ORIGINAL ARTICLE

Effect of Fluid Replacement Therapy on Complication and Recovery Time of Diabetic Ketoacidosis: Comparison of Two Protocols

Zahra Razavi, Ali Amanati*

Hamadan University of Medical sciences, Hamadan, Iran

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ABSTRACT

OBJECTIVES: To evaluate the effect of two simultaneous protocols in reducing recovery time and assessment of adverse effects of different fluid replacement therapy in management of diabetic ketoacidosis.

MATERIALS AND METHODS: In this randomized clinical trial study, two standard protocols were chosen to evaluate recovery time and incidence of DKA complications.

RESULTS: 18 subjects who had severe diabetic ketoacidosis were included in our analysis. In the course of treatment, hypokalemia happened in 5 cases in protocol 1 and 4 cases in protocol 2. Hypernatremia occurred in 2 cases of protocol 1 and 4 cases in protocol 2. Hyponatremia occured in 4 cases of protocol 1 and 2 cases in protocol 2. The mean recovery time of acidosis in protocol 1 was 21 ± 5.9 (mean ± SD) hours and 23 ± 10.9 hours in protocol 2. None of them had any signs and symptoms of cerebral edema or mental status deterioration in the course of treatment.

CONCLUSION: According to our study, different volume deficit calculated as a base for dehydration which was replaced in different times and in a similar clinical setting, had not added any risk of complications during the treatment. Also no significant differences were found in recovery time related to the different fluid replacement protocols. We also found that complication of therapy increases with the severity of diabetic ketoacidosis.

KEYWORDS: Diabetic ketoacidosis, Fluid replacement therapy, Recovery time.

INTRODUCTION

DKA is a serious, acute decompensation and preventable complication of diabetes mellitus which is characterized by hyperglycemia, dehydration, electrolyte abnormalities, ketosis and metabolic acidosis. Occurrence of DKA is directly attributable to insulin deficiency. It is commonly seen in patients with type 1 diabetes mellitus, either as an initial presentation of diabetes or in the setting of intercurrent illness, poor glycemic control, non-compliance with insulin therapy, or major psychosocial turmoil in the family (1). Patients with type 2 diabetes are also susceptible to DKA in some stressful conditions, such as trauma, surgery, or infections. DKA with mortality rate of about 2-5% is the leading cause of morbidity and mortality in children with type 1 diabetes mellitus (2,3). It accounts for more than 100,000 hospital admissions and at least 4000 deaths per year in the US, Europe, Australia and North America (4). Frequency of DKA, as the first presentation of diabetes mellitus has been estimated 15% to

*Correspondence: Ali Amanati, Hamadan University of Medical sciences, Hamadan, Iran.
Tel: (+98) 912 444 5685. **Email:** ali_amanati_1356@yahoo.com

70% (5-10) and mortality rate remains unchanged in national population (11-13). The successful outcome in the treatment of DKA is obviously related to the prompt recognition of the diagnosis and precipitating or underlying illness. Particular attention should be given to clinical assessments, neurologic deterioration and biochemical response (14). Mortality is predominantly related to the occurrence of cerebral edema that occurs in 0.3-1% of all episodes of DKA (2,12 and 15). Other causes of morbidity and mortality are hypokalemia, hyperkalemia, hypoglycemia, infections and changes in the central nervous system (CNS), adult respiratory distress syndrome (ARDS), pneumomediastinum (16) and pulmonary edema, aspiration of gastric content and cardiac arrhythmias. Although there is no universal agreement on how patients with DKA should be treated, the general principles of DKA management are adequate fluid and electrolyte replacement over the first 24–48 hours to restore intravascular volume (17) and correct acidosis by administration of intravenous fluid and intravenous insulin (18,19). Particular attention should be centered on optimal fluid management (13,20). A number of important controversies remains unresolved about the type, optimal rate of fluid administration and appropriate volume to correct the volume deficit in diabetic ketoacidosis (13,21 and 22). Piva et al. recommended that every service should have its own protocol adjusted to local operational resources for management of patients with DKA (16). Furthermore, certain points need further investigation such as complications of DKA during fluid resuscitation other than cerebral edema because there is a little data about incidence of other complications (especially in different protocols of fluid resuscitation) during treatment of DKA. We also found that there is a wide variation in the amount of fluid administrated for patients with DKA in the first 24-36 hours of treatment. As a result of these concerns and in order to establish a standardized and uniform protocol for management of patients with DKA in our hospital, this study has been designed. The purpose of this study was to compare the recovery time of acidosis and complications of traditional versus Milwaukee protocols for DKA management.

MATERIALS AND METHODS

Setting

Hamadan is a province in north west Iran, with almost 1,700,000 inhabitants. Besat is a 400-bed tertiary-care referral University Hospital in the capital city of Hamadan, providing different clinical services. Besat's pediatric intensive care unit (PICU) is a 6-bed clinical ward.

Inclusion Criteria and Study Population

Any known or new cases of type 1 diabetes mellitus who fulfilled all the following criteria were included in the study: 1) Serum glucose level greater than 200 mg/dl; 2) Serum pH <7.3; 3) urinary keton greater than two plus in dipstick urine test; and 4) past history of polyuria, polydipsia, nocturia and weight loss in newly recognized patients. Severity of diabetic ketoacidosis (DKA) defined by serum pH and categorized in three groups: mild as 7.2 <pH <7.3, moderate as 7.1< pH <7.2 and severe as pH <7.1 (23). Because most of our cases were severe DKA, we chose only severe cases. All patients admitted in PICU for management and monitoring of DKA.

Exclusion Criteria

Exclusion criteria were any corresponding chronic hepatic, cardiac or renal disease, and probable case of inborn error of metabolism, other concurrent endocrinopathies, bicarbonate therapy in the course of treatment and any patient clinically and laboratory suspected to sepsis. Six patients were excluded; three of them for bicarbonate therapy, one for sepsis, another patient for probability of inborn error of metabolism and finally a case of hypothyroidism with mixedema coma.

Methods

Each patient who had inclusion criteria was enrolled in a protocol (1 or 2) according to the list which was provided previously by

computerized randomization. After exclusion process, nine patients were enrolled in protocol 1 and eight patients in protocol 2. In protocol 1, basic dehydration was calculated as 10% and in protocol 2 as 8.5%. We administered initial fluid resuscitation of 20 cc/kg of 0.9% saline. Patients with persistently poor perfusion or hemodynamic instability after the initial intravenous fluid resuscitation were given additional infusions of 0.9% saline until perfusion was normalized and hemodynamic stability was achieved. In protocol 1 initial bolus therapy with normal saline (20 cc/kg) was subtracted from volume deficit but not in protocol 2. Volume deficit in protocol 1 was compensated in 24 hours and in protocol 2 half of the volume deficit was replaced in the first 12 hours and the remainder in subsequent 24 hours. In both protocols insulin therapy delayed until bolus therapy was achieved if patient did not have hypokalemia (according to ECG finding, or laboratory test) or any sign and symptom of shock. Potassium replacement was administered initially as 30 mEq potassium chloride (15%) per liter of intravenous fluids with subsequent adjustment to maintain serum potassium concentrations within the normal range. Patients were not treated with bicarbonate. Glucose was added to the intravenous fluids when the serum glucose concentration was less than 300 mg/dl.

Definition of Complications

Hypoglycemia: Serum glucose level less than 70 mg/dl

Hypokalemia: Serum potassium level below 3.5 mmol/lit

Hypernatremia: Corrected serum sodium level higher than 150 mmol/lit

Hyponatremia: Corrected serum sodium level lower than 135 mmol/lit

Hypocapnea: Partial pressure of Co_2 less than 35 mmHg

Corrected serum sodium: The measured concentration of sodium was adjusted for the presence of hyperglycemia as follows:

Na + [({glucose - 100}/100) × 1.6] (glucose: mg/dl)

Effective Osmolality: 2 × Na + glucose/18 (glucose: mg/dl)

Cerebral edema:

1. Sudden or unexpected deterioration in level of consciousness in the course of treatment.
2. Any death during assessment or management of DKA.
3. Unexplained seizure, signs and symptoms of increased intracranial pressure.

Study Periods and their Characteristics

This is a randomized clinical trial study which was conducted from October 2005 to September 2008. Our study was designed in two protocols; in each protocol patients were categorized in three groups as mild, moderate and severe. Flow sheets were prepared for data collection according to American Family Physician (AFP) flow sheet (24). Data entry was supervised by Dr. Amanati and controlled by review of ward files.

Statistics

A two-tailed chi-square test and Fisher's exact test were performed to find statistically significant differences in subjects' demographics and complications occurred between two protocols. We also employed chi-square for trend to investigate whether there was a linear incremental or decremental trend in effective osmolality, serum glucose level, serum potassium and serum sodium.

RESULTS

During this 3-year surveillance period, 24 cases that referred to Besat Hospital with severe diabetic ketoacidosis (DKA) were included in our study. Six subjects were excluded, yielding enrollment of 18 subjects in our analysis. General demographics of the overall study group were as follows (Table 1): 8 females in protocol 1; 5 females in protocol 2; mean age of 7.5 ± 3.7 yr (mean ± SD) in protocol 1 and 10.8 ± 4.4 yr in protocol 2; except for two cases all of our patients in severe group were new case of TIDM.

Table 1- Subject demographics by DKA status

	Protocol 1 (n = 9)	Protocol 2 (n = 9)	*P* value
Age (year)	7.5 ± 3.7	10.8 ± 4.4	0.10
Gender (Female)	8	5	0.29
New–onset diabetes	8	8	1
Duration of treatment (hour)	21 ± 5.9	23 ± 10.9	0.63

Among 33 patients who fulfilled criteria for DKA, 54.5% were in severe group, 24.2% in moderate group and 21.2% in mild group. None of them had any signs and symptoms of cerebral edema or mental status deterioration in the course of treatment. Serum pH was less than 7.1 in two protocols (severe DKA). At the end of the treatment, hypokalemia happened in 5 cases in protocol 1 and 4 cases in protocol 2. One case in each group was complicated with hypoglycemia. Hypernatremia occurred in 2 cases of protocol 1 and 4 cases in protocol 2. The overall rate of hyponatremia was 33.3% and seen in 4 cases in protocol 1 and 2 cases in protocol 2. The mean recovery time in protocol 1 was 21 ± 5.9 (mean ± SD) hours and 23 ± 10.9 hours in protocol 2.

DISCUSSION

DKA is a life-threatening condition in which the treatment should be performed by experienced physicians with close observation and meticulous clinical care of the patient throughout the entire course of the treatment. The hallmarks of management of DKA are replacement of fluid, electrolytes and low-dose insulin therapy. We found that the majority of our patients had new-onset diabetes (30 cases of 33 patients; 90.9%). In Felner´s study (2001) 40% of the patients were new cases of diabetes mellitus (25) but in more recent study by Maniatisa (2005) and Rewers (2008) significant increases were found in DKA at the onset of diabetes diagnosis (9,26). It seems that our patients with established TIDM complied moderately with diabetes management. There are no statistically significant differences in age and sex between two protocols but the majority of our cases were female which was similar to those of previous reports in severe ketoacidosis. Of 33 cases, 54.5% were in severe group, these data support recent reports (Ko SH et al. 2005) that note increases in severity of DKA at presentation despite advanced and newer modalities in treatment of TIDM.

Incidence of Complications

In a study by Bui (2002), he had reported the frequency of hypokalemia as 6% (5), whereas the frequency of hypokalemia was 50% in our study. The incidence of hypoglycemia and hypernatremia reported by Bui (2002) were 3.4% and 1.2%, respectively (5). The frequency of hypernatremia, hyponatremia and hypoglycemia were 33.3%, 33.3% and 11.1%, respectively.

Risk Factors for Cerebral Edema

It is noteworthy that despite majority of patients with DKA in our center were in severe group, clinically apparent cerebral edema did not occur. Durr (1992) emphasized an association between severity of acidosis and risk of cerebral edema (27). It may be due to less number of the cases in this study. In addition we cannot definitively exclude the possibility of development of subclinical brain swelling during treatment in our patients as previous reports (28-30). Risk factors that contributed in progression of cerebral edema include: new-onset type 1 diabetes mellitus, younger age, longer duration of symptoms, greater hypocapnia and elevated BUN at presentation. None of these risk factors were found in our study except for hypocapnia.

Potassium

Hypokalemia is the most common electrolyte imbalance during treatment of DKA (31) and one of the most serious and fatal complications due to life threatening cardiac arrhythmias. Hypokalemia at presentation may be related to prolonged duration of disease. In a study by Felner (2001), no statistically significant differences were found between standard protocols. There are a few studies that report the incidence of hypokalemia in management of DKA (25). In a study by Bui (2002), he had

reported the frequency of hypokalemia as 6%, whereas it was 50% in our study (5). Hypokalemia was the most common complication in our study. Serum potassium level decreased at a same rate in two protocols. These changes were statistically significant with time ($P < 0.0001$) but not between two protocols ($P = 0.6$).

Sodium

Measured serum sodium level increased at a same rate in two protocols in the first 6 hours after beginning of the treatment (Figure 1). These changes were statistically significant with time ($P < 0.0001$) but not between two protocols ($P = 0.2$). Hoorn demonstrated that moderate hypernatremia (between 150-160 meq/lit) should be considered protective in children. Glaser showed that lack of an increase in the serum sodium level during treatment of DKA is associated with an increased probability of cerebral edema since moderate hypernatremia maintains plasma osmolarity and it seems to be a protective factor in the development of cerebral edema in DKA (32). The consensus statement that an attenuated rise in measured serum sodium concentrations during therapy for DKA may be associated with increased risk of cerebral edema (2,33). Finally, in this study a gradual increase in measured serum sodium along with gradual decreases in serum glucose level is predictor of successful management according to a study by Hoorn (34).

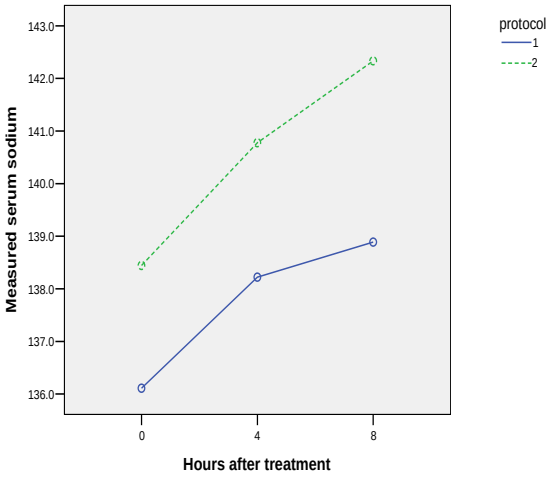

Figure 1: Measured Na in protocols 1 and protocol 2

Fluid Replacement Therapy and Change in Serum Osmolality

Mean sodium infusion rate was greater in protocol 2 (143 vs. 154 meq/lit). A possible explanation for this finding is the shorter duration and greater volume that was replaced, and consequently lower sodium infusion rate in the first 6 hr of treatment in protocol 2. Of special note, the volume of fluid replaced in first 6 hours of treatment was not statistically significant between two protocols but was greater in protocol 2 ($P = 0.117$). The rate of change in serum glucose was statistically significant ($P < 0.0001$) in two protocols

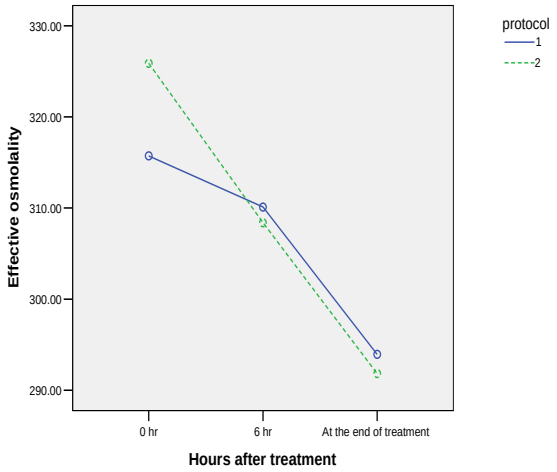

Figure 3. Effective osmolality calculated by corrected Na

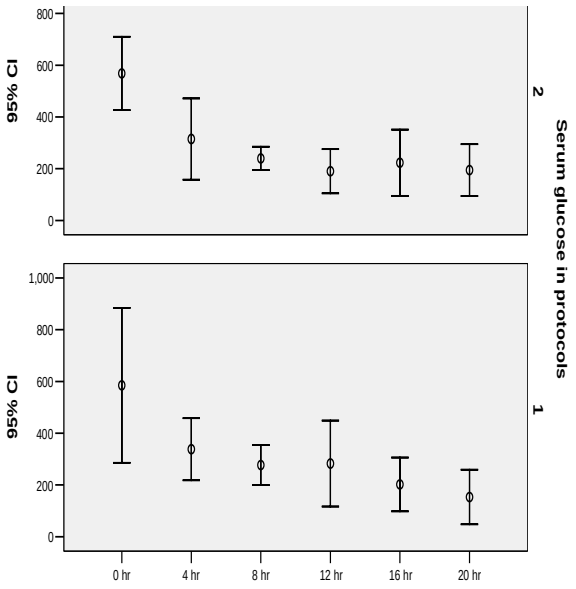

Figure 2- Serum glucose in the course of treatment in protocol 1 and protocol 2

Table 2- Treatment charactristics in protocol 1 and protocol 2

	Protocol 1	Protocol 2	*P* value
Total serum in the first 6 hr (ml)	1168 ± 541	1744 ± 892	0.117
Na administrated in the first 6 hr (meq/lit/h)	154	143 ± 17.1	0.078
K administrated in the first 6 hr (meq/lit/h)	33 ± 4.8	31 ± 7	0.448
Insulin infusion rate in the first 6 hr (unit/h)	0.07 ± 0.02	0.05 ± 0.01	0.26
Fluid infusion rate in the course of treatment (ml/h)	128 ± 52.7	166 ± 69.2	0.65
Decrease in effective osmolality during 6 hr of treatment (%)	5.025	6.050	0.500

*Plus–minus values are means ± SD

during the treatment (decreasing with time) but not between two protocols (Figure 2). The rate of change in measured serum sodium was statistically significant ($P = 0.02$) in two protocols during the treatment (increasing with time) but concomitant decreases in effective osmolality occurred in the course of fluid therapy in each protocol which were also statistically significant ($P < 0.0001$) (Figure 3). Other aspects of treatment are summarized in Table 2. None of our patients had cerebral edema clinically. Thus, our study supported previous data to minimize the role of fluid replacement therapy in developing cerebral edema. This study also showed that single factor (such as hypocapnia) does not contribute in progression of clinical cerebral edema and combinations of known risk factors are necessary. Low partial pressure of arterial carbon dioxide ($PaCO_2$) levels and a higher serum sodium concentration at presentation have been identified as particular risk factors for the development of cerebral edema (13, 28).

Several hypotheses exist about the role of volume and sodium content of intravenous fluid in the development of cerebral edema in DKA. In an article by Hoorn et al., significant drop in effective plasma osmolality during the first 6 hours of treatment was associated with increasing the likelihood of clinical cerebral edema (32). Mel suggests that the rates of salt and water replacement in diabetic ketoacidosis are not key determinants of the appearance of cerebral edema (35). Harris claimed that successful therapy requires gradual deficit replacement (evenly over 48 hours) (36). Accurate monitoring of the volume deficit along with clinical assessments, neurologic evaluation and biochemical response may therefore be advisable if there is no compelling evidence to be aggressive.

Recovery Time

The mean recovery time of acidosis in protocol 1 was 21 ± 5.9 (mean ± SD) hours and 23 ± 10.9 hours in protocol 2 which was more than previous studies on patients with severe acidosis complicated with cerebral edema, meaning that in our study the rate of fluid replacement was suitable and met the criteria of such standard protocols (37,38).

Limitations

Because Besat is a referral pediatric hospital some patients took such medications out of our protocols (bolus insulin in unusual doses, bicarbonate therapy and initial fluid resuscitation with dextrose saline) and therefore they were excluded from our study.

CONCLUSION

There is no significant difference in age and sex between protocols, although the incidence of female population was high in our region similar to those reported in other studies. The majority of our cases ranged from 10 to 15 years of age.

A great number of them were new case and had severe acidosis as noted in other recent study (2,37,39-41).

Table 3- Incidence of complications during treatment

	Protocol 1 (n = 9)	Protocol 2 (n = 9)	Total incidence (%)	*P* value
Hypoglycemia*	1	1	11.1	1
Hypokalemia	5	4	50	1
Hypernatremia	2	4	33.3	0.62
Hyponatremia	4	2	33.3	0.62

Number of patients*

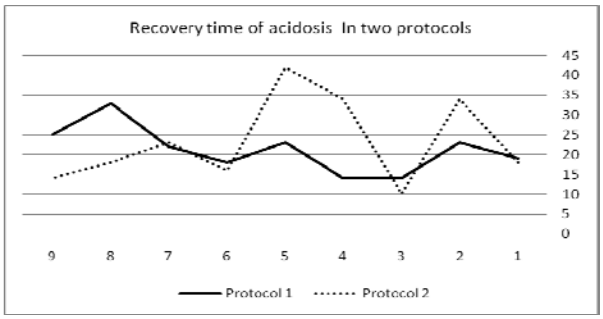

Figure 4- Recovery time of acidosis in protocol 1 and protocol 2

Table 4- Biochemical characteristics of patients in two protocols*

	Protocol 1	Protocol 2	*P* value
Initial Partial pressure of arterial carbon dioxide ($PaCO_2$) (mmHg)	9.93 ± 2.46	15.31 ± 6.22	0.028
Initial glucose (mg/dL)	663 ± 195	598 ± 163	0.45
Initial serum urea nitrogen (mg/dL)	15.1 ± 8.2	15.7 ± 8.2	0.86
Hemoglobin (mg/dl)	13.02 ± 2.2	13.46 ± 1.3	0.62
Initial measured serum sodium (mmol/L)	136 ± 7.5	138 ± 5	0.45
Initial corrected serum sodium (mmol/L)	145 ± 6	146 ± 5.5	0.64
Mean E_{osm} at the onset of protocol by measured Na (mmol/L)	308 ± 10	309 ± 12	0.78
Mean E_{osm} at the onset of protocol by corrected Na (mmol/L)	315 ± 31.2	325 ± 16.8	0.403
Initial potassium (mg/dL)	4.2 ± 0.5	4.6 ± 1.1	0.36

E_{osm}, Effective osmolality, *Biochemical characteristics are pretreatment values.

There was no statistically significant difference in age of sub-groups between two protocols. There was no statistically significant difference in complications such as hypokalemia, hypernatremia, hyponatremia and hypoglycemia (Table 3) and there was also no statistically significant difference in recovery time in two protocols (Figure 4). According to our study different volume deficit calculated as basic dehydration which was replaced in different times (24 hours vs. 36 hours) in similar circumstances (no difference in age and sex) and in a similar clinical setting (no difference in pretreatment serum glucose, sodium, potassium, effective osmolality, hemoglobin and serum urea nitrogen), had not added any risk of complications during the treatment (Table 4). There is a logical decrease in effective osmolality in the course of treatment which is not dependent on the volume deficit or duration of replacement if replacing is achieved in more than 24 hours and if insulin therapy is attained cautiously.

What was already known about the topic?

● Hypokalemia is one of the most common complications in DKA management.

● The rate of serious complications reduces by more caution in insulin infusion rate and by volume deficit replacement over 24 hours.

What this study added to our knowledge?

● Of special note is an increased frequency of severe DKA at presentation.

● Except for two patients, all of them were new case of type l diabetes mellitus which may be because of close follow-up and accurate glucose monitoring in known cases in addition to well sick-day management.

● Despite of significant different in initial PaCO2, none of them were complicated with clinical cerebral edema, meaning it was a multi-factorial event.

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