The Two-bag System for Intravenous Fluid Management of Children with Diabetic Ketoacidosis: Experience from a Community-Based Hospital

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Abstract

Objectives: Intravenous fluid (IVF) administration using the two-bag system compared with the one-bag system in children with diabetic ketoacidosis (DKA) admitted between January 1, 2015 and December 31, 2016. Design: Retrospective cohort study. Setting: Community-based hospital. Results: A total of 109 patients were enrolled with a mean age of 13.24 years. The 2 groups had comparable demographics. Initial laboratory results were similar except for initial PH and Sodium. The two bag system had significantly less number of calls compared to one bag system (25.2 vs 5.2 P = .0001). One bag system had fewer hypoglycemia <60 mg/dl (4 vs 12 P = .049). No statistically significant observations noted in regards to glucose drop rate, number of intravenous fluid bags used, amount of fluid boluses given, hospital stay and Pediatric ICU stay. Conclusions: The two-bag system has less resource utilization and slower blood glucose drop rate, but higher hypoglycemic events

Keywords
diabetic ketoacidosis, fluid, two bag

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Introduction

Diabetic Ketoacidosis (DKA) is the most dreaded complication of insulin dependent diabetes mellitus (IDDM) and accounts for up to 20% of mortality in children with IDDM.1 Poor adherence to treatment is often considered to be the most common precipitating factor for the development of DKA in children with IDDM.1,2 Prompt and appropriate intravenous fluid (IVF) management of DKA is essential in order to minimize the risk of development of complications resulting from treatment of DKA.3,4

Hyperglycemia causes Fluid and electrolyte losses secondary to osmotic diuresis in DKA, which in turn can lead to an increase in the levels of counter-regulatory hormones, causing more hyperglycemia, polyuria and volume depletion.3,5 Mainstay of DKA management is insulin and fluid replacement.5 Current recommendation is generous rehydration in an effort to minimize the effects of counter regulatory hormones, hence avoiding worsening hyperglycemia and further dehydration. Optimal fluid therapy has shifted from slow low volume towards faster and higher rehydration method since a recent randomized trial showed no difference in neurological outcome between the slow low volume and faster higher volume of fluid administration in children with DKA.3

Initial IVF composition has traditionally been dextrose-free IVF until serum glucose level declines to between 250 and 300 mg/dl, when dextrose is added to intravenous fluid therapy.5,6 Since serum glucose level can fluctuate in patients with DKA, repeated and multiple IVF bag changes are required during the management

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of DKA. This approach is referred to as the traditional one bag system and has some limitations, including, restricted variations in fluids administered and a higher cost. Since a new bag of IVF is needed to be ordered from pharmacy each time there is a need to change the concentration of glucose in the IVF administered, it is also expected to lead to a slower response time in patient management. To overcome these shortcomings, a new system called the two-bag system was introduced by children’s hospital in Philadelphia in 1994, which composed of two bags with identical electrolyte contents, but different dextrose concentrations (one bag has 0% and another has 10% dextrose). This method was adapted from the euglycemic clamp experiment. Because some clinical studies have suggested that the two-bag system has some advantages compared to one-bag system, the two-bag system has been implemented as standard of care in DKA patients.

However, data on the comparison of the two-bag method with the one bag method in the IVF management of children with DKA are limited. The purpose of the current study was to compare the two-bag system with one bag system with regards to the decline in blood glucose, the number of calls made by the bedside nurse to the treating physicians and response time to changing the IVF. Secondary outcomes assessed included, correction of acidosis, total numbers of hours of insulin infusion, the numbers of IVF bags utilized until the patient was transitioned to subcutaneous insulin, incidence of complications of DKA and ICU and hospital length of stays.

Materials and Methods

Study Design and Participants

This was a retrospective cohort study conducted in the pediatric emergency department (ED) and the pediatric intensive care unit (PICU) of Hurley Medical Center, a community-based Hospital located in a midsize midwestern city in Michigan state- United States of American (USA). The PICU is a 16-bed multi-disciplinary unit with 1100 admissions per year and is staffed by 3 full-time pediatric critical care physicians, 2 physician’s assistant and 3 residents from pediatrics and emergency medicine residencies. Therapy for DKA is initiated in the ED and the care will be continued into the PICU. Since our center adopted the two bag system as the standard of care in January 2016; our study period was from January 1, 2015 until December 31, 2016.

Using Hurley Medical Center Registry, standardized data were collected and the information stored in an excel sheet. Collected data included all patients aged 20 years or younger admitted with DKA (DKA was defined as a blood pH of 7.3 or less and/or a serum bicarbonate of < 15 mEq/L, a blood glucose greater than 250 mg/dL and the presence of ketonemia as measured by a serum level of beta-hydroxybutyric acid greater than normal).

Ethical aspects: The study was approved by the institutional review board (IRB) at Hurley Medical Center (reference number IRB 1337249-1), but considering the retrospective nature of the study; exemption from obtaining informed consent was obtained from the IRB. Children with other comorbid conditions such as adrenal insufficiency, children who were receiving high dose oral or intravenous corticosteroid therapy, or those with evidence of cerebral edema at presentation were excluded.

Procedure

The initial fluid resuscitation in the ED consisted of administration of 20 mL per kg body weight of isotonic saline over 1 hour for all patients and remained the same throughout the study period. This was followed by administration of IVF at 1.5 maintenance. In the one-bag system. The IVF consisted of 0.9 sodium chloride with 20 mEq/L of potassium chloride or 15 mMol/L of potassium phosphate, which was adjusted by adding dextrose when blood glucose was below 300 mg/dl. In the two-bag system; there was no difference in electrolyte concentration in both bags (0.9 Normal Saline, 20 mEq/L of potassium chloride or 15 mMole/L of potassium phosphate), however; one bag contained 10% dextrose and the other bag contained no dextrose. In the two-bag system; Initially when the blood glucose was > 300 mg/dL, 100% of the prescribed IVF was delivered from the bag that did not contain dextrose, both groups were receiving regular insulin at a rate of 0.1 u/kg/hr.

The ratio of the IVF in the two-bag system was adjusted, by the bedside nurse, based on the following protocol (Table 1):

Monitoring

Using a standard DKA protocol, patients were monitored hourly for vital signs, neurological assessment using the Glasgow coma scale and blood glucose level. DKA panel One (Na, K, Cl, Glucose, anion gap, PH) And DKA panel two (BUN, Creatinine, Phosphate, Magnesium, bicarbonate) were measured every 2 and 4 hours respectively.

Assessment of mental status: The Glasgow Coma Scale (GCS) were assessed at the time of presentation to
the ED and hourly thereafter. Whenever the GCS was less than 13, it was repeated in 15 minutes later by a second nurse. GCS for infants was used for children less than 1 year of age. When the GCS was confirmed to be less than 13, the patient was immediately assessed by a physician and the patient was considered to have cerebral edema and computerized tomography of the brain was obtained. We did not monitor ketonemia or ketonuria during the treatment of DKA.

**Outcome Measures**

The primary outcome measures were the decline in blood glucose (mg/dL per hour), PICU and hospital length of stay in hours, the number of calls made by the bedside nurse to the treating physicians and response time to changing the IVF. The number of calls were defined as any communication between the bedside nurse and the treating health care provider either in person or via telephone. Secondary outcomes measured were the numbers of IVF bags utilized until the patient was transitioned to subcutaneous insulin, incidence of cerebral edema. Patients were transferred to a pediatric ward when the DKA had resolved and a bed was available on the pediatric ward, but discharge from hospital was left to the discretion of the treating physician. Cerebral edema was diagnosed in patients who had a GCS of < 14 and computerized tomography findings that were consistent with cerebral edema.

**Statistical Analysis**

Initial data was collected and descriptive statistics was used to compare both arms of patients included. Using STATA® We calculated mean with standard deviations for normally distributed variables and we used t-test to compare means between both arms of the study with its 95% confidence interval. For categorical data; Chi² was used to determine statistically significant differences between both arms. We implemented regression analysis to assess if the outcome was predicted by the bag system used after adjusting for variables that were different in both arms of the study at presentation. We set a P-value of less than .05 was considered statistically significant difference.

**Results**

**Baseline Characteristics**

This study included 109 patients with a mean age of 13.24 years and a median age of 14 years. 52 patients were included in the traditional one bag group and 57 were included in two bag group. The two groups were comparable with regard to age, gender, weight, race and the percentage of patients with new onset insulin dependent diabetes (Table 2). All patients in both groups had a GCS of 15 at presentation. With exception of statistical difference in initial Sodium and PH value at presentation; There were no statistically significant difference between the 2 groups with regard to the biochemical profile at presentation (Table 3).

**Primary and Secondary Outcomes**

The number of calls by the bedside nurse to the treating physician/health care provider were higher in the one bag system (25.2 ± 9 vs 5.2 ± 0.5 times, P < .0001). Two bag system had higher hypoglycemic events which is defined as blood sugar below 60 mg/dl compared to one bag system (12 vs 4 P = 0.049) (Table 4).

Our study found no statistically significant difference between the 2 groups with regards to hospital length of stay (48.9 vs 42, P = .212), PICU length of stay (26.9 vs 30.5 P = .127, and numbers of IVF bags (3.28 vs 3.66 P = .233), amount on normal saline bolus

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**Table 1.** Two bag system protocol applied for fluid management in DKA.

| Blood glucose (mg/dL) | % Of hourly IVF rate from bags without dextrose | % Of hourly IVF rate from the bag with D10 | Final dextrose concentration |
|-----------------------|-----------------------------------------------|------------------------------------------|------------------------------|
| More than 300         | 100% of hourly rate                            | 0% of hourly rate                       | 0% dextrose                 |
| 250-299               | 75% of hourly rate                             | 25% of hourly rate                      | 2.5% dextrose               |
| 200-249               | 50% of hourly rate                             | 50% of hourly rate                      | 5% dextrose                 |
| 150-199               | 25% of hourly rate                             | 75% of hourly rate                      | 7.5% dextrose               |
| 100-149               | 0% of hourly rate                              | 100% of hourly rate                     | 10% dextrose                |
| aLess than 100        | aLess than 0% of hourly rate                   | aLess than 100% of hourly rate           | aLess than 10% dextrose     |

aA call to treating physician is needed to adjust insulin infusion rate in addition to continuing dextrose containing fluid. A call was defined as any communication between the bedside nurse and the treating health care provider.
in mL (1627 vs 1348 \( P = .0585 \)), Glucose drop rate per hour (49.76 ± 36.9 ± 30 mg/dL per hour, \( P = .0648 \)) (Table 4). However, since initial PH and sodium were lower in one bag group that were statistically significant, Regression analysis was obtained which failed to show any difference in hospital stay, PICU stay or number of IVF bags used after adjusting for initial PH, Sodium, and gender (Table 5).

**Neurological Complications**

One patient developed clinical features consistent with cerebral edema (GCS of \( \leq 14 \)) in the one bag system compared with no incidence of clinical cerebral edema in two bag system. Computerized tomography showed loss of gray-white matter differentiation and effacement of basal cisterns. She was treated with hypertonic saline and she made a full neurological recovery and was neurologically normal 6 months following the incident.

**Discussion**

This study demonstrated that the two-bag system for IVF administration was associated with a slower decline in the serum glucose, lower frequency of calls from the bedside nurse to the treating physician/health care provider and a faster response time to changing IVF after the results of blood glucose levels were available. However two bag system has higher hypoglycemic events, this might be partially explained by more confidence from the treatment team that since D10 is contained in the two bag system, hypoglycemia is less likely to happen, which as shown in our paper is not a correct assumption. This study did not demonstrate any differences in PICU, in hospital length of stay or num-

### Table 2. Initial Patient Characteristics.

| Group            | Observation number | Mean    | Standard deviation | Standard of error | 95% CI          |
|------------------|--------------------|---------|--------------------|-------------------|-----------------|
| Weight in kilogram |                    |         |                    |                   |                 |
| One bag          | 52                 | 48.86   | 17.122             | 2.37              | 44.09-53.63     |
| Two bag          | 57                 | 50.9    | 16.253             | 2.15              | 46.59-55.22     |
| Combined         | 109                | 49.935  | 16.627             | 1.59              | 46.77-53.09     |
| \( P = .523, t = -6.40 \) |

| Patient’s age in years | Observation number | Mean    | Standard deviation | Standard of error | 95% CI          |
|------------------------|--------------------|---------|--------------------|-------------------|-----------------|
| One bag                | 52                 | 12.96   | 4.78               | 0.66              | 11.63-14.29     |
| Two bag                | 57                 | 13.5    | 2.91               | 0.38              | 12.73-14.28     |
| Combined               | 109                | 13.24   | 3.90               | 0.37              | 46.77-53.09     |
| \( P = .4679, t = -0.6402 \) |

| Gender                | Observation number | Male | Female | Chi\(^2\) | \( P \) value |
|-----------------------|--------------------|------|--------|-----------|--------------|
| One bag               | 52                 | 18   | 34     | 0.1468    | .702         |
| Two bag               | 55\(^a\)           | 21   | 34     |           |              |
| Combined              | 109                | 39   | 68     | 0.1468    | .702         |
| \(^a\)Two has undisclosed gender |

| Race                  | Observation number | White | Black or AA | Other | Chi\(^2\) | \( P \) value |
|-----------------------|--------------------|-------|-------------|-------|-----------|--------------|
| One bag               | 52                 | 41    | 8           | 3     |           |              |
| Two bag               | 57                 | 41    | 13          | 3     |           |              |
| Combined              | 109                | 82    | 21          | 6     |           |              |
| \( Chi^2 = 1.0604, P = .588 \) |

| New onset DM          | Observation number | Yes = 7 | No = 45 | Yes = 8 | No = 47 | \( Chi^2 = 0.0261, P = .872 \) |
|-----------------------|--------------------|----------|--------|--------|--------|-----------------------------|
| One bag               | 52                 | 7        | 45     | 8      | 47     |                            |
| Two bag               | 55\(^b\)           | 8        | 47     |        |        |                            |
| Combined              | 107                | 15       | 92     |        |        |                            |
| \(^b\)Two patients had unknown status in regards to their diabetes onset |
Diabetic ketoacidosis is a life-threatening complication of insulin dependent diabetes that results from lack of insulin in the setting of high levels of counter regulatory hormones. This results in hyperglycemia because of increased gluconeogenesis, accelerated glycogenolysis associated with impaired glucose utilization.\textsuperscript{1,2} The tissues undergo lipolysis with increased beta oxidation of fatty acids leading to production of ketoacids including beta-hydroxybutyric acid, acetoacetic acid and acetone.\textsuperscript{1-3} Accumulation of these ketoacids results in metabolic acidosis that is the hallmark of DKA. DKA is the most serious complications of IDDM and accounts for 20% of mortality in patients with insulin dependent diabetes.\textsuperscript{6}

Therapy of DKA consists of administration of IVF and insulin. Most protocols involve administration of an initial bolus of isotonic saline followed by administration of IVF that contains appropriate amounts of electrolytes.\textsuperscript{1-4} Data on the comparison of the two bag system with the one bag system for fluid administration in children with DKA has been conflicting.\textsuperscript{6,11,12} Initial studies performed over twenty years ago demonstrated that the two bag system was more efficient compared to one bag system. Grimberg et al\textsuperscript{11} demonstrated in a retrospective study of 20 children with DKA, that the two bag system improved response time to adjustment of the IVF and the therapy of DKA was more effective. Subsequently, Poirier et al\textsuperscript{12} demonstrated in a prospective study of 33 children with DKA a faster response time for IVF change with the two bag system compared to the one bag system, however, there was no difference between the groups with regard to the rate of serum glucose decline or the rate of correction of the metabolic acidosis as reflected in the serum bicarbonate.

Further work by So and Grunewalder\textsuperscript{13} also demonstrated that the two bag system was associated with a

| Table 3. Initial Laboratory Values. |
|------------------------------------|
| Group | Observation number | Mean | Standard deviation | Standard of error | 95% CI |
|-------|--------------------|------|--------------------|-------------------|-------|
| Initial glucose | | | | | |
| One bag | 52 | 568 | 222.9 | 30.9 | 506.7-630.8 |
| Two bag | 57 | 578 | 226.4 | 29.9 | 518.5-638.7 |
| Combined | 109 | 573 | 223.7 | 21.4 | 531.4-616.7 |
| P = 0.8192, t = -0.2292, df = 107 |
| Initial PH | | | | | |
| One bag | 52 | 7.188 | 0.109 | 0.015 | 7.157-7.218 |
| Two bag | 57 | 7.131 | 0.125 | 0.016 | 7.098-7.165 |
| Combined | 109 | 7.158 | 0.120 | 0.011 | 7.135-7.181 |
| P = 0.0144, t = 2.4881, df = 107 |
| Initial bicarbonate | | | | | |
| One bag | 52 | 10.76 | 4.327 | 0.6 | 9.56-11.97 |
| Two bag | 57 | 10.24 | 4.437 | 0.587 | 9.06-11.42 |
| Combined | 109 | 10.49 | 4.372 | 0.418 | 9.66-11.32 |
| P = 0.5349, t = 0.6226, df = 107 |
| Initial sodium | | | | | |
| One bag | 52 | 134.6 | 6.61 | 0.91 | 132.9-136.5 |
| Two bag | 57 | 132.2 | 5.63 | 0.74 | 130.7-133.7 |
| Combined | 109 | 133.3 | 6.21 | 0.59 | 132.2-134.5 |
| P = 0.0397, t = 2.0828, df = 107 |
| Initial potassium | | | | | |
| One bag | 52 | 5.11 | 0.833 | 0.115 | 4.88-5.34 |
| Two bag | 57 | 4.86 | 0.898 | 0.119 | 4.62-5.099 |
| Combined | 109 | 4.98 | 0.873 | 0.083 | 4.81-5.149 |
| P = 0.127, t = 1.53, df = 107 |
| Initial chloride | | | | | |
| One bag | 52 | 100.01 | 8.17 | 1.13 | 97.74-102.29 |
| Two bag | 57 | 100.12 | 7.48 | 0.99 | 98.13-102.10 |
| Combined | 109 | 100.0734 | 7.78 | 0.74 | 98.59-102.10 |
| P = 0.9451, t = -0.0691, df = 107 |
shorter time to correction of serum bicarbonate and keto-
sis compared to one bag system in 31 patients with DKA. More recently, Velasco et al\textsuperscript{14} reported that in comparison of the two bag system with the one bag system in a small group of children with DKA. In this retrospective study, 38 children were treated with the one bag method and 23 children were treated with the two-bag method. The one bag method was associated with lower frequency of hypoglycemia and a shorter PICU length of stay.

Our study sheds further light into the current litera-
ture on the management of DKA in children with the two-bag system compared to the one bag system. Our results are consistent with previous studies that show that the two bag system introduces efficiency in the management of children with DKA in that it lowers the frequency of calls from the bedside nurse to the treating physician and the response time of the changing the IVF rate is faster with the two bag system, However, the total numbers of bags of IVF utilized during the management of DKA is not different between the two groups. In this respect it is not consistent with previous studies by Grimberg et al\textsuperscript{11} and Poirier et al\textsuperscript{12} who did demonstrated advantages of the two bag method with regard to the numbers of bags of IVF utilized and length of stay. Additionally considering current pan-
demic, two- bag system might be preferred since it reduces the point of contact between the patient and patients family, and treating medical staff, however

### Table 4. Results.

| Group                  | Observation number | Mean    | Standard deviation | Standard of error | 95% CI      |
|------------------------|--------------------|---------|--------------------|-------------------|-------------|
| Glucose drop rate/hour |                    |         |                    |                   | P = .0648, t = −1.8660, df = 107 |
| One bag                | 52                 | 49.76923| 41.20138           | 5.713603          | 38.29-61.23 |
| Two bag                | 57                 | 36.92982| 30.22999           | 4.00406           | 28.90-44.95 |
| Combined               | 109                | 43.05505| 36.2902            | 3.47597           | 36.16-49.94 |
| Normal saline boluses_ml|                   |         |                    |                   | P = .0585, t = 1.9123, df = 106 |
| One bag                | 52                 | 1627.115| 836.8577           | 16.0513           | 1394-1860  |
| Two bag                | 56                 | 1348.214| 675.2753           | 90.23746          | 1167-1529  |
| Combined               | 108                | 1482.5  | 766.6777           | 73.77359          | 1336-1628  |
| Number of IVF bags used|                    |         |                    |                   | P = .2330, t = −1.1993, df = 107 |
| One bag                | 52                 | 3.288462| 1.210032           | 0.1678013         | 2.951-11.97 |
| Two bag                | 57                 | 3.666667| 1.95789            | 0.2593289         | 1.147-11.42 |
| Combined               | 109                | 3.486239| 1.647752           | 0.157826          | 3.173-3.799 |
| Hospital stay/hour     |                    |         |                    |                   | P = .2129, t = 1.2530, df = 107 |
| One bag                | 52                 | 48.96   | 35.7               | 4.95              | 39.02-58.90 |
| Two bag                | 57                 | 42      | 21.03              | 2.78              | 36.41-47.58 |
| Combined               | 109                | 45.32   | 29                 | 2.78              | 39.80-50.83 |
| PICU stay/hour         |                    |         |                    |                   | P = .127, t = 1.53, df = 107 |
| One bag                | 52                 | 26.98   | 11.81              | 1.63              | 4.88-5.34  |
| Two bag                | 57                 | 30.57   | 13.91              | 1.8               | 4.62-5.099 |
| Combined               | 109                | 28.86   | 13.02              | 1.24              | 4.81-5.149 |
| Number of calls by bedside nurse |   |         |                    |                   | P = .0001 |
| One bag                | 52                 | 25.2    | 9.27               | 1.28              | 22.68-27.72 |
| Two bag                | 57                 | 5.2     | 0.59               | 0.07              | 5.056-5.355 |
| Combined               | 109                | 20.0    | 7.78               | 1.230             | 17.56-22.43 |
| Hypoglycemia < 60      | Patient number     | Hypoglycemia | No hypoglycemia   |                   | Chi² = 3.8756, P = .049 |
| One bag                | 52                 | 4       | 48                 |                   |
| Two bag                | 57                 | 12      | 45                 |                   |
| Combined               | 109                | 16      | 93                 |                   |
more studies need to be conducted to see if indeed this approach reduces exposure to covid-19. Furthermore, the length of the PICU stay and hospital length of stay were also not different between the groups. This is in contradiction to the study of Velasco et al\(^{14}\) that demonstrated that the two bag system was associated with fewer hours of PICU stay compared to the one bag system. It is possible that the conflicting results may be related to the variations in the definitions of LOS and the variations in the transfer policies of patients with DKA from the PICU to a pediatric ward.

Our study had several limitations, it is retrospective in nature, was conducted in a single center and lacked randomization. Another limitation of the current study is the small sample size of patients involved in the study. We did not include any transitional period following implementation of the two bag system and this may have introduced bias into the results of the study. The study is also underpowered to evaluate the two groups with regard to secondary outcomes. In order to overcome these limitations, a larger multicentered randomized control trial is needed in order to study if the two bag method does have advantages over the one bag system. However, our study is relevant to global pediatric health because it was conducted in a resource limited environment and thus may be helpful to certain regions of the world where health care resources are scares.

### Table 5. Regression Analysis.

|                          | P value | Standard error | 95% CI       |
|--------------------------|---------|----------------|--------------|
| **PICU stay/hour**       |         |                |              |
| Bag system               | .452    | 2.475          | -3.043 to 6.779 |
| Initial PH               | .007    | 10.32          | -48.80 to -7.853 |
| Initial sodium           | .792    | 0.194          | -0.437 to 0.334 |
| Gender                   | .297    | 2.465          | -2.308 to 7.472 |
| **Hospital stay/hour**   |         |                |              |
| Bag system               | .100    | 5.77           | -21.01 to 1.875 |
| Initial PH               | .011    | 24.05          | -109.9 to -14.52 |
| Initial sodium           | .921    | 0.45           | -0.854 to 0.94 |
| Gender                   | .853    | 5.74           | -12.46 to 10.32 |
| **Number of IV fluid bags used** |         |                |              |
| Bag system               | .678    | 0.331          | -0.519 to 0.795 |
| Initial PH               | .019    | 1.381          | -6.042 to -0.559 |
| Initial sodium           | .359    | 0.026          | -0.075 to 0.027 |
| Gender                   | .905    | 0.330          | -0.694 to 0.615 |

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