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Clinical Investigation

A Pediatric Diabetic Ketoacidosis Management Protocol Incorporating a Two-Bag Intravenous Fluid System Decreases Duration of Intravenous Insulin Therapy

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OBJECTIVES: Diabetic ketoacidosis (DKA) is a leading cause of morbidity and mortality in children with type 1 diabetes. We implemented a standardized DKA management protocol by using a 2-bag intravenous (IV) fluid system. The purpose of the study was to examine if the protocol improved clinical outcomes and process efficiency.

METHODS: This was a retrospective study of patients who did and did not undergo the protocol. Patients were included if they were 18 years of age or younger, were diagnosed with DKA, admitted to an intensive care unit or stepdown unit, and received continuous IV insulin.

RESULTS: Of 119 encounters evaluated, 46 (38.7%) received treatment with the protocol and 73 (61.3%) did not. The median time to normalization of ketoacidosis was 9 hours (IQR 5-12) and 9 hours (IQR 6.5-13) for protocol and non-protocol groups, respectively (p = 0.14). The median duration of IV insulin therapy was 16.9 hours (IQR 13.7-21.5) vs. 21 hours (IQR 15.3-26) for protocol and non-protocol groups (p = 0.03). The median number of adjustments to insulin drip rate was 0 (IQR 0-1) and 2 (IQR 0-3) for protocol and non-protocol groups (p = 0.0001). There was no difference in the incidence of hypokalemia, hypoglycemia, or cerebral edema.

CONCLUSIONS: The protocol did not change time to normalization of ketoacidosis but did decrease the duration of insulin therapy, number of adjustments to insulin drip rate, and number of wasted IV fluid bags without increasing the incidence of adverse events.

INDEX TERMS: diabetes, diabetic ketoacidosis, hyperglycemia, insulin, pediatrics, two-bag system

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INTRODUCTION

Diabetic ketoacidosis (DKA) is the leading cause of diabetes-related death in childhood.[1] Diabetic ketoacidosis is defined as hyperglycemia (blood glucose > 200 mg/dL), venous pH < 7.3 or bicarbonate < 15 mmol/L, and ketonemia and ketonuria.[2] Diabetic ketoacidosis results from absolute or relative deficiency of circulating insulin in combination with the effects of increased concentrations of counterregulatory hormones. Early manifestations of DKA include vomiting, polyuria, polydipsia, lethargy, and dehydration.[2,3] Laboratory values of DKA include hyperglycemia, ketonemia, glycosuria, ketonuria, metabolic acidosis, hyponatremia, and hypokalemia.[3] Treatment should be individualized and is aimed at rehydration, normalization of blood glucose, correction of electrolyte abnormalities, and subsequent resolution of metabolic acidosis, all while carefully monitoring the patient and avoiding adverse outcomes such as cerebral edema and hypoglycemia. Published guidelines on the management of DKA recommend fluid resuscitation with boluses and continuous fluids to correct dehydration, monitoring of electrolytes, and intravenous (IV) insulin drip administration until resolution of acidosis.[4]

Studies have shown time and cost benefits associated with implementing a protocol for management of pediatric DKA, using a 2-bag IV fluid system.[5-7] A 2-bag system consists of 2 fluid bags with identical electrolyte concentrations but different dextrose concentrations (0% and 10%)

administered intravenously and simultaneously via a Y-site. This enables insulin and electrolyte therapy to be maintained while titrating the dextrose concentration to meet the patient's requirements without having to order, prepare, and administer additional fluid bags when a change in dextrose concentration is needed.

Although studies have shown time and cost benefits with DKA management protocols, minimal information is available regarding clinical benefit of the 2-bag system. The purpose of the study was to examine if the protocol improved clinical outcomes and process efficiency.

MATERIALS AND METHODS

Study Design and Setting

This study took place at Arnold Palmer Hospital for Children (APH), a 158-bed, tertiary care, free-standing children's hospital in Orlando, Florida. In 2012, a team of pediatric critical care physicians, pediatric endocrinology physicians, nurse educators, and pharmacists developed a protocol for management of pediatric DKA that included a 2-bag system with 2 IV fluid bags: one containing 10% dextrose with 0.45% sodium chloride with potassium acetate and potassium phosphate, and another containing 0% dextrose with 0.45% sodium chloride with potassium acetate and potassium phosphate, to be initiated within the APH emergency department or upon patient's arrival to the APH pediatric intensive care unit or pediatric stepdown unit (Table 1). The team provided physician and nursing education, developed pharmacy guidelines, implemented the protocol, and began encouraging its use at the end of 2012.

For this study, we performed a retrospective chart review of pediatric patients admitted with a diagnosis of DKA, as determined by ICD-9 coding for DKA or other abnormal glucose values, between January 1, 2012, to October 1, 2012 (preprotocol implementation) and August 1, 2013, to August 1, 2014 (postprotocol implementation). This study was approved by the Arnold Palmer Medical Center Institutional Review Board.

Subjects

Patients were included if they were 18 years or younger, admitted to the pediatric intensive care unit or stepdown unit, had a diagnosis of DKA, and were receiving a continuous IV insulin drip. Patients were excluded from the study if they were pregnant, had a history of adrenal insufficiency, or were taking systemic steroids during admission.

Outcomes

The primary outcome was the time to normalization of acidosis. Normalization of acidosis was defined as a serum bicarbonate concentration of >15 mmol/L. Secondary outcomes included the time from order entry to the start of a new IV fluid bag being administered, the number of IV fluid changes, duration of IV insulin therapy, number of adjustments to IV insulin therapy, number of wasted IV fluid bags, and adverse events of DKA management, including hypokalemia, hypoglycemia, and cerebral edema.

Statistical Analysis

Continuous variables were analyzed by using Student's *t* test if parametric or Mann-Whitney *U* if non-parametric. Nominal data were analyzed by using chi-square or Fisher's exact test. Mann-Whitney *U* was used to analyze ordinal data. Analysis was performed with Minitab (version 16, Minitab Inc, State College, PA). We estimated that a total sample of 56 patients would provide the study with 80% power, assuming a 2-sided alpha of 0.05, to detect a difference of 0.343 mmol/L/hr in bicarbonate correction rates between a 2-bag system and a 1-bag system as shown in a previous study.[7] We assumed a p value of less than 0.05 to be statistically significant.

RESULTS

In total, we reviewed 500 admissions of patients with hyperglycemia. From the 500 admissions reviewed, 380 were excluded because the patient did not meet criteria to be diagnosed with DKA, and 1 admission was excluded because the patient was taking systemic steroids. One hundred nineteen encounters met inclusion criteria. A total of 46 encounters (38.7%) from 43 individual patients received treatment via the DKA management protocol with the 2-bag system. A total of 73 encounters (61.3%) from 71 individual patients did not receive treatment with the 2-bag system (Table 1). Ten of the encounters included in the non-protocol group occurred postprotocol implementation. There were no differences between the groups in age, weight, or sex (Table

Table 1. Diabetic ketoacidosis management protocol.

Initial management	No bicarbonate bolus, no insulin bolus. Administer 10 mL/kg 0.9% NS bolus (give over first hour of resuscitation). Repeat 10 mL/kg 0.9% NS bolus over second hour as needed for inadequate organ perfusion
Insulin	0.1 units/kg/hr
IVF	Rate in mL/hr = 1.5x maintenance rate or (84 mL/kg – bolus given)/23 hr + maintenance rate. Maximum rate of 2x maintenance
Serum Potassium	
≥ 5.5 mEq/L	use 2-bag system without potassium
4-5.4 mEq/L	use 2-bag system with 20 mEq/L potassium acetate + 20 mmol/L potassium phosphate
< 4 mEq/L	use 2-bag system with 30 mEq/L potassium acetate + 30 mmol/L potassium phosphate
< 3 mEq/L	hold insulin drip until IVFs are started

Two-bag system Order both bags simultaneously STAT*	Bag 1	Bag 2
	½ NS + Potassium Acetate + Potassium Phosphate	D_{10} ½ NS + Potassium Acetate + Potassium Phosphate
Initial Serum Glucose < 500 mg/dL		
> 350 mg/dL	100%†	0%†
250 - 349 mg/dL	50%†	50%†
100 - 249 mg/dL	0%†	100%†
< 100 mg/dL	Notify physician	
Initial Serum Glucose ≥ 500 mg/dL		
≥ 500 mg/dL	100%†	0%†
400 - 499 mg/dL	75%†	25%†
300 - 399 mg/dL	50%†	50%†
200 - 299 mg/dL	25%†	75%†
100 - 199 mg/dL	0%†	100%†
< 100 mg/dL	Notify physician	

D_{10}, Dextrose; IVFs, intravenous fluids; NS, normal saline

* If blood glucose drops by more than 100 mg/dL in 1 hour, contact physician.

† Percent IVF

2). There was also no difference between the protocol and non-protocol groups in the initial bicarbonate concentration (10 mmol/L [IQR 7-12.3] vs. 9 mmol/L [IQR 7-12], respectively [p = 0.29]) or initial anion gap (22 [IQR 19-25] vs. 21 [IQR 18-24], p = 0.25). Subjects in the protocol group had lower starting blood glucose concentrations (375 mg/dL [IQR 303-500]) than the non-protocol group (452 mg/dL [IQR 317–640]) (p = 0.05). There were more patients admitted to the intensive care unit in the protocol versus the non-protocol group (37% vs. 13.7%; p = 0.003).

For the primary outcome, no difference was seen between groups for the median bicarbonate correction rate (0.87 mmol/L/hr [IQR 0.61-1.25] in the protocol group vs. 0.88 mmol/L/hr [IQR 0.64-1.2] in the non-protocol group, p = 0.92) or median time to resolution of ketoacidosis (9 hours [IQR 5-12] vs. 9 hours [IQR 6.5-13], p = 0.14). For the secondary outcomes, there was no difference in the median time to initial 1-bag or 2-bag system IV fluid bags hanging (42 minutes [IQR 24.8-66] vs. 48.5 minutes [IQR 21.3-89.8], p = 0.36), or median number of fluid bags used (4

Table 2. Demographics

	Non-protocol (n = 73)	Protocol (n = 46)	p Value
Age (yr)*	12 (10 - 14)	13 (9.8 - 15)	0.99
Weight (kg)†	47 ± 21.5	45 ± 19.2	0.59
Sex, male (%)	26 (35.6%)	18 (39.1%)	0.7
Initial Na (mmol/L)*	135 (131 - 138)	133 (129 - 137)	0.11
Initial K (mmol/L)*	4.5 (3.8 - 5.3)	4.9 (4.2 - 5.5)	0.11
Initial serum HCO3 (mmol/L)*	9 (7 - 12)	10 (7 - 12)	0.29
Initial serum blood glucose (mg/dL)*	375 (303 - 500)	452 (317 - 640)	0.05
Initial anion gap*	21 (18 - 24)	22 (19 - 25)	0.25
Length of hospital stay (days)*	3 (2 - 3)	2 (2 - 3)	0.2
Presented from outside hospital (%)	37 (50.7%)	16 (34.8%)	0.09
PMH of type 1 DM, yes (%)	38 (52.1%)	27 (58.7%)	0.48
IV insulin received at outside hospital/before admission, yes (%)	27 (37%)	12 (26.1%)	0.22
Treated in the pediatric intensive care unit (%)	10 (13.7%)	17 (37%)	0.003

DM, diabetes mellitus; HCO3, bicarbonate; IQR, interquartile range; IV, intravenous; K, potassium; Na, sodium; PMH, past medical history
* Reported as median (IQR)
† Reported as mean ± SD

in both groups [p = 0.76]) (Table 3). The median duration of IV insulin therapy was 16.9 hours (IQR 13.7-21.5) for the protocol group and 21 hours (IQR 15.3-26) for the non-protocol group (p = 0.03). The median number of adjustments to insulin drip rates was 0 (IQR 0-1) for the protocol group and 2 (IQR 0-3) for the non-protocol group (p = 0.0001). In the protocol group, 21 of the encounters (45.7%) required a change in initial insulin rate, compared to 53 encounters (72.6%) in the non-protocol group. There was no difference in the length of hospital stay between groups (median 3 days [IQR 2-3] vs. 2 days [IQR 2-3], p = 0.2).

We evaluated the number of IV fluid bags that were dispensed and did not have a time recorded when administration began. These bags were therefore considered to be waste. Before protocol implementation, 35 bags were prepared and dispensed that were not administered to the patient. After protocol implementation, only 1 bag did not have a correlating administration time.

Hypokalemia, defined as serum potassium concentration less than or equal to 3 mmol/L, occurred in 6 patients (13%) in the protocol group vs. 14 patients (19%) in the non-protocol group (p = 0.38). In the protocol group, 12 patients (26.1%) had at least 1 blood glucose < 100 mg/dL, compared to 11 patients (15.1%) in the non-protocol group (p = 0.14). A total of 3 patients developed cerebral edema manifested by altered mental status or lethargy: 1 in the protocol group and 2 in the non-protocol group (p = 1). There were no deaths in either group.

DISCUSSION

In this study, we found that a protocol for pediatric diabetic ketoacidosis management using a 2-bag IV fluid system decreased the duration of IV insulin therapy, lowered the number of adjustments to insulin drip rate, and decreased the number of wasted IV fluid bags without increasing the incidence of hypoglycemia, hypokalemia, and cerebral edema.

This study found a shorter duration of the insulin infusion when using the 2-bag system and a decrease in the median number of times the insulin rate had to be adjusted. This finding had not been reported in previous published studies. The ability to readily titrate the dextrose concentration administered with the 2-bag system should provide the ability to maintain the insulin rate. In the non-protocol group, insulin drip rates were often decreased owing to the inability to quickly increase dextrose administration. In the protocol group, the 2-bag system permitted quick adjustments to dextrose administration,

Table 3. Primary and Secondary Outcomes

	Non-protocol (n = 73)	Protocol (n = 46)	p Value
Bicarbonate correction rate (mmol/L/hr)*	0.88 (0.64 - 1.2)	0.87 (0.61 - 1.2)	0.92
Bicarbonate correction time (hr)*	9 (6.5 - 13)	9 (5 - 12)	0.14
Insulin duration (hr)*	21 (15.3 - 26)	17 (13.7 - 21.5)	0.03
No. of adjustments to insulin drip rate*	2 (0 - 3)	0 (0 - 1)	0.0001
No. of IV fluid bags administered*	4 (3 - 5)	4 (3 - 5)	0.76
Time to initial IV fluid bag hanging (min)*	49 (21.3 - 89.8)	42 (24.8 - 66)	0.36

IQR interquartile range; IV, intravenous
* Reported as median (IQR)

allowing clinicians to maintain the insulin drip rate at 0.1 units/kg/hr. Therefore, the protocol group would have received a larger total dose of insulin in the same period of time, and potentially be less likely to have persistent hyperglycemia after correction of ketoacidosis. We believe that this feature of the protocol led to a shorter duration of IV insulin in the protocol group. Although the duration of IV insulin decreased, it was still greater than the time to resolution of ketoacidosis, likely because a patient must be able to tolerate oral food before an order is placed to transition to subcutaneous insulin, and therefore, a delay until a meal time may have occurred.

In regard to the time to resolution of acidosis, this study found results similar to previously published studies. So et al[7] also found no difference between a 1-bag system and 2-bag system when evaluating the time to pH correction, but they did find a difference in the rate of bicarbonate correction, with a rate of 0.949 mmol/L/hr with the 2-bag system compared to 0.606 mmol/L/hr with the 1-bag system. We did not see a difference in the rate of bicarbonate correction between the 2 groups. However, the bicarbonate correction rate seen at our institution in the non-protocol group, 0.88 mmol/L/hr, was higher than that seen pre intervention by So et al[7] and may contribute to a difference not being found in this study.

A study conducted by Poirier et al[6] found a clinically and statistically significant reduction in response time of IV fluid changes, with the 1-bag system taking 42 minutes and the 2-bag system taking 1 minute ($p < 0.001$). In our study, the time to administration of the first IV fluid bag was similar to that of previous studies. This study did not find a difference in the time to IV fluid administration time between groups. This may be due to a delay in starting IV fluids until after an optional fluid bolus over 1 hour per our protocol. Therefore, the administration time charted for the 2-bag system IV fluids should occur at approximately 1 hour. This is consistent with the median time of 49 and 42 minutes to administration of IV fluids in the protocol and non-protocol groups, respectively. The initial order for the 2-bag system at our hospital provides nursing staff with the ability to adjust rates as determined by the patient's blood glucose results and therefore should happen at the time the results are available, similar to the response time of 1 minute reported by Poirier et al[6] and 7.4 minutes found by Grimberg et al[5] with a 2-bag system.

Limitations of this study include the possibility that the improvements seen may have resulted from standardizing practice rather than the protocol itself. Previously, there was a lack of standardization in the management of DKA at our institution. Patients were admitted to either the pediatric intensive care unit or stepdown unit on the basis largely of bed flow and availability. Pediatric Intensive Care Unit (PICU) admission guidelines for DKA were defined concurrently with implementation of our protocol, but were not part of the protocol itself. Therefore, once the process was standardized, more patients were admitted to the PICU post protocol. Individual IV fluid orders were placed depending on the patient's blood glucose and electrolyte concentrations and changed frequently. The fluids were approved and made by pharmacy before delivery to the floor, creating potential delays in therapy. However, we believe that the decrease in duration of IV insulin, decrease in number of insulin rate adjustments, and reduction in

wasted IV fluid bags can at least partially be explained by specifics in the protocol such as the 2-bag system. This study was also single site and retrospective in nature. The data collected relied on accurate timing and charting to be recorded by the nursing staff. Strengths of this study include the systematic development of a protocol and comprehensive collection of data on clinical outcomes, process changes, and adverse events. Other studies on pediatric DKA management protocols have focused on clinical outcomes but have not examined individual process measures.

CONCLUSIONS

A pediatric DKA management protocol using a 2-bag IV fluid system did not change time to normalization of ketoacidosis but did decrease the duration of insulin therapy, decrease the number of adjustments to insulin rate, and decrease the number of wasted IV fluid bags without increasing the incidence of hypoglycemia, hypokalemia, and cerebral edema.

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Abbreviations APH, Arnold Palmer Hospital for Children; DKA, diabetic ketoacidosis; IQR, interquartile range; IV, intravenous

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