

Comparison of a 'two-bag system' versus conventional treatment protocol ('one-bag system') in the management of diabetic ketoacidosis

Iqbal Munir,¹ Ramiz Fargo,¹ Roger Garrison,¹ Almira Yang,¹ Andy Cheng,² Ilho Kang,¹ Ali Motabar,¹ Karen Xu,³ Lawrence K Loo,² Daniel I Kim¹

To cite: Munir I, Fargo R, Garrison R, *et al*. Comparison of a 'two-bag system' versus conventional treatment protocol ('one-bag system') in the management of diabetic ketoacidosis. *BMJ Open Diab Res Care* 2017;**5**:e000395. doi:10.1136/bmjdr-2017-000395

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/bmjdr-2017-000395>)

Received 25 January 2017
Revised 23 April 2017
Accepted 23 May 2017



CrossMark

¹Department of Medicine, Riverside University Health System Medical Center, Moreno Valley, USA
²Department of Medicine, Loma Linda University Medical Center, California, USA
³Department of Statistics, UCR School of Medicine, Riverside, USA

Correspondence to
Dr Iqbal Munir;
i.munir@ruhealth.org

ABSTRACT

Objective We compared the conventional 'one-bag protocol' of management of diabetic ketoacidosis (DKA) with the 'two-bag protocol' which utilizes two bags of fluids, one containing saline and supplemental electrolytes and the other containing the same solution with the addition of 10% dextrose.

Research design and methods A retrospective chart review and analysis was done on adult patients admitted for DKA to the Riverside University Health System Medical Center from 2008 to 2015. There were 249 cases of DKA managed by the one-bag system and 134 cases managed by the two-bag system.

Results The baseline patient characteristics were similar in both groups. The anion gap closed in 13.56 hours in the one-bag group versus 10.94 hours in the two-bag group (p value <0.0002). None of the individual factors significantly influenced the anion gap closure time; only the two-bag system favored earlier closure of the anion gap. Plasma glucose levels improved to <250 mg/dL earlier with two-bag protocol (9.14 vs 7.82 hours, p=0.0241). The incidence of hypoglycemic events was significantly less frequent with the two-bag protocol compared with the standard one-bag system (1.49% vs 8.43%, p=0.0064). Neither the time to improve serum HCO₃ level >18 mg/dL nor the hospital length of stay differed between the two groups.

Conclusions Our study indicates that the two-bag protocol closes the anion gap earlier than the one-bag protocol in adult patients with DKA. Blood glucose levels improved faster with the two-bag protocol compared with the one-bag protocol with fewer associated episodes of hypoglycemia. Prospective studies are needed to evaluate the clinical significance of these findings.

INTRODUCTION

Nearly 10% of the population in the USA has diabetes mellitus.¹ Diabetic ketoacidosis (DKA) is a well-known, serious, acute metabolic complication. While it is primarily associated with type 1 diabetes mellitus two-thirds of the time, it also occurs in type 2 diabetes mellitus approximately 34% of the time², often as a manifestation of the syndrome of ketosis-prone diabetes.³ The incidence of DKA continues to rise. The

Significance of this study

What is already known about this subject?

► The two-bag protocol for treating diabetic ketoacidosis (DKA) has been used in pediatric patients with some benefit and cost savings as outlined in the introduction section.

What are the new findings?

► This study was conducted in adult subjects with DKA. Our study indicates that the two-bag protocol closes the anion gap earlier than the one-bag protocol in adult patients with DKA. Blood glucose levels improved faster with the two-bag protocol compared with the one-bag protocol with fewer associated episodes of hypoglycemia.

How might these results change the focus of research or clinical practice?

► The two-bag protocol could potentially be beneficial in treating patients with DKA compared with the conventional one-bag protocol. Prospective studies need to be designed to evaluate the benefit of the two-bag system in reducing intensive care unit stay and overall cost reduction in DKA management.

Centers for Disease Control and Prevention (CDC) estimates that there were 140 000 hospital discharges from DKA in 2009 in the USA, about 75% increase over the last two decades⁴ with an estimated cost annually of >\$2 billion and accounts for >500 000 hospital days per year.²

Along with identification of triggering factors, management of DKA involves correction of hyperglycemia, volume depletion, acid-base derangements and electrolyte imbalances.² Because of the complexities in the management protocol, many cases of DKA are managed in intensive care units (ICUs) across the USA.⁵ Losses of fluids and electrolytes are significant causes of mortality and morbidity

in DKA. The mortality is <1% in American adults⁶; however, rises to >5% in the elderly population with significant comorbidities.^{7,8} In the USA, the age-adjusted mortality rate for hyperglycemic crisis declined between 1980 and 2009. In 2009, hyperglycemic crises caused 64% lower mortality than in 1980.⁶

Evidence-based guidelines for the diagnosis and management of DKA have been published periodically in North America^{2,9} and Europe¹⁰ improving the understanding and facilitating the development of management protocols. The outcomes of DKA have been shown to improve with adherence to treatment guidelines.^{11–15} Minor variants of the commonly used treatment protocol for DKA based on the published guidelines use insulin infusions and intravenous electrolyte solution and dextrose solution when blood sugar drops below 250 mg/dL.² In order to correct dehydration in patients with DKA, intravenous electrolyte solutions are administered at the beginning of the treatment. As the blood glucose levels fall, a new bag of intravenous fluid with different dextrose concentrations would be ordered, and multiple sequential changes of bags would occur during the course of treatment. Despite their proven effectiveness, a varying degree of non-adherence to guidelines has been documented in the literature compromising the success of published protocols.^{16–19} Successful implementation of the conventional DKA protocol requires not only careful assessment of the clinical status of the patient and laboratory values, but frequent changes to intravenous fluids between saline and dextrose solutions.²

The 'two-bag system' was first described in the early 1990s in pediatric patients. As opposed to the conventional protocol (one-bag system), the two-bag system uses two bags of fluids with identical electrolyte content but different dextrose concentrations, 0% and 10%.^{20,21} The two bags are connected in a 'Y' fashion and by adjusting the infusion rates from each bag, the concentration of dextrose can be customized to prevent unpredictable excursions in blood glucose. The two-bag system has been more commonly used and exclusively studied in the pediatric population and has been found to be cost effective.^{21,22} It has also been shown to result in more rapid improvement in bicarbonate and ketone correction and a trend toward faster improvement of hyperglycemia in DKA.²² In one study, the two-bag system was well received by nursing and house staff because it was less labor intensive than the traditional one-bag system.²³

To our knowledge, the two-bag system has not been compared with the one-bag system in the adult DKA population in the published literature. We performed a retrospective cohort study comparing the traditional one-bag protocol previously used at our institution with the newly initiated two-bag protocol. The primary purpose of our study is to compare the time to correction of the anion gap in adult patients with DKA.

RESEARCH DESIGN AND METHODS

Our study focused on adult patients with the diagnosis of DKA between the years of 2008 and 2015 who were admitted to the inpatient services of Riverside University Health System Medical Center. Our hospital is a safety-net hospital that serves the residents of Riverside County, California, with approximately 189 000 outpatient visits, 21 900 inpatient admissions, and 100 000 emergency room visits annually. Our hospital treated patients with DKA with a hospital-wide protocol that used the conventional one-bag system until 2013 when the treatment approach transitioned to the two-bag system (supplementary appendix 1). In our hospital, after initial diagnosis of DKA in the emergency room, the DKA protocol is initiated by ER physicians. In our institution, the DKA protocol is a hospital-wide protocol, which is followed in the inpatients units as well as in the emergency room. Any patient who requires an insulin drip automatically gets admitted to the ICU. If there is a delay in getting an ICU bed, the protocol is carried out in the ER. In our patient population, except a small group of patients with a diagnosis of mild DKA in the ER who improved on subcutaneous insulin therapy, all other patients were admitted for ICU care.

All adult patients over the age of 18 years with an admitting diagnosis of DKA were retrospectively identified from the medical record searching through ICD-9-CM codes 250.10 (DKA in type 1 diabetes) and 250.11 (DKA in type 2 diabetes) diagnosis. Once a list of the patients was gathered, the diagnosis of DKA was verified. The following criteria were used to define DKA, a blood glucose ≥ 250 mg/dL and two of the following three criteria: serum bicarbonate (HCO_3^-) <18 mEq/L; serum beta-hydroxybutyrate (BHB) >3 mmol/L; and pH <7.30. Patients with a diagnosis of hyperosmolar hyperglycemic state as a final diagnosis in the chart were excluded. Ketosis from any other etiology, for example, alcoholic ketoacidosis, starvation ketosis, as a final diagnosis in the chart was excluded. Our chart review confirmed that there were no pregnant patients on our list eliminating any case of DKA associated with pregnancy. During initial chart review, we did not include any patient with DKA who was not started on an insulin drip eliminating cases of DKA treated with a subcutaneous insulin protocol. We identified 383 patients admitted with DKA that received treatment with either the one-bag system (n=249) or the two-bag system (n=143). Data were extracted from individual chart review using a standard data collection instrument that recorded the following information at the time of admission: patient's age and sex, hemoglobin A1c (HgbA1c), body weight, body mass index (BMI), pH, anion gap, admission blood glucose, comorbidities, HCO_3^- , serum BHB, and the time of initiation and discontinuation of the DKA protocol. We also captured changes in anion gap, serum glucose, and bicarbonate level as patients received treatment for DKA.

Study outcomes

During the treatment of DKA, hyperglycemia is corrected faster than the ketoacidosis. Thus, we chose closure of the anion gap as our primary outcome measure which served as a surrogate for the resolution of DKA. Our secondary outcome was time to reach plasma glucose <250 mg/dL, time to reach HCO₃ level >18 mmol/L, and hospital length of stay.

Sample size calculation

Because we could not find any prior study focusing on the timing of the closure of the anion gap addressing our research question, we took a small convenience sample of seven patients who were recently admitted with the diagnosis of DKA. The average time to close the anion gap was 10.4 hours with an SD of 6.4 hours. We decided that a 15% difference in time from this average would be considered clinically significant. Using an effect size of 0.25, an unpaired two-sided t-test, an alpha of 0.05, a beta of 0.2, and a power of 80%, the calculated sample size was 199 per group.

Data analysis

The descriptive analysis comparing the baseline characteristics of the two cohorts used the two-independent samples t-test for continuous variables and χ^2 test for proportions for categorical variables. Outcome measures comparing the one-bag versus two-bag protocols used the two independent samples t-test to compare the time to closure of the anion gap (primary outcome measure) and time to reach plasma glucose <250 mg/dL, time to reach HCO₃ level >18 mmol/L, and hospital length of stay (secondary outcome measures). The relationship between the time to closure of the anion gap and admission variables was assessed using the Pearson product-moment correlation. To further compare the times to closure of the anion gap between the two protocols while statistically controlling for the effects of admission variables that were not of primary interest, an analysis of covariance (ANCOVA) model was developed using time to closure of the anion gap as the dependent variable, and the following admission variables as covariates: patient's age, weight, BMI, admission pH and anion gap, BHB, blood urea nitrogen (BUN), serum creatinine, serum blood glucose, HgbA1c, and the Charlson Comorbidity Index.²⁴ A stepwise model selection method was used to determine the significant variables in the ANCOVA model. Data were entered into a Microsoft Excel spreadsheet and analyzed using SAS V.9.3.

This study was prospectively approved by the Institutional Review Board (IRB) of the Riverside University Health System Medical Center.

RESULTS

A total of 383 patients admitted with DKA to our hospital were eligible for the study. In total, 249 patients admitted with DKA had received the conventional one-bag system

and 134 patients were treated with the newly adopted two-bag system.

As shown in Table 1, the mean age of the patients was approximately 37 years and similar in the one-bag and two-bag cohorts. Patients of both groups had uncontrolled diabetes mellitus, with an average HgbA1c over 11 (11.7% vs 11.6%). Average BMIs were comparable in both groups (25.8 vs 24.4) as were body weights (75.5 vs 71.3 kg). Patients presented with a serum pH averaging 7.20 in both groups, and similar corrected anion gap levels (23.4 vs 23.8). Overall, the severities of patients' DKA at presentation were comparable with 25.70% versus 24.63% in mild DKA, 31.33% versus 38.81% in moderate DKA, and 42.97% versus 36.57% in severe DKA between one-bag and two-bag groups, respectively. Patients in both groups presented with significant hyperglycemia with blood glucose levels exceeding 400 mg/dL (473 vs 511 mg/dL). Interestingly, the BHB level was significantly higher in the two-bag group cohort (7.8 vs 4.4 mmol/L). BUN and serum creatinine levels were similar in both groups as was the Charlson Comorbidity Index.

Closure of anion gap was considered as a measure of correction of acidosis status and was considered as the surrogate of resolution of DKA in our analysis. The time to close anion gap was 13.56 hours in the conventional one-bag system protocol (table 2). This time period was decreased significantly to 10.94 hours in the patient group treated with two-bag protocol ($p=0.0002$). Time to reach plasma glucose below 250 mg/dL was significantly shorter with the two-bag protocol ($p=0.0241$). Time to raise serum HCO₃ >18 mmol/L was not statistically significant between the two groups, although it was shorter in the two-bag group ($p=0.90$). The incidence of hypoglycemic events, defined as a blood sugar <70 mg/dL, was significantly less frequent with the two-bag protocol compared with the standard one-bag system (1.49% vs 8.43%, $p=0.0064$). The length of hospital stay was also modestly decreased by one half day in the two-bag group, although this difference did not reach statistical significance ($p=0.099$). The correlation coefficients between time to closure of the anion gap and admission variables are close to zero, indicating a very weak correlation between time to closure of the anion gap and the admission variables (table 3). In the ANCOVA model, the effects of all admission variables were not significant, except for the Charlson Comorbidity Index ($t=-2.97$, $p=0.003$). The protocol effect adjusted for the Charlson Comorbidity Index was significant in the ANCOVA model ($t=3.10$, $p=0.0021$), which further indicates the significant difference in the time to closure of the anion gap between the two protocols.

CONCLUSIONS

The purpose of this retrospective cohort study was to determine if a two-bag system significantly influenced resolution of DKA in adult patients presenting with DKA. Since anion gap is widely used by clinicians as a surrogate

Table 1 Clinical characteristics of the study population

Variable	One-bag system (total number=249)		Two-bag system (total number=134)		p Value
	Number	Mean (\pm SD)	Number	Mean (\pm SD)	
Age (years)	249 (100%)	37.7 (\pm 14.9)	134 (100%)	36.1 (\pm 14.8)	0.23
Male	249 (100%)	144 (57.8%)	134 (100%)	73 (54.5%)	0.60
Weight (kg)	173 (69%)	75.5 (\pm 22.7)	134 (100%)	71.3 (\pm 20.5)	0.06
BMI (kg/m ²)	152 (61%)	25.8 (\pm 7.1)	125 (93%)	24.4 (\pm 5.86)	0.11
Initial pH	177 (71%)	7.21 (\pm 0.14)	102 (76%)	7.24 (\pm 0.16)	0.94
BHB (mmol/L)	156 (63%)	4.4 (\pm 4.4)	127 (95%)	7.8 (\pm 5.0)	<0.01
BUN (mg/dL)	249 (100%)	23.1 (\pm 14.4)	134 (100%)	23.8 (\pm 14.3)	0.49
Creatinine (mg/dL)	249 (100%)	1.48 (\pm 1.68)	134 (100%)	1.40 (\pm 0.90)	0.12
Admission serum glucose (mg/dL)	233* (94%)	473.6 (\pm 198.0)	134 (100%)	511.7 (\pm 193.3)	0.05
Anion gap (mmol/L)	249 (100%)	23.4 (\pm 6.3)	134 (100%)	23.8 (\pm 5.9)	0.52
HgbA1c (%)	204 (82%)	11.7 (2.0)	105 (78%)	11.6 (2.0)	0.70
Charlson comorbidity index	249 (100%)	1.66 (\pm 1.18)	134 (100%)	1.54 (\pm 1.11)	0.36

Baseline data are means \pm SD. Some data are missing or not recorded in the chart to account for less than the total numbers in each group.

*Sixteen missing values were recorded as 'high' by the glucometer (ie, >600 mg/dL) and were recorded as unmeasurable in the chart.

BHB, beta-hydroxybutyrate; BMI, body mass index; BUN, blood urea nitrogen; HgbA1c, hemoglobin A1c.

measure of resolution of acidosis in DKA, we evaluated the time to close anion gap as a primary end point for our study. Our results showed a reduction of 2.62 hours in the anion gap closure from 13.56 to 10.94 hours ($p=0.0002$) using the two-bag system. Plasma glucose levels improved to <250 mg/dL earlier with two-bag protocol (9.14 vs 7.82 hours, $p=0.0241$), and there were significantly fewer episodes of hypoglycemia associated with the two-bag protocol (8.43% vs 1.49%, $p=0.0069$). However, neither the time to improve serum HCO₃ level >18 mg/dL nor the hospital length of stay differed in a statistically significant manner between the two groups. Both groups of the patients had similar comorbidities as measured by the Charlson Comorbidity Index indicating that the treatment protocol, rather than the disease-specific factors, played a greater role in the early closure of the anion gap. None of the other patient-specific factors played a significant role in the resolution of the anion gap (table 3).

The two-bag protocol has been used in pediatric patients with DKA and studies showed mixed results. In one study, the rate of serum HCO₃ correction and the time to ketone correction were superior in the two-bag system²² compared with the one-bag system; however, in the second study, there were no differences between the two groups.²³ Both studies were limited by small sample sizes (31 and 33 patients, respectively). Pediatric studies have demonstrated benefits of the two-bag system including decreased total number of intravenous bags used per patient, decreased cost of intravenous therapy,²¹ and decreased response time for intravenous fluid changes^{21,23}. In contrast to the few published studies on DKA management using the two-bag protocol, we compared anion gap closure. We have also used a significantly larger data set, potentially eliminating some of the limitations of the prior studies. However, we did not compare the volume of intravenous fluid used in each

Table 2 Primary and secondary outcomes

	One-bag system Mean (\pm SD)	Two-bag system Mean (\pm SD)	p Value
Primary outcome			
Time to close anion gap (hours)	13.57 (\pm 1.75)	10.95 (\pm 1.63)	<0.01
Secondary outcomes			
Time to reach plasma glucose <250 mg/dL (hours)	9.15 (\pm 1.38)	7.82 (\pm 1.28)	0.02
Time to reach serum HCO ₃ >18 mmol/L (hours)	19.95 (\pm 1.99)	18.50 (\pm 2.28)	0.36
Hospital length of stay (days)	4.86 (\pm 3.63)	4.33 (\pm 2.53)	0.09
	%	%	
Hypoglycemia (BS <70 mg/dL)	8.43	1.49	<0.01

Outcome measures comparing the one-bag versus two-bag protocols used the two independent samples t-test. For details, see online supplementary appendix 2.

Table 3 Correlation coefficients between time to closure of the anion gap and admission variables

Variable	n	Correlation coefficient	p Value	Variable	n	Correlation coefficient	p Value
Age (years)	383	-0.07887	0.11	BUN (mg/dL)	383	-0.00017	0.99
Weight (kg)	307	-0.06908	0.21	Creatinine (mg/dL)	383	-0.07177	0.10
BMI	277	-0.08167	0.16	Admission serum glucose (mg/dL)	367	0.04744	0.35
Initial pH	279	0.09654	0.09	Anion gap (mmol/L)	383	-0.08352	0.09
BHB (mg/dL)	283	-0.02508	0.66	HgbA1c (%)	309	-0.03936	0.48

The relationship between the time to closure of the anion gap and admission variables was assessed using the Pearson product-moment correlation. To further compare the times to closure of the anion gap between the two protocols while statistically controlling for the effects of admission variables, an analysis of covariance model was developed using time to closure of the anion gap as the dependent variable, and admission variables as covariates.

BHB, beta-hydroxybutyrate; BMI, body mass index; BUN, blood urea nitrogen; HgbA1c, hemoglobin A1c.

of the groups given the limitation of collecting accurate data in our retrospective study. A comparison of the published studies to date on the two-bag DKA protocol has been summarized in [table 4](#).

To our knowledge, this is the first study comparing the two-bag protocol with the conventional one-bag protocol in an adult population. Strengths of this study include the large sample size and similar patient populations as evidenced by the baseline characteristics of the study groups. The two study groups did not differ in age, BMI, HgbA1c, BUN/creatinine, initial blood sugar, anion gap, initial serum pH or severity of DKA; however, the serum BHB levels were higher in the two-bag system group. The significantly elevated BHB concentration in the two-bag cohort may indicate patients in that group were more insulin deficient or had higher levels of metabolic stress. Despite that possibility, the two-bag protocol was associated with faster closure of the anion gap.

The key diagnostic feature in DKA is the elevation of total blood ketone concentrations in the background of relative or absolute insulin deficiency.² In patients with DKA, metabolic alterations due to insulin deficiency result in the accumulation of ketoacids causing an anion gap metabolic acidosis. In our study, BHB, the main metabolic product of ketosis,^{25 26} was measured in the serum with a quantitative assay by the central laboratory as opposed to a semiquantitative nitroprusside reaction. Although the anion gap reflects the degree of acidosis in most situations, it is unreliable in cases of mixed acid-base disorders or in hyperchloremic metabolic acidosis presenting without a significant anion gap.²⁷ Similarly, there are limitations in the interpretation of the bicarbonate level as a measure of acidosis as well. For example, many patients with DKA present with nausea and vomiting, resulting in metabolic alkalosis. The bicarbonate level does not reflect the true level of acidosis in

Table 4 Review of the published studies on the two-bag diabetic ketoacidosis protocol

Reference	Study design	Hospital setting	Patients	Outcome measure
Grimberg <i>et al</i> ²¹	Retrospective case-control	Single center inpatient—Philadelphia, Pennsylvania	20 pediatric patients (mean age 12–13): 10 one-bag, 10 two-bag	Two-bag system decreased number of intravenous bags used, response time by nursing to make changes in intravenous fluids, and costs of intravenous fluid therapy
Poirier <i>et al</i> ²³	Prospective non-blinded clinical trial	Single-center pediatric emergency room—Norfolk, Virginia	33 pediatric patients (mean age 11–14): 16 one-bag, 17 two-bag	Two-bag system decreased the time for nursing to make changes in intravenous fluids No difference in blood glucose or bicarbonate correction nor the number of intravenous bags used
So and Grunewald <i>et al</i> ²²	Retrospective series	Single-center inpatient—Greensboro, North Carolina	31 pediatric patients (mean age 13–14): 9 one-bag, 22 two-bag	Two-bag system corrected bicarbonate and ketone levels faster No time difference for blood glucose and pH correction
Current series 2010–2015	Retrospective cohort	Single-center inpatient—Riverside, California	383 adult patients (mean age 36–37): 249 one-bag 134 two-bag	Two-bag system closed the anion gap faster (10.94 vs 13.56 hours) No significant time difference in hospital length of stay

such situations or during severe volume contraction.²⁷ Therefore, the clinical decision-making involves evaluating multiple parameters of acid–base imbalance including serum anion gap, serum bicarbonate level, and measurement of serum pH. Our study did not compare resolution of acidosis by serial pH or beta-hydroxybutyrate measurements, which were not available in a large number of patients in our data set.

In our study, although the AG corrected earlier in DKA patients treated with the two-bag protocol, the time for serum bicarbonate level to reach >18 was similar in both groups. Additionally, improvement of the bicarbonate level lagged behind the anion gap closure. This may indicate that relative hyperchloremia, resulting from the large volume of normal saline infusions during volume resuscitation, leads to the correction of the AG. However, ketone levels remained elevated for a longer duration accompanied by reduced serum bicarbonate levels until finally correcting with the insulin infusion. Both protocols were based on guidelines of fluid resuscitation in patients with DKA published by ADA². Clinicians made the final decision regarding how much fluid was needed for a patient based on clinical findings, dehydration, and comorbidities. We could not collect the data on the total volume of intravenous fluid containing sodium chloride in our study population and do not know whether there was any difference in the intravenous fluid administered.

In this study, we only included patients with DKA admitted to the ICU setting. The pattern of ICU utilization for patients with DKA varies among institutions. More than 50% of patients with DKA are admitted to the ICU.⁵ The financial burden of DKA management is significant, with estimated mean expenses for a single hospitalization ranging from \$7470 to \$20 864.²⁸ The itemized expense calculation of DKA costs shows that a significant cost in DKA management involves the cost of the ICU stay and laboratory testing.²⁸ Although we found that the anion gap closure was earlier with two-bag protocol, whether this will result in any reduction of cost was not addressed in this study. A randomized prospective study needs to be designed to answer these questions. In our population, the average length of stay was >4 days in both groups. Although we could not compare duration of ICU stay, in patients treated with the two-bag protocol, the average length of hospital stay decreased by half a day, although the difference did not reach statistical significance. In a recent report published by the CDC,⁴ the average length of hospital stay was found to be decreased to 3.4 days for hospital discharges with DKA as the first-listed discharge diagnosis. The average length of hospital stay in our study was above the national average regardless of the protocol used. Multiple factors have contributed to the shortened length of hospital stay in the published literature including widespread use of protocols for DKA management, enhanced staff training, and involvement of specialized diabetes nurses.²⁹ There are additional disease-specific factors that could influence the length of hospital stay including gastroparesis,

concurrent infection, cognitive impairment, and rehabilitation requirements.²⁹ Our study did not compare the disease-specific factors that potentially could have influenced the length of hospital stay. Although, as a safety net medical center, we serve a patient population with a low socioeconomic status and higher burden of comorbidities, which may contribute the longer length of stay in our study. Another study, in an inner-city population with predominantly African American patients, showed the average length of stay of 4.5 days, which is similar to our study.³⁰

This study had several limitations including a retrospective study design and a patient population limited to a single safety net medical center, which may limit its external applicability. The large Hispanic population that our hospital serves has a very high prevalence of obesity and uncontrolled diabetes. In addition, we could not reach our calculated sample size for 199 for the two-bag group (fell short by 56 patients), raising possibility of a type II error. Because of the retrospective nature of our study, we also cannot exclude the possibility that temporal changes in the management of DKA other than the introduction of the two-bag protocol could have occurred during the time span of the study that were not collected by our standardized data collection instrument. To minimize this bias, management of DKA from 2008 to 2015 was driven by standardized hospital-wide protocols and the Charlson Comorbidity Indices in the two groups were comparable. In spite of this, some key laboratory information such as pH, BHB, and admission HbA1c was not systematically collected in all patients. For these three variables, no differences were found on admission between the two groups and in our ANCOVA model. While we found an approximate half-day reduction in the length of stay using the two-bag protocol, this difference was not statistically significant and our study may have been underpowered to detect this secondary outcome. Finally, inherent in any retrospective study, residual confounding from other unmeasured or inaccurately measured variables excludes any definitive statements of causality and we can only state that the two-bag protocol was associated with a faster time to closure of the anion gap and significantly fewer episodes of hypoglycemia.

Our study supports the use of the two-bag protocol as another method of DKA treatment. The fundamentals of DKA treatment, for example, volume repletion and correction of electrolyte imbalance, are similar in both groups. Two-bag protocol may be beneficial in certain clinical settings due to faster resolution of anion gap, faster rate of improvement of blood sugar, and lesser episodes of hypoglycemia. Future studies will indicate whether faster anion gap closure results in overall cost reduction of DKA management. Reduction of hypoglycemic events associated with the two-bag protocol has a direct impact on patient safety. The two-bag system can be easily adapted as an ICU protocol with minimal staff training. This study supports the use of the two-bag system in treating adult patients with DKA. A larger,

randomized prospective study to further study this issue would be beneficial.

Acknowledgements The authors appreciate Hayley Lee at RUHS Medical Center Research office for assisting to conduct this study. Part of this work was presented in 76th scientific sessions of ADA in a poster session.

Contributors IM researched, analyzed and interpreted the data; drafted and revised the manuscript for important intellectual content; and approved the final draft of the manuscript. RF, LL, DK, CG, AM and IK helped to analyze, and interpret the data; reviewed and revised the manuscript for important intellectual content; and approved the final version of the manuscript submitted. AY and AC helped to acquire and interpret the data; reviewed the manuscript for important intellectual content; and approved the final version of the manuscript submitted. KX performed the statistical analysis, reviewed the manuscript for important intellectual content, and approved the final version of the manuscript submitted.

Competing interests None declared.

Ethics approval Institutional Review Board of RUHS Medical Center.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Further details of the data and analysis for this study could be obtained by contacting the corresponding author (IM) of this manuscript. They have included almost all the data generated for this study in the manuscript. They did not include data of anion gap closure and serum bicarbonate improvement according to the severity of DKA (severity based on only admission serum bicarbonate level).

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

1. "2014 Statistics Report | Data & Statistics | Diabetes | CDC". <https://www.cdc.gov/diabetes/data/statistics/2014statisticsreport.html> (accessed 25 Dec 2016).
2. Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32:1335–43.
3. Balasubramanyam A, Nalini R, Hampe CS, et al. Syndromes of ketosis-prone diabetes mellitus. *Endocr Rev* 2008;29:292–302.
4. CDC. "Average Length of Stay (LOS) - Hospitalization for Diabetic Ketoacidosis - Data & Trends - Diabetes DDT," 2014. <http://www.cdc.gov/diabetes/statistics/dkafirst/fig2.htm> (accessed 28 May 2016).
5. Gershengorn HB, Iwashyna TJ, Cooke CR, et al. Variation in use of intensive care for adults with diabetic ketoacidosis*. *Crit Care Med* 2012;40:2009–15.
6. "CDC - Rate per 100,000 Diabetic Population - Mortality Due to Hyperglycemic Crises - Data & Trends - Diabetes DDT". <https://www.cdc.gov/diabetes/statistics/mortalitydka/fRateDKADiabTotals.htm> (accessed 26 Dec 2016).
7. Graves EJ, Gillum BS. "Detailed diagnoses and procedures, National Hospital Discharge Survey, 1995". *Vital Health Stat* 1997;130:1–146.
8. Malone ML, Gennis V, Goodwin JS. Characteristics of diabetic ketoacidosis in older versus younger adults. *J Am Geriatr Soc* 1992;40:1100–4.
9. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care* 2006;29:2739–48.
10. Dunger DB, Sperling MA, Acerini CL, et al. . European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society consensus statement on diabetic ketoacidosis in children and adolescents. *Pediatrics* 2004;113:e133–40.
11. Ilag LL, Kronick S, Ernst RD, et al. Impact of a critical pathway on inpatient management of diabetic ketoacidosis. *Diabetes Res Clin Pract* 2003;62:23–32.
12. Konstantinov NK, Rohrscheib M, Agaba EI, et al. Respiratory failure in diabetic ketoacidosis. *World J Diabetes* 2015;6:1009–23.
13. Thuzar M, Malabu UH, Tisdell B, et al. Use of a standardised diabetic ketoacidosis management protocol improved clinical outcomes. *Diabetes Res Clin Pract* 2014;104:e8–11.
14. Volkova NB, Fletcher CC, Tevendale RW, et al. Impact of a multidisciplinary approach to guideline implementation in diabetic ketoacidosis. *Am J Med Qual* 2008;23:47–55.
15. Wallace TM, Matthews DR. Recent advances in the monitoring and management of diabetic ketoacidosis. *QJM* 2004;97:773–80.
16. Glaser NS, Kuppermann N, Yee CK, et al. Variation in the management of pediatric diabetic ketoacidosis by specialty training. *Arch Pediatr Adolesc Med* 1997;151:1125–32.
17. Henriksen OM, Prah J, Røder ME, et al. Treatment of diabetic ketoacidosis in adults in Denmark: a national survey. *Diabetes Res Clin Pract* 2007;77:113–9.
18. Jervis A, Champion S, Figg G, et al. Prevalence of diabetes ketoacidosis rises and still no strict treatment adherence. *Curr Diabetes Rev* 2013;9:54–61.
19. Singh RK, Perros P, Frier BM. Hospital management of diabetic ketoacidosis: are clinical guidelines implemented effectively? *Diabet Med* 1997;14:482–6.
20. Collett-Solberg PF. Diabetic ketoacidosis in children: review of pathophysiology and treatment with the use of the "two bags system". *J Pediatr* 2001;77:9–16.
21. 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;134:376–8.
22. So TY, Grunewald E. Evaluation of the two-bag system for fluid management in pediatric patients with diabetic ketoacidosis. *J Pediatr Pharmacol Ther* 2009;14:100–5.
23. Poirier MP, Greer D, Satin-Smith M. A prospective study of the "two-bag system" in diabetic ketoacidosis management. *Clin Pediatr* 2004;43:809–13.
24. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
25. Kahn CR, Weir GC, Kitabchi AE, et al. Diabetic ketoacidosis and the hyperglycemic hyperosmolar nonketotic state. *In Joslin's Diabetes Mellitus* 1994 .
26. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 2001;24:131–53.
27. Halperin ML, Kamel KS. Some observations on the clinical approach to metabolic acidosis. *J Am Soc Nephrol* 2010;21:894–7.
28. Maldonado MR, Chong ER, Oehl MA, et al. Economic impact of diabetic ketoacidosis in a multiethnic indigent population: analysis of costs based on the precipitating cause. *Diabetes Care* 2003;26:1265–9.
29. Yong KW, Moore MP, Lunt H. Medically facilitated discharge of adult diabetic ketoacidosis admissions: precipitants and average length of stay. *N Z Med J* 2014;127:86–94.
30. Randall L, Begovic J, Hudson M, et al. Recurrent diabetic ketoacidosis in inner-city minority patients: behavioral, socioeconomic, and psychosocial factors. *Diabetes Care* 2011;34:1891–6.