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redakcja@pediatricendocrinology.pl
www.pediatricendocrinology.pl
www.pteidd.pl

Initial Fluid Therapy in Pediatric Diabetic Ketoacidosis: A comparison of Hypertonic Saline Solution and Normal Saline Solution

Początkowa terapia płynowa cukrzycowej kwasicy ketonowej u dzieci – porównanie nawodnienia hypertonicznym i izotonicznym roztworem soli fizjologicznej

Obeid Shafi, Virendra Kumar

Division of Pediatric Intensive Care, Department of Pediatrics, Lady Hardinge Medical College and associated Kalawati Saran Children's Hospital, New Delhi – 110001, India

Abstract

Introduction. The optimal fluid therapy in children with DKA is a matter of debate, especially if we take into account its association with cerebral edema, the most important complication. Hypertonic Saline Solution is used in the treatment of cerebral edema, and also has been used for volume resuscitation in children with shock. **Aim of study.** To compare the effects of 3% saline and 0.9% saline solutions on changes in vital parameters, sodium and chloride levels, lactate and pH; time needed for the correction of hyperglycemia; time needed for the control of ketoacidosis and incidence of cerebral edema. **Methods.** Open-label prospective RCT in which 40 children with moderate to severe DKA were randomized to receive either 3% saline or 0.9% saline as initial fluid therapy. **Results.** There was no significant difference between the two groups in the clinical vital parameters, time for the correction of hyperglycemia and the resolution of acidosis. Patients in the 3% saline group had a higher increase in sodium and chloride from baseline compared to the 0.9% saline group. The acidemia was noted to worsen in both groups after the initiation of fluid therapy, which was not associated with clinical deterioration. The frequency of cerebral edema was similar in both groups. **Conclusions.** Both 0.9% saline and 3% saline were equally effective as initial fluid in children with DKA with respect to hemodynamic improvement, the resolution of acidosis and the correction of hyperglycemia, but the use of 3% saline solution did not preclude the development of cerebral edema and has the potential to cause hypernatremia, hyperchloremia and hyperchloremic metabolic acidosis.

Key words.
diabetic ketoacidosis, diabetes mellitus, type 1, cerebral edema, hypertonic saline solution

Streszczenie

Wstęp. Wybór optymalnej metody terapii płynowej cukrzycowej kwasicy ketonowej (DKA) u dzieci pozostaje kwestią dyskusyjną, szczególnie w związku z ryzykiem obrzęku mózgu, najważniejszego powikłania. Hypertoniczny roztwór soli fizjologicznej jest używany w leczeniu obrzęku mózgu oraz był używany w leczeniu wstrząsu u dzieci. **Cel badania.** Porównanie wpływu leczenia 3% i 0,9% roztworem soli fizjologicznej na stan kliniczny oraz zmiany stężenia sodu, mleczanu i ph krwi, czasu korekty hiperglikemii oraz leczenia kwasicy i występowania obrzęku mózgu u dzieci. **Metody.** Przeprowadzono randomizowane badanie prospektywne, typu open-label, w grupie 40 dzieci z umiarkowaną do ciężkiej cukrzycową kwasicą ketonową. Dzieci losowano do grupy otrzymującej jako początkową terapię płynową 3% lub 0,9% roztwór soli fizjologicznej. **Wyniki.** Pomiędzy obiema grupami nie było istotnych różnic w stanie klinicznym, czasie korekty hiperglikemii oraz czasie wyrównania kwasicy. W grupie pacjentów, którzy otrzymali 3% roztwór soli stwierdzono większy wzrost stężenia sodu oraz chloru w porównaniu z grupą, która otrzymywała 0,9% roztwór soli. Obserwowano przejściowe pogorszenie pH po rozpoczęciu terapii płynowej w obu grupach, co jednak nie było związane z pogorszeniem stanu klinicznego. Częstość występowania obrzęku mózgu była podobna w obu grupach. **Wnioski.** Zarówno 0,9% jak i 3% roztwór soli fizjologicznej są równie efektywne w początkowej terapii płynowej u dzieci z DKA, wpływają na poprawę stanu układu krążenia, poprawę kwasicy i korektę hiperglikemii. Użycie 3% NaCl nie chroni jednak przed rozwojem obrzęku mózgu i może potencjalnie powodować hipernatremię, hiperchloremię oraz hiperchloremiczną kwasicę metaboliczną.

Słowa kluczowe
kwasica ketonowa, cukrzyca typu 1, obrzęk mózgu, hipertoniczny roztwór soli fizjologicznej

Obeid Shafi, MD
Chief Resident Department of Pediatrics,
Flushing Hospital Medical Center, New York- 11355, USA
4370 Kissena Blvd Apt 10A, Flushing, New York- 11355, USA
Email: obeidshafi@gmail.com
Phone: +17182197642

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Introduction

Diabetic ketoacidosis (DKA) is the most common cause of morbidity and mortality in children with Type I Diabetes Mellitus (T1DM) [1,2], while cerebral edema is the leading cause of death in pediatric diabetic ketoacidosis [3]. The mortality rate for DKA in children in the developed countries has declined to 0.15% – 0.31% [4,5]. But the mortality rate is 21% to 24% in patients who develop cerebral edema with DKA, hence cerebral edema accounts for most of the DKA deaths and also has a high rate of permanent neurologic morbidity [1, 6–8]. Cerebral edema complicating DKA is more common in children than in adults. Although symptomatic and catastrophic cerebral edema has been reported in about 0.5-3% of children with DKA, asymptomatic or subclinical cerebral edema is thought to be much more common, if not universal, during the treatment of DKA [9].

Cerebral edema is primarily a clinical diagnosis and should be suspected when there is an unexpected deterioration in neurological status after an initial improvement or persistence of a comatose state without an obvious cause [10]. Early warning signs of cerebral edema include headache (especially new onset of headache during treatment), irritability, or altered behavior [10,11]. Typically, symptomatic cerebral edema occurs 4-12 hours after the initiation of the treatment for DKA, but there have been cases in which it occurred before the initiation of the therapy and as late as 24-48 after the initiation of the therapy. Once clinical symptoms other than lethargy and behavioral changes occur, mortality is high (>70%), with only 7-14% of the patients recovering without permanent morbidity. Rapid improvement in the neurological status in response to intravenous administration of either 3% saline or hypertonic mannitol further confirms the presumptive diagnosis of early cerebral edema [10]. Children who experienced DKA demonstrated poor performance in tests of memory capacity compared to children with diabetes who had never had DKA [12].

The cause of cerebral edema in DKA is not exactly known [13]. The theories which have been put forward to explain these associations include those of osmotic abnormalities wherein there is the generation of the so-called "idiogenic osmoles" within brain cells [10,13], and that of overhydration and hyponatremia occurring during the rehydration as part of the management of DKA [11,14,15]. Other studies suggest that cerebral hypoperfusion and the detrimental effects of reperfusion during the treatment may play a prominent role in the development of cerebral edema [7,16–18]. Hypertonic saline is currently used in the management of cerebral edema which has developed during the treatment of DKA. Hypertonic saline is preferred by some as osmotherapy, overtaking mannitol as the most widely used agent for the control of cerebral edema in DKA [19]. The use of hypertonic saline causes concerns for developing an acutely hyperosmolar state, hypernatremia, hyperchloremic metabolic acidosis (HMA), local tissue injury from extravasation, and dilutional coagulopathy. Even though there is no clear evidence for any significant adverse effects from the use of hypertonic saline, and 3% saline infusions appear to be well tolerated in the pediatric patients, close monitoring is warranted with the use of hypertonic saline solutions [20–23]. The exact clinical significance of HMA on patient outcome is unknown [24].

Fluid therapy forms a cornerstone in the management of diabetic ketoacidosis, but controversies persist regarding this aspect of the management of the child presenting with DKA, especially related to the rate and sodium content in the fluid. This largely stems from a lack of clinical trials comparing the various intravenous fluids used during the DKA management. The objectives of fluid and electrolyte replacement therapy are to restore the circulating volume, replace sodium and the fluid deficit of water (intracellular and extracellular), improve glomerular filtration with an enhanced clearance of glucose and ketones from the blood, and to reduce the risk of cerebral edema [25].

Aim of study

During the management of DKA, the first priority for the treatment is to restore the volume deficit with crystalloid. This restores intravascular volume, decreases counter-regulatory hormones and lowers blood sugar levels [26]. However, the optimal type of crystalloid has yet to be determined. No treatment strategy can be definitely recommended as being superior to the other based on evidence [27], as issues relating to decreases in serum sodium levels and drop in plasma osmolality resulting in episodes of cerebral edema during treatment still remain. The current guidelines recommend the use of 10 to 20 mL/kg of an isotonic crystalloid solution to correct initial severe volume deficit, followed by the replacement with isotonic fluids for a duration of 4 to 24 hours in order to make up for the subsequent fluid deficit [1,27].

Although the use of hypertonic saline has not been extrapolated to its administration during initial volume expansion in the management of DKA, keeping in view the likely pathophysiology of the development of cerebral edema, its use might improve recovery from DKA and prevent the chance of the development of cerebral edema. Moreover, studies show that cerebral edema may also be present in some patients before the initiation of the therapy [28,29], thus the rationale of using hypertonic saline as initial fluid therapy in patients with DKA for the purpose of this study.

Materials and methods

Design

This was an open-label Randomized Control Trial (RCT), conducted in the Emergency and Pediatric Intensive Care Unit (PICU) of a tertiary care children's hospital from November 2011 to April 2013. The trial was approved by the Ethical Committee of the Institute. Patients fulfilling the eligibility criteria were enrolled after obtaining a written consent from parents/ caregivers.

Participants

Subjects with age ≤18 years with a diagnosis of DKA were screened for the inclusion in the study and were included if they met the criteria for having moderate-severe DKA, namely blood glucose >11 mmol/L (200 mg/dl) *and* pH<7.25 or bicarbonate <10 mmol/L *and* ketonemia and/or ketonuria.

Exclusion criteria-

- Patients with a history suggestive of chronic systemic illnesses.
- Patients with underlying neurological abnormalities or concomitant head trauma, meningitis or other conditions which would affect mental status evaluation and monitoring
- Patients who have already received intravenous fluid (≥ 5 mL/kg) prior to the enrollment into the study
- Refusal of consent

Sample size and randomisation-

A total of 40 consecutive eligible patients (20 in each group) were enrolled in the study. Randomization was performed using computer-generated random number sequences.

Treatment protocol-

After enrolling in the study, the patient was randomized to either the Normal Saline (NS) arm or Hypertonic Saline (HS) arm. Children randomized to the NS arm received 20 ml/kg of Normal Saline (0.9% NaCl) solution during the initial 1 hour of fluid therapy, while a 20 mL/kg of Hypertonic Saline (3% NaCl) solution was administered to the children randomized to the HS arm during the initial 1 hour of fluid therapy. The rest of the fluid and management in both arms was as per the written DKA management protocol followed by the treating unit, which is based on the ISPAD clinical practice consensus guidelines [27]. After the initial fluid, all the patients received isotonic fluid (0.9% saline) solution for a duration of 4 hours followed by a fluid solution consisting of 0.45% saline, with an aim to correct the dehydration over 48 hours. We use the two-bag system for fluid management in DKA patients in our unit [30]. Insulin infusion was started after 1 hour, upon the completion of initial fluid therapy. The starting dose of insulin infusion for all patients was 0.1 unit/kg/hr, and the solution was prepared by diluting 50 units of regular (soluble) insulin in 50 mL of Normal Saline (1 mL of the solution=1 unit). All the patients who were enrolled in the study were further managed in the PICU.

Statistical analysis

Discrete variables were analyzed using chi-square test. Continuous variables were analyzed for distribution and skewness. Normally distributed variables were compared using standard t-test for independent samples, while variables showing non-Gaussian distribution were subjected to Mann-Whitney U test. "p-value" of <0.05 was considered to indicate statistical significance.

Comparison and outcome:

- The two groups were compared for:
- Changes in heart rate, blood pressure (Systolic [SBP], Diastolic [DBP] and Mean [MBP]), respiratory rate, sodium levels, chloride levels, lactate, pH and blood sugar at 1, 2, 4, 6, 12, 24 and 48 hours.
- Time needed for the correction of hyperglycemia (< 250 mg/dL).
- Time needed for the resolution of ketoacidosis: defined as bicarbonate >18 mEq/L, venous pH ≥7.3, anion gap <14 mEq/L [any two].
- Cerebral edema: occurrence of an abnormal Glasgow Coma Scale (GCS<14) during the treatment.

Results

The majority of patients were between 11-18 years old (42.5%), while 32.5% of the cases were in the age group of 6-10 years, and 25% in the age group of 2-5 years. Female preponderance was seen in the number of cases (57.5%). In total, 21 out of the 40 patients presented with DKA at onset (i.e. were new cases of T1DM). There was no significant difference between the two groups in the age and sex distribution (p= 0.198 and p=0.333 respectively). The difference between the two groups in terms of the number of patients with new-onset DKA and known diabetic cases was not statistically significant (p=0.527). The majority of the enrolled patients (80%) had altered sensorium at arrival in the emergency department. Fever, abdominal pain and/or vomiting were also a presenting complaint in more than half of the cases. 9 patients were noted to be in circulatory shock at presentation, 4 and 5 patients in the NS group and HS group respectively. In the NS group, 16 patients presented with severe DKA while 4 had moderate DKA. In the HS group, 15 cases had severe DKA and 5 cases presented with moderate DKA. The difference between the two groups in terms of severity of DKA was not statistically significant (p=1.00).

The baseline vital parameters and initial laboratory values (Table I) were comparable in both groups. There was no significant difference between the two groups in terms of serial change in the heart rate, respiratory rate, SBP, DBP, and the MBP. There was a significant improvement in SBP, DBP, and the MBP at 30 mins from baseline observed in both the NS and HS Groups. This improvement was sustained for 48 hours.

The mean baseline sodium was comparable in both groups (Fig. 1). There was a significant increase in serum sodium levels in both groups observed at 30 mins and sustained for 48 hours (p<0.01 in both groups). The serum sodium level was also significantly higher in the HS group compared to NS group at 2 hours of the observation [NS: 139.6±8 vs. HS: 145.3±6.7; p= 0.020]. The maximum serum sodium levels observed in the NS and HS groups were 154 (at 1 hour of the therapy) and 158 (at 2 hours of the therapy) respectively, while the minimum levels observed were 126 (at admission) and 127 (at admission)

Table I. Baseline vital parameters and laboratory values of study population

Parameters	Normal Saline Group MEAN±SD	Hypertonic Saline Group MEAN±SD	p Value
HR (per minute)	135.6±13.41	136±12.71	0.923
RR (per minute)	41.55±5.9	44.35±8.45	0.464
SBP (mm Hg)	85.7±14.1	84.9±9.97	0.837
DBP (mm Hg)	54.9±11.54	54.4±9.59	0.882
MBP (mm Hg)	65.26±12.06	64.55±9.39	0.837
Altered sensorium (number of patients)	16	18	0.661
pH	7.011±0.138	7.013±0.103	0.963
Blood Sugar (mg/dl)	529.95±43.58	540.95±27.91	0.348
Lactate (mmol/L)	1.88±0.62	1.96±0.82	0.747
Sodium (mEq/L)	132.9±6.2	131.2±5.3	0.363
Bicarbonate (mEq/L)	5.6±1.36	5.67±1.91	0.45
Chloride (mEq/L)	107.55±7.95	107.15±7.66	0.872
Potassium (mEq/l)	4.71±0.77	4.81±0.64	0.645
Blood Urea (mg/dl)	39.3±24.07	30.6±12.48	0.160
Creatinine (mg/dl)	0.67±0.35	0.58±0.15	0.278

HR – Heart rate, RR – Respiratory rate, SBP – Systolic blood pressure, DBP – Diastolic blood pressure, MBP – Mean blood pressure

respectively. Subsequently, there was no further difference in the serum sodium concentration between the two groups.

The baseline chloride was comparable in both groups (Fig. 2). There was a significant rise in the chloride concentration from baseline in both groups observed at 30 minutes and sustained for 48 hours. The observed chloride concentration was significantly higher in the HS group compared to the NS group at 30 minutes (NS: 110.55±6.45 vs. HS: 115.05±5.58; p= 0.024), 1 hour (NS: 115.15±7.05 vs. HS: 120.85±6.18; p= 0.010) and 2 hours (NS: 116.8±5.04 vs. HS: 120.6±5.75; p= 0.032) after the initiation of the fluid therapy. However, no statistically significant difference was noted between the groups at 4, 6, 12, 24 and 48 hours.

The lactate levels at admission in both groups were comparable at admission. Significant reduction in the lactate levels was observed in both groups beginning at 1 hour of observation. The baseline pH was comparable in both groups at admission (Fig. 3). The pH in both groups was noted to decrease at 30 minutes (NS: 6.987±0.126 vs. HS: 6.973±0.11; p= 0.723), and 1 hour of the therapy (NS: 6.992±0.135 vs. HS: 6.929±0.117; p= 0.127), and, subsequently, the acidemia gradually resolved. There was no significant difference between the groups in terms of the serial trend of pH.

Blood sugar levels were comparable between the two groups. Significant reduction in blood sugar levels from baseline levels was observed at 4 hours in both groups which were sustained for 48 hours.

Average time needed for the correction of hyperglycemia was 7.13 hours and 7.15 hours in the NS and 3% Saline group respectively (p= 0.974). Time needed for the resolution of acidosis was 17.35 hours in NS group and 18 hours in HS group (p= 0.782).

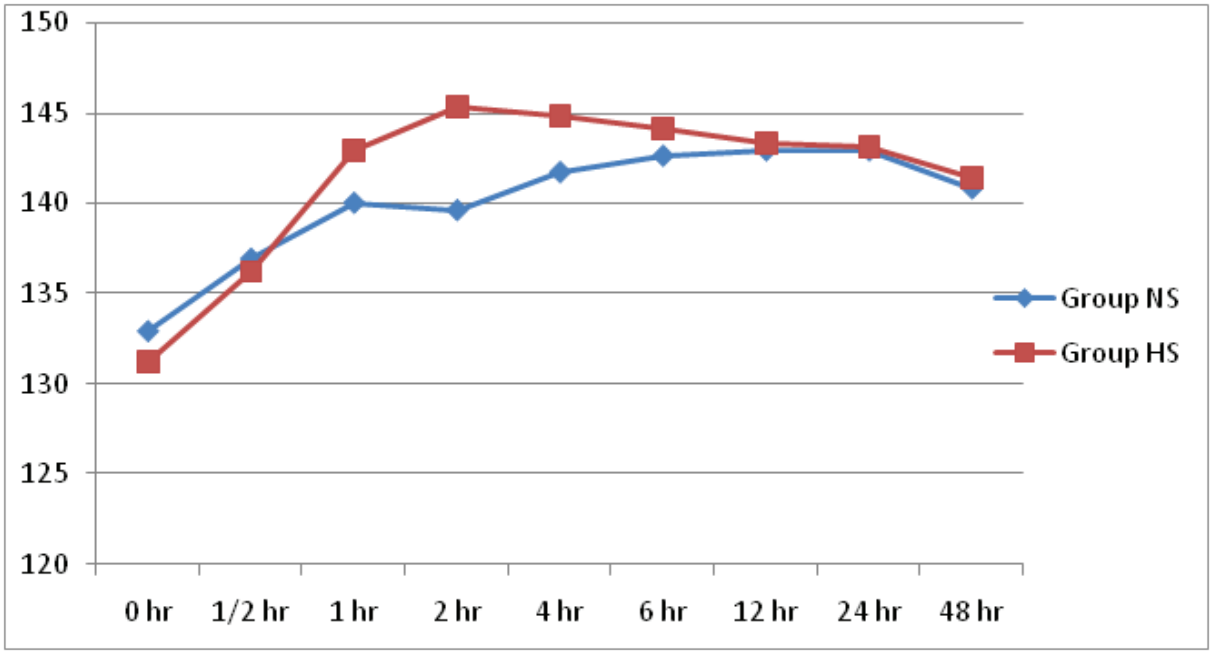

Fig. 1. Serial changes in Sodium levels (in mEq/L)

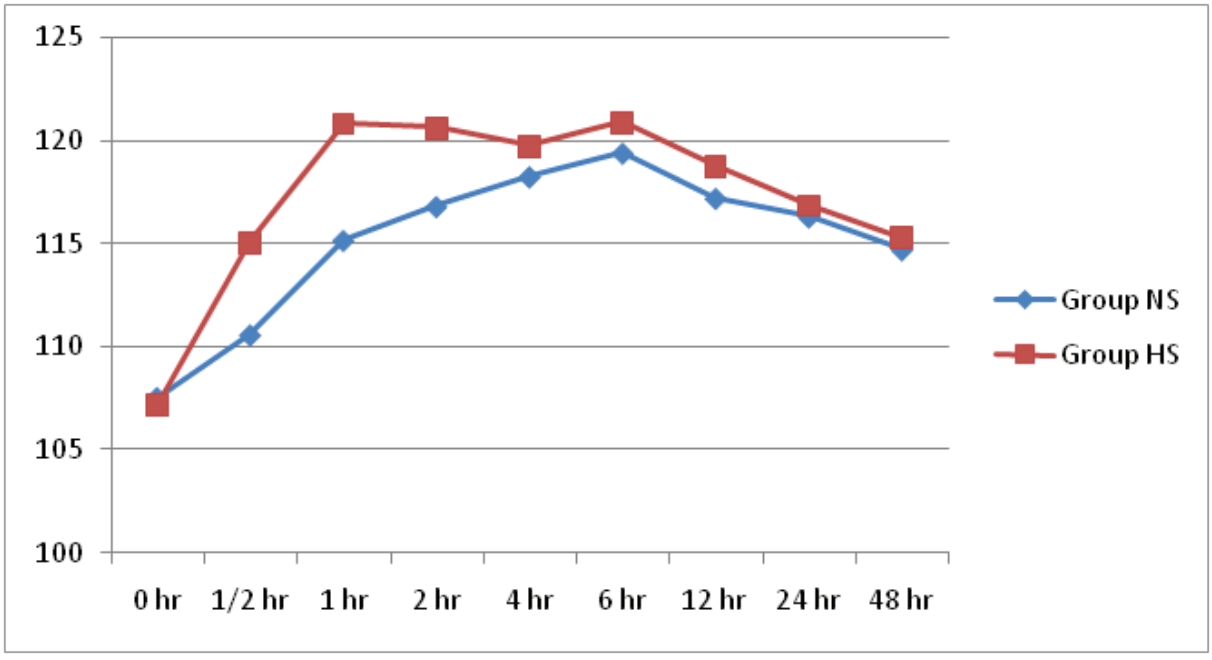

Fig. 2. Serial changes in Chloride levels (in mEq/L)

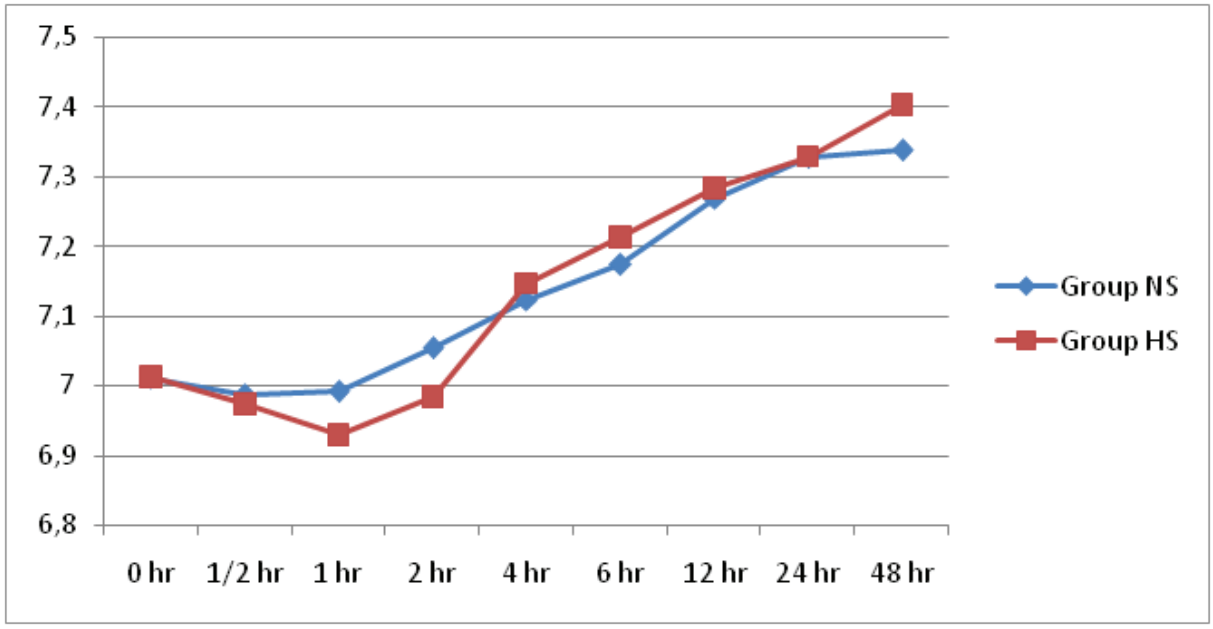

Fig. 3. Serial changes in pH

One patient in each group showed signs of cerebral edema (p=1.000), both of which responded to therapy with mannitol. The respective patients developed evidence of cerebral edema at 6 hours in the Normal Saline group and at 4 hours in the HS group. None of the patients received sodium bicarbonate in either group during the management of DKA.

Discussion

The optimal regimen of the fluid therapy for the management of pediatric DKA has been a matter of debate for years, especially regarding the osmolarity and the rate of fluid used. Cerebral edema is the most feared complication of DKA [3]; the various factors associated with increased incidence of cerebral edema include younger patients, pH<7.1 at presentation, DKA at onset of T1DM, greater volumes of intravenous fluid within the initial 4 hours, rapid drop in serum sodium level, an attenuated rise in measured serum sodium concentrations during the therapy, the administration of bicarbonate and hyperventilation after intubation [10,11].

A study which compared the use of Hypertonic Saline solution and Normal Saline in pediatric septic shock concluded that both 0.9% saline and 3% saline were equally effective as resuscitative fluids for septic shock in children with respect to restoration of hemodynamic stability, vasopressor use, ICU stay, and mortality; with the volume of 3% saline required for resuscitation being approximately half the amount of 0.9% saline [31]. The various effects of hypertonic solutions on infusion are the expansion of plasma volume by mobilizing water along an osmotic gradient, the improvementof myocardial contractility, the reduction in vascular resistance, and the improvement in tissue perfusion, the release of vasodilating substances, especially prostacyclins, and immunomodulatory effects [32]. 3% saline has a tonicity almost 3 times that of 0.9% saline and would be theoretically better retained in the intravascular compartment compared to normal saline. However, the use of Hypertonic Saline also contributes to a higher chloride load compared to Normal Saline. The excess chloride load may be a cause of concern for a delay in the resolution of acidosis because of the hyperchloremic metabolic acidosis (HMA) resulting from it. Also, HMA has been associated with various adverse effects which include decreased gastric mucosal perfusion on gastric tonometry and gastrointestinal symptoms (nausea and vomiting), coagulation abnormalities, and increased need for blood products in postoperative patients, renal vasoconstriction and decreased GFR [33–35]. However, clinical studies have not revealed effects of HMA on clinically adverse implications or outcomes [24,36].

The two groups were comparable in terms of age, gender, and weight. Baseline hemodynamic parameters of HR, RR, SBP, DBP and MBP were comparable. Baseline laboratory parameters were comparable in both groups. Hence, these factors are unlikely to influence the outcome in our study. No significant difference was observed between the two groups in terms of the trends of hemodynamic parameters of HR, SBP, DBP or MBP.

A significant increase in serum sodium levels from baseline was observed at 1 hour of the fluid therapy in both groups, which were sustained for 48 hours. Moreover, the serum sodium level

at 2 hours in the HS group was significantly higher than the serum sodium level at 2 hours in the NS group. This difference between the two groups was not sustained and the values of serum sodium at the other intervals were not significantly different. This can be explained by the higher sodium content of 3% saline and has been observed in previous studies comparing 0.9% saline and 3% saline [31]. A decreasing trend in serum sodium levels in both groups was observed beginning at 12 hours and this can be attributed to the distribution of sodium into extravascular and interstitial compartments and also to the volume expansion [37]. The chloride level was also significantly higher in the HS group compared to the NS group at 1 and 2 hours of the fluid therapy. This statistically significant difference between the two groups was not sustained and was not observed at any other time over 48 hours. This observation can be explained by the greater chloride content of 3% saline, which contains 3 times the concentration of chloride compared to 0.9% saline. The chloride concentrations in both groups at 48 hours were slightly higher than the normal range (97 to 107 mmol/L) [38]. This has been reported previously and is known to occur during the recovery from DKA if fluids like Normal Saline are used during resuscitation [24,39]. However, no adverse events which could be related to hyperchloremia were noted in either group.

The serial changes in pH revealed an interesting phenomenon, whereby there was a statistically non-significant decrease in the pH in both groups from baseline observed at 30 mins and 1 hour of the fluid therapy (Fig. 3). However, the clinical status and the perfusion of the subjects continued to improve during this period, and the pH in both groups started to improve beyond that point of time. This initial decrease in pH might be due to the relatively higher chloride content of the administered fluids, resulting in the magnification of the acidosis due to hyperchloremia. This hyperchloremic acidosis would be added to the underlying ketoacidosis. Another theoretical mechanism could be the mobilization of the preformed lactate from the tissues with the improvement in the perfusion, although the serial trends in measured lactate level do not support this theory.

There was no difference noted between 0.9% Saline and 3% Saline in the time needed to achieve euglycemia and the control of acidosis. One subject in each of the groups had clinical evidence of cerebral edema, which was corrected by the administration of mannitol in both groups. Neuroimaging to confirm the diagnosis of cerebral edema in children with DKA is not routinely performed in our unit [40]. The patient enrolled in the NS group was a 12 years old male, a known case of T1DM who presented with severe DKA and shock. He developed clinical features of cerebral edema at 6 hours and his course was further complicated by an acute kidney injury. The patient in the HS group was a 9 years old female who presented with new-onset severe DKA and circulatory shock, developing features of cerebral edema at 4 hours which was treated with mannitol. No mortality was witnessed in either group.

A limitation of our study was the relatively small sample size and, since DKA-related cerebral edema is rare, a larger study population might be needed to conclusively tell that there is no difference in the two types of fluids. Also, future studies could compare the effect of the different rates of fluid administration during the DKA management.

Conclusions

In our prospective study, in which 3% saline was used as the initial fluid in the children with DKA, hypertonic saline had a similar effect on the hemodynamic parameters as normal saline. We did not observe any significant difference in the development of cerebral edema during the management of DKA between the two groups in our small study population, suggesting that osmotic fluctuations may not be the only variable playing a role in the pathogenesis of DKA-related cerebral edema in children, and that this CE is likely the result of the interplay of various factors. We also noted the pH to decrease in both groups during the initial 1 hour of resuscitation, which did not correlate with the deterioration in clinical status. Thus, 3% saline is comparable to normal saline as initial fluid therapy in children with DKA in terms of improving clinical vital parameters and expanding intravascular volume, but does not provide any additional benefit in prevention of cerebral edema during the therapy and also carries the risk of hyperchloremia.

Ethical committee approval

The project was approved by institutional ethical committee, with approval number LHMC/IEC/2011-S.no 113.

Trial registration

Trial has been registered with the Controlled Trial Register of India with registration number CTRI/2014/07/004751.

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