentially an insulin-deficient state. In the past, high doses of insulin have been used. However, low-dose insulin therapy has been shown to be as effective in decreasing serum glucose and clearance of ketones [10].

pH correction

We did not find any significant difference for pH correction between the one-bag and two-bag systems. This finding is likely because correction of acidosis is related more to insulin administration than fluid administration. This is similar to a previous study that did not find any difference in pH correction between the one-bag and two-bag systems [4]. Our study with a larger sample size replicates this finding. Severe acidosis is reversible by fluid and insulin replacement. Insulin stops further ketoacid production and allows ketoacids to be metabolized, which generates bicarbonate [13]. Treatment of hypovolemia improves tissue perfusion and renal function, thereby increasing the excretion of organic acids.

Recently, serial beta-hydroxybutyrate (BHOB) testing was used to improve quantification of the clinical trajectory of DKA and its resolution.It was also used as a discharge criterion from the ICU in another institution which resulted in reduction in ICU length of stay [21]. Serum BHOB concentrations at bedside could be a useful marker to monitor response to treatment as well as resolution of acidosis [14].

Study Limitations and Future Research

There are several study limitations. First, our sample size was relatively small, although it is much larger than previous studies on this topic. Second, we did not study the rate of serum glucose decline between the one-bag and two-bag system. Third, our study is retrospective. We recommend future research with a randomized controlled trial to assess clinical benefits of the two-bag versus the one-bag system in fluid management of pediatric DKA patients.

Conclusion

In conclusion, we found that the two-bag system is associated with lower incidence of hypoglycemia and faster discharge from the PICU for pediatric DKA patients. We recommend that clinicians consider using the two-bag system for fluid management in pediatric DKA patients.

Appendix

Two-bag System

Step 1: Fluid resuscitation in ED: 10 ml/kg 0.9% NS bolus followed by IVF at 1.5-2 times maintenance. Use 20 ml/kg if peripheral perfusion is inadequate and repeat if necessary.

Step 2: Insulin administration for acidotic patients (pH<7.3 or bicarbonate <15)
Insulin dose – 0.1 units/kg/hour for serum glucose <900 mg/dl or 0.05 units/kg/hour for serum glucose >900 mg/dl or child is less than 7 y.o.
Drip concentration: Mix 100 units regular insulin in 100 ml of 0.9% NS (unit/ml)

Step 3: Use the Two-bag method with an IV fluid rate at 1.5-2 times maintenance according to the following table:

Bag 1: ½ NS or NS (% total hourly rate)	Bag 2: D10 ½ NS or D10 NS (% total hourly rate)	Patient's serum glucose (mg/dl)	Glucose concentration delivered to patient(%)
100	0	>300	0
75	25	275-300	2.5
50	50	250-275	5
25	75	225-250	7.5
0	100	<225	10

Potassium is added to IV fluid when K level < 5meq/L and patient is making urine. Add 20 meq/L KCl + 20mmol KPhos/L or 10 meq KCl + 10 mmol KPhos/L for children < 7 years.

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