Ten-year experience in management of diabetic ketoacidosis and ketosis: 140 episodes at pediatric age

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One hundred and forty episodes in 112 patients (58 boys) with diabetic ketoacidosis (96 episodes) and diabetic ketosis (44 episodes) were studied to elucidate the clinical and laboratory risk factors for altered level of consciousness at presentation and to analyze the outcome of a distinct protocol in the treatment of diabetic ketoacidosis.

The patients were analyzed according to demographic data and clinical and laboratory findings at admission. The treatment protocol involved use of 0.45% sodium chloride (NaCl) in 2.5% dextrose as the initial fluid therapy following volume expansion. Dextrose content of the fluid was doubled once the serum glucose level fell below 250 mg/dl.

The mean ages at presentation with diabetic ketoacidosis and ketosis were 10.3 ± 4.4 and 10.2 ± 4.0 years, respectively. Thirty-one percent of patients had altered consciousness at presentation. The level of consciousness correlated negatively with serum bicarbonate level ($r=-0.485$; $p<0.001$). A serum bicarbonate level below 15 mmol/L was a risk factor for altered consciousness. There was no correlation between effective osmolality and the level of consciousness. Serum effective osmolality above 320 mOsm/kg H_2O did not appear to be a risk factor for altered consciousness. No mortality or any signs of clinical brain edema were observed in patients treated with the distinct treatment protocol.

In conclusion, acidosis appears to be the major factor in the pathogenesis of altered consciousness at presentation. Serum effective osmolality does not seem to be a risk factor as suggested previously.

Dextrose added to the infusion fluid early in treatment seems to prevent the development of brain edema, and this may be due to a protective effect of higher osmolality in the resultant solution.

Key words: diabetic ketoacidosis, consciousness, altered level of consciousness, osmolality, brain edema, management, complications.

Diabetic ketoacidosis is one of the critical acute complications of type 1 diabetes mellitus. At the time of presentation, 23.3-45.2% of diabetic ketoacidosis (DKA) cases had altered consciousness of varying severity[1,2]. The level of consciousness at presentation may either ameliorate or deteriorate during treatment. Furthermore, alterations in consciousness may evolve at any time during the course of treatment. Alterations that occur during treatment are suggested to arise from cerebral edema. On the other hand, pathogenesis of such alterations at presentation has not yet been resolved. The treatment of DKA has been modified over time in order to avoid brain edema, which is reported in 0.6-1% of cases[3-5].

One hundred and forty episodes in 112 patients with DKA and diabetic ketosis (DK) followed between 1988 and 1998 in our center were analyzed retrospectively. The aim of this study was to elucidate the clinical and laboratory risk factors for altered consciousness on admission, and to analyze safety and efficacy of a distinct treatment protocol in terms of morbidity and mortality.

Material and Methods

One hundred and forty episodes of DKA and DK in 112 patients with type 1 diabetes mellitus (58 male, 54 female) were analyzed. The ages at admission, the number of episodes of DKA, vital signs, degree of dehydration, the level of consciousness, serum glucose, electrolytes, blood urea nitrogen, creatinine, pH, HCO_3, and ketone levels at presentation were extracted from files. Effective serum osmolality and corrected Na levels were calculated as below:

Serum effective osmolality: 2 x (Na) + Glucose/18

Corrected Na: Na + 1.6 x (Glucose-100)/100

All patients had hyperglycemia and ketonemia. The criteria for a diagnosis of DKA were serum HCO_3 <15 mmol/L and pH <7.3. Those patients with a serum HCO_3 ≥15 mmol/L and pH ≥ 7.3 were diagnosed as DK. All of the cases with DKA, as well as selected cases with DK who had new-onset diabetes or were young, were treated with intravenous fluid and insulin therapy.

Treatment Protocol

All patients were monitored for vital signs continuously in the intensive care unit (ICU). Dehydration, consciousness and serum glucose levels were recorded hourly, whereas the serum electrolyte levels and blood gases were measured every two hours.

Fluid and Electrolyte

1. An initial bolus of normal saline (0.9% sodium chloride - NaCl) at a dose of 10-20 ml/kg/hr over one or two hours was administered for volume expansion in patients with moderate to severe dehydration.

2. The total amount of fluid was calculated as:

- 2500-3000 ml/m^2 per 24 hours in mild dehydration.
- 3000-3500 ml/m^2 per 24 hours in moderate dehydration.
- 3500-4000 ml/m^2 per 24 hours in severe dehydration.

Half of the total daily fluid was administered in the first eight hours, and the remaining half in 16 hours. The initial bolus of saline was subtracted from the first 8 hour hydration fluid volume.

3. The composition of the fluid following the initial bolus was 2.5% dextrose in 0.45% NaCl with a resultant osmolality of 280 mOsm/L. This fluid was continued until the serum glucose level fell below 250 mg/dl.

4. Once serum glucose fell below 250 mg/dl, the composition of fluid was changed to 5% dextrose in 0.45% NaCl with a resultant osmolality of 405 mOsm/L.

5. Potassium chloride at a dose of 30-40 mEq/L was added to the fluid once the patient voided.

6. Bicarbonate was withheld until the serum bicarbonate fell below 7.1.

The fluid infusion was continued until dehydration, acidemia and ketonemia resolved and oral feedings were tolerated.

Insulin Treatment

Following expansion of the intravascular compartment by saline infusion, low dose intravenous regular insulin infusion was started. The dose of insulin was 0.05-0.15 U/kg per hour, and it was adjusted to achieve a decrement of 50-100 mg/dl per hour in serum glucose.

Complications during and just after the treatment were also analyzed.

Statistical Analysis

Student's t-test and correlation analysis were used for the analysis of data. Odds ratio was also calculated to determine a threshold for risk factor in altered consciousness.

Results

Ninety-six (69%) episodes out of 140 were DKA and 44 (31%) were DK.

Of 140 episodes, 97 (69.3%) were in new onset and 43 (30.7%) were in established diabetes. Nineteen patients had recurrent episodes (15 patients 2, 3 patients 3, and 1 patient 8 recurrences). The etiology of recurrences was insulin omission in 19/43 (44%) and infection in 18/43 (42%) of the cases. The etiology in six cases was unknown.

The mean ages of DKA and DK cases were 10.3 ± 4.4 years (range 1.3-19.2 years) and 10.2 ± 4.0 years (range 1.1-16.3 years), respectively.

The mean age of cases with new onset diabetes was 9.1 ± 4.3 years (range 1.1-16.3 years) versus 12.9 ± 2.8 years (range 4.8-19.2 years) in cases with established diabetes.

The clinical findings of 140 episodes at admission are shown in Table I.

Table I. Clinical Findings of 140 Episodes of DKA and DK

Number of episodes	DKA n: 96 (69%)	DK n: 44 (31%)
Age		
<5 years	18 (19%)	4 (9%)
5-10 years	17 (18%)	15 (34%)
11-15 years	49 (51%)	22 (50%)
>15 years	12 (12%)	3 (7%)
New onset diabetes	60 (63%)	37 (84%)
Established diabetes	36 (37%)	7 (16%)
Sex		
Female	53 (55%)	18 (41%)
Male	43 (45%)	26 (59%)
Dehydration		
Mild	7 (7%)	30 (68%)
Moderate	72 (75%)	14 (32%)
Severe	17 (18%)	- (0%)
Consciousness		
Alert	66 (69%)	44 (100%)
Stupor	21 (22%)	- (0%)
Coma	9 (9%)	- (0%)

DKA: Diabetic ketoacidosis, DK: Diabetic ketosis.

None of the patients with DK had altered consciousness at presentation, whereas 31% of patients with DKA presented with varying degrees of altered consciousness (Table I).

The laboratory findings of 140 episodes on admission are recorded in Table II.

The level of consciousness of the patients at presentation was positively correlated with serum bicarbonate level ($r=0.485$, $p<0.001$). Serum bicarbonate level less than 15 mmol/L was a risk factor for alteration in consciousness (odds ratio: 1.454, 95% CI=1.271 - 1.664).

There were negative correlations between the degree of dehydration, serum ketone and the level of consciousness ($r = -0.409$, $p<0.001$; $r= -0.3852$, $p<0.001$), whereas serum glucose level was weakly correlated with the level of consciousness ($r=-0.214$, $p=0.011$).

There was no correlation between the level of consciousness and serum effective osmolality ($r=0.1238$, $p=0.147$). Serum effective osmolality more than 320 mOsm/L was not found to be a risk factor for alteration in consciousness (odds ratio: 0.656, 95% CI=0.343 - 1.252). Similarly, there was no correlation between level of consciousness and corrected Na ($r=0.060$, $p=0.480$). The results of the treatment protocol in patients with DKA and DK are summarized in Table III.

Table II. Laboratory Findings and Statistical Analysis of Some Laboratory Parameters of DKA and DK Episodes

	DKA Mean (SD)	DK Mean (SD)	Statistics
Glucose (mg/dl)	554.2 (193.7) (234-1142)	526.5 (159.3) (245-770)	p=0.409
HCO_3 (mmol/L)	7.48 (3.58) (1.3-14.9)	20.18 (3.00) (15.0-27.7)	p<0.001
pH	7.1 (0.14) (6.75-7.29)	7.34 (0.05) (7.30-7.44)	p<0.001
Corrected Na (mEq/L)	144.4 (7.4) (130.4-167.7)	145.4 (4.8) (135.6-155.5)	p=0.336
K (mEq/L)	4.82 (0.84) (2.20-7.2)	4.65 (0.65) (3.1-6.4)	p=0.196
BUN (mg/dl)	20.93 (12.3) (6.0-87.0)	16.29 (4.8) (8.0-27.0)	p=0.006
Effective osmolality (mOsm/kg H_2O)	314.8 (16.9) (282.2-370.8)	315.8 (11.1) (291.2-340.5)	p=0.693

DKA: Diabetic ketoacidosis, DK: Diabetic ketosis.

Table III. Responses of DKA and DK Cases to the Specific Treatment Protocol

Hours	DKA Mean (SD)	DK Mean (SD)	Statistics
Disappearance of serum ketone	12.25 (6.18) (4-34)	6.20 (4.47) (2-22)	p<0.001
Duration of IV fluid infusion	16.49 (7.70) (6-42)	9.64 (6.31) (3-35)	p<0.001
Duration of IV insulin infusion	15.18 (7.22) (3-42)	7.70 (3.81) (3-25)	p<0.001
Switching to oral feeding	15.58 (7.27) (6-42)	8.11 (4.98) (3-35)	p<0.001

DKA: Diabetic ketoacidosis, DK: Diabetic ketosis.

Bicarbonate was not used in episodes of DK, whereas 60 (63.2%) of 96 cases of DKA needed bicarbonate according to the treatment protocol. In 30 cases, varying abnormalities in consciousness at the time of admission improved during treatment. During the course of treatment neither deterioration nor evolution of abnormalities in consciousness was observed. In the records no clinical finding suggestive of brain edema that could be attributed to treatment was detected in any of the patients. Three cases were complicated by hypoglycemia and one by hypocalcemia during the treatment. There was no mortality.

Discussion

Diabetic ketoacidosis is one of the most important complications of type 1 diabetes mellitus. The most frequent causes of DKA are insulin omission and relative insulin inadequacy (e.g. infection, trauma). New onset diabetes as a cause has accounted for only 25–37.3% of all admissions in previous reports[3,6,7], whereas this was found to be 69.3% (n=97) in our institute. In this series the causes of DKA in established diabetes were omission of insulin (19/43 cases) and infection (18/43 cases), and no etiology could be found in a small number of patients (6/43 cases). White[8], however, stated that omission of insulin doses was the leading cause of DKA and occurred in two-thirds to three-quarters of the cases.

The mortality and morbidity of DKA are directly related to the status of the patient on admission[4,9]. The alterations in consciousness at presentation may result from metabolic changes that occur during the ketoacidotic state. However, the role of these changes as well as the degree to which they contribute to coma have not been entirely substantiated. Fulop et al.[10] strongly emphasized that altered consciousness in DKA was highly correlated with serum osmolality. They suggested that in order for the coma to ensue in DKA, the serum osmolality should be more than 320 mOsm/kg H_2O. In this analysis we did not observe any correlation between level of consciousness and serum osmolality. Furthermore, serum effective osmolality above 320 mOsm/kg H_2O was not found to be a risk factor for altered consciousness. Level of consciousness correlated negatively with three factors (degree of dehydration and serum ketone and glucose levels), whereas it correlated positively with serum bicarbonate. The state of consciousness at the time of presentation seems to be a consequence of acidosis, ketonemia, the degree of dehydration and hyperglycemia. In contrast, serum effective osmolality and electrolyte levels do not have any effect on consciousness.

Brain edema is seen in 0.6-1% of cases during DKA therapy[3-5]. The etiology of brain edema has not yet been well documented. Brain edema typically develops during treatment of DKA but it can manifest even before treatment[11,12]. Various mechanisms including hypoxia, reductions in serum osmolality, and idiogenic osmoles have been postulated in the pathogenesis of brain edema[13,14]. The risk factors for the development of brain edema in DKA at presentation were found to be severe acidosis[9], high blood urea nitrogen concentration and low partial pressure of arterial carbon dioxide[4], and low serum glucose and effective osmolality[14]. Moreover, rapid rehydration, large volumes of fluid administration (>4 L/m^2/24 hr)[15] and failure to increase serum sodium effectively[5,15] were cited as risk factors of brain edema during treatment.

Silver et al.[16] showed that serum osmolality played the major role in the development of brain edema during treatment.

Virtually all treatment protocols declared previously do not contain dextrose in the first phase of fluid therapy. Rosenbloom[17] proposed 0.45% NaCl infusion after an initial bolus of 0.9% NaCl, while Lebovitz[7] continued with 0.9% NaCl infusion after the bolus if serum sodium level was less than 150 mEq/L. Harris et al.[5] concluded that a fluid containing 125 mEq/L NaCl in early therapy would protect against a rapid decline in serum osmolality. Finally, a consensus statement on DKA treatment in children suggested a fluid therapy with the content of at least 0.45% NaCl[12]. A fluid therapy containing less sodium chloride than that of normal saline (0.9% NaCl) is hypoosmolar. Use of high amounts of sodium chloride to increase the osmolality of fluid is a cause of hyperchloremic acidosis[12]. In our treatment protocol, the sodium content of the initial fluid was approximately 150 mEq/L. Afterwards, the composition of the intravenous fluid was changed to 75 mEq/L sodium in 2.5% dextrose, which had an osmolality of 280 mOsm/L until the serum glucose level declined to 250 mg/dl. When glucose reached this level, the concentration of dextrose in the fluid was increased to 5% while the sodium content was unchanged. The osmolality of the latter fluid was higher than the former. Therefore, addition of dextrose in 0.45% NaCl provided an increase in the osmolality of fluid in our protocol. A rapid decline in serum osmolality during therapy and hence brain edema can be prevented by a fluid that is not hypoosmolar. No signs of clinical brain edema or mortality in our patients suggested that increasing the osmolality of fluid could prevent brain edema. On the other hand, addition of dextrose to fluid therapy in our protocol did not lead to an increase in serum glucose levels and duration of therapy. The mean duration of therapy was 16 hours, which was shorter than in recent reports[12].

In conclusion, no signs of clinical brain edema or mortality have been recorded in the last 15 years with our treatment protocol, suggesting that osmolality, rather than sodium content of fluid, is the major factor in preventing the development of brain edema during treatment of DKA in patients with type 1 diabetes.

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