Outcome of the use of 0.9% saline versus 0.45% saline for fluid rehydration in moderate and severe diabetic ketoacidosis in children

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Abstract

Background: The debate for the optimum sodium concentration in the rehydration solution in diabetic ketoacidosis (DKA) persists till the moment. The aim was to compare the outcome of 0.9% saline versus 0.45% saline in children with moderate and severe (DKA) regarding the effect on serum electrolytes, duration of DKA resolution and the incidence of hyperchloremia.

Results: A retrospective analysis of 121 children with moderate or severe DKA was done. After the initial 4 h in which both groups received normal saline, patients were divided into two groups continuing on 0.9% (N=72) or switched to 0.45% saline (N=49). Serum chloride and Cl/Na ratios were significantly higher in 0.9% saline group at 4 and 8 h. The 0.9% saline group had significantly higher proportion of hyperchloremia at 4 and 8 h (P value: 0.002, 0.02). The median duration of correction of DKA (14 h among 0.9% saline versus 10 h among 0.45% saline) without significant difference (P value= 0.43). The change in plasma glucose, effective osmolarity, corrected Na levels were comparable between groups.

Conclusion: There is an unavoidable iatrogenically induced rise in serum chloride with higher incidence of hyperchloremia with the use of normal saline in rehydration of children presenting in DKA and shock. The use of 0.45% saline as post-bolus rehydration fluid is not associated with a decline in the corrected serum sodium concentration and does not affect the rate of correction of acidosis or rate of drop in blood glucose or duration of DKA resolution when compared to normal saline.

Keywords: DKA, Hyperchloremia, 0.45% saline, Normal saline, Rehydration

Background

Diabetic ketoacidosis (DKA) is an earnest acute complication of type one diabetes which can occur at any age, often can occur at the onset of disease or in the already diagnosed patients due to discontinuation of insulin or improper sick day management [1]. The goal of all existing DKA management protocols to do instantaneous fluid replacement to correct the intracellular dehydration and the ongoing electrolytes losses [2]. The fluid replacement must be prompt but very careful to avoid the cerebral edema [3]. Cerebral edema is known to be the leading cause of death in diabetic ketoacidosis (DKA) and the treatment centers around avoiding this complication of management [4]. Argument is still present regarding the type, amount, and rate of intravenous (IV) replacement fluid therapy. International Society for Pediatric and Adolescent Diabetes (ISPAD), 2018 © The Author(s). 2021 Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.
consensus guidelines advise that after the initial resuscitation, fluids used may be in the form of solution with tonicity ranging between 0.45 and 0.9% according to the clinical evaluation of the patients [2], but till now based on the present evidence there is no particular treatment strategy preferable than the other [5].

The rationale for the use of half NS is to minimize the risk of cerebral edema through declined rise in corrected serum sodium and drop in effective serum osmolality [6].

The normal saline (0.9%) is the most appropriate physiological solution used for the initial rehydration however it carries the risk of increasing the chloride load which results in development of hyperchloremic metabolic acidosis [7]. Hyperchloremic metabolic acidosis (DKA) may be observed during management and is caused either by urinary loss of bicarbonate precursors as ketones and/or iatrogenically from chloride administration in rehydration fluids [8]. The acidifying effect of chloride was blamed in masking the resolution of DKA [9]. With the shortage of availability of costly laboratory investigations (such as β-hydroxybutyrate) in many developing countries identifying the cause of protracted metabolic acidosis in DKA patients is not always feasible. In the current study we aimed to compare the outcome of using 2 different concentrations of sodium in the rehydration fluids (0.9% NS versus 0.45% saline) in moderate and severe DKA with regards to the effect on serum electrolytes, effective osmolarity, duration of DKA resolution, the incidence of hyperchloremia.

**Methods**

**Participants**

This is a retrospective cohort study included 49 children 1–15 years with moderate or severe DKA who received rehydration solution using 0.45% saline at intermediate care unit of Diabetes, Endocrine, and Metabolism Pediatric Unit (DEMPU), Children’s Hospital over the period from August to October 2016. This was compared to historical cohort of 72 patients with moderate and severe DKA who received 0.9% saline as rehydration solution at the same unit during the preceding period from March to July 2016.

DKA was defined as having blood glucose >200 mg/dL (11.4 mmol/L), a venous pH <7.30 or a plasma bicarbonate level <15 mmol/L, and ketonemia or ketonuria and arterial blood gases (ABG) showed moderate DKA if arterial pH >7.1 and <7.2 with bicarbonate <10 and >5mmol/L or severe DKA if arterial pH <7.1, bicarbonate <5 mmol/L [10]. Patients were excluded if they had (1) any neurological abnormality or Glasgow Coma Scale (GCS) <13, (2) received any therapy (HCO3, mannitol, fluid, insulin) before admission to our hospital or were referred after the first 4 h of management, (3) any cause of acidosis other than DKA, (4) corrected serum sodium ≤130 and ≥150 mmol/L.

Data on age, sex, onset of diabetes whether newly diagnosed or known, duration of diabetes, precipitating factor for DKA development, duration of insulin infusion, dose of insulin infusion, volume of fluid infused, and the use of bicarbonate therapy were collected.

All patients included in the study were managed according to ISPAD guidelines for DKA treatment [2] which is the protocol adopted at our unit which allow consistency concerning treatment. The protocol adopted at our unit as follows:

All included patients were managed accordingly: immediate measurement of blood glucose and capillary BHOH using glucometer (Free style Optium, Abbott) were performed when available, weighing the patient and assessment of level of consciousness according to Glasgow Coma Scale [11] and severity of dehydration, full examination for a precipitating factor, and laboratory investigations

Subsequent clinical and biochemical monitoring included hourly assessment of vital signs, hourly (or more frequently as indicated) neurological observations (GCS) for warning signs and symptoms of cerebral edema, hourly capillary blood glucose concentrations, measurement of serum glucose, Na, K, CL, BUN, creatinine, and blood gases at the time of admission and every 4 h till DKA resolution. N.B. Blood glucose was measured in mg/dl, where 1mg/dl=18mmol/L.

- Calculation of:
  - Anion Gap using the following formula:
    - (Na+) – (HCO3- + Cl-). Normal= 12 ± 2 mmol/L
  - Corrected Na = Measured Na+2(blood glucose –100)/100
  - Serum osmolality (mosmol/kg); effective:
    - 2 (Na) + glucose/18 [12].
  - Hyperchloremia is defined as ratio of chloride: sodium [Cl-: Na+] > 0.79 [13].

- Fluid therapy

A. Resuscitation fluid (0.9% saline) was used for restoration of the peripheral circulation. The volume administered is 10 ml/kg over 1–2 h, this bolus fluid is given to patients with severe volume depletion and may be repeated until tissue perfusion is adequate. However, shocked patients with impaired peripheral perfusion were given 20 ml/kg as rapidly as possible.

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B. Deficit replacement fluid therapy: First 4 h
0.9% saline was used then fluid with tonicity either 0.45% saline (half NS) or 0.9% saline was used.

C. Patients were divided into two groups according to the type of rehydration fluid used after 4 h: group 1 (N=72): Rehydration solution using 0.9% saline; group 2 (N=49): Rehydration solution using 0.45% saline provided that those patients had normal Na concentration. The volume of total fluid replacement therapy and its rate were calculated based on data from Darrow study [2, 14].

D. Glucose 10% was added to replacement fluids (ratio 1:1) when plasma glucose reached approximately 300 mg/dL or if the rate of blood glucose dropped very rapidly (>88 mg/dL/h) after initial fluid expansion.

E. Potassium replacement was initiated after measurement of its serum level at concentration of 40 meq/L after initial volume expansion and concurrent with starting insulin therapy. If the patient was hyperkalemic, potassium replacement therapy was postponed until urine output was documented.

F. Bicarbonate therapy was considered in cases of severe acidosis (PH<6.9) with life threatening cardiac decompensation and also indicated in cases of life threatening hyperkalemia. It is given intravenously at a dose of 1–2 meq/kg over 1 h.

G. Cerebral edema: monitoring of clinical symptoms and signs suggestive of development of cerebral edema (headache, deterioration of neurological status, development of any neurological deficit, convulsion, Cushing’s triad) is a crucial part of DKA management. Once clinically suspected, immediate management is initiated. The rate of rehydration fluid is adjusted to maintain good perfusion and normal blood pressure while avoiding overhydration. Hypertonic solution (mannitol or hypertonic saline) is given slowly over 10–15 min. Other measures to decrease intracranial pressure must be applied (elevation of the head 30°, intubation with hyperventilation if patient had severe deterioration of neurologic status).

- Insulin therapy

Insulin infusion was started after 1 h of initiation of volume expansion by fluid replacement therapy at a dose ranging from 0.05 U to 0.1 U/kg/h. Criteria for shifting to subcutaneous insulin included resolution of acidosis (PH ≥ 7.3, HCO3≥15 mEq/L), a good general condition and hemodynamic stability, tolerating oral intake, patient no longer on vasopressors and BOHB < 3 mmol/L.

The study protocol received approval from our Institutional Research Ethics Committee.

Statistical analysis
Data were statistically described in terms of mean ± standard deviation (± SD), median and range for numerical variables or frequencies, and percentages for categorical variables. Comparison of numerical variables between the study groups was done using Student’s T test. For comparing categorical data, chi-square (χ²) test was performed. Exact test was used instead when the expected frequency is less than 5. P values less than 0.05 was considered statistically significant. All statistical calculations were done using IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Results
The total number of included patients was 121 participants. They were divided into two groups according to the type of rehydration fluid used after 4 h: group 1 (0.9% saline) included 72 participants and group 2 (0.45% saline) included 49 participants. Clinical characteristics and initial biochemical parameters at admission are illustrated in Table 1.

|                | Group 1 (N=72) | Group 2 (N=49) |
|----------------|----------------|----------------|
| Age            | 7 years (range 1–14) | 8 years (range 1–13) |
| Gender         | 65 females (53.7%) | 56 males (46.3%) |
| Severe DKA     | 27 patients (22.3%) | 94 patients (77.7%) |
| Moderate DKA   | 49 patients (45.5%) | 55 patients (45.5%) |
| Dehydration    | 94 patients (77.7%) | 72 patients (54.5%) |

Our patients were 65 females (53.7%) and 56 males (46.3%), their ages ranging from 1 to 14 years and all patients were neurologically free with GCS≥13. The patients were divided according to the degree of dehydration at presentation into moderate dehydration 27 patients (22.3%) and severe dehydration 94 patients (77.7%). Of the whole group, 55 patients were known to have diabetes (45.5%) while for 66 patients (54.5%) DKA was their first presentation. Concerning the severity of DKA, 49 patients had moderate DKA while 72 patients had severe DKA. Corrected sodium levels of our patients at presentation and after 4 h (at time of change of fluid) ranged from 135 to ≤ 150 and their ABG correlated with the criteria of moderate and severe DKA. BHOH at presentation ranged from 3.1–8.3 mmol/L. The duration of correction of ketoacidosis among the whole group ranged from 6 to 40 h.

The age of participants of both groups was comparable, the median age of normal saline NS (group 1) was 8 years (range, 1–13) while that of group 2 (half normal saline) was 7 years (1–14) P value=1.000. The number (%) of patients in NS group who had new onset T1DM was 47/72 (58.3%) compared to 24/49 (49%) in the other group, the difference was not significant P value=0.59.
Table 1 Demographic and baseline biochemical variables at time of admission

| Parameters                                      | Group 1 (0.9%) (N=72) | Group 2 (0.45%) (N=49) | P value |
|------------------------------------------------|-----------------------|------------------------|---------|
| Age (years) (mean ± SD)                        | 7.11 ± 3.77           | 7.39 ± 3.87            | 0.69    |
| Sex n (%)                                       |                       |                        |         |
| Male                                           | 39 (45.8%)            | 17 (34.7%)             | 0.03    |
| Female                                         | 33 (54.2%)            | 32 (65.3%)             |         |
| Degree of dehydration n (%)                    |                       |                        |         |
| Moderate                                       | 17 (23.6%)            | 10 (20.4%)             | 0.43    |
| Severe                                         | 55 (76.4%)            | 39 (79.6%)             |         |
| DKA presentation n (%)                         |                       |                        |         |
| Newly diagnosed                                | 42 (41.7%)            | 24 (51%)               | 0.59    |
| Known to have diabetes                         | 30 (58.3%)            | 25 (49%)               |         |
| Shock therapy (ml/kg) n (%)                    |                       |                        | 0.001   |
| No                                             | 15 (20.8%)            | 25 (51%)               |         |
| 10 ml/kg                                       | 15 (20.8%)            | 3 (6.1%)               |         |
| 20 ml/kg                                       | 19 (26.4%)            | 4 (8.2%)               |         |
| 30 ml/kg                                       | 23 (31.9%)            | 17 (34.7%)             |         |
| Rate of fluids (maintenance + deficit) (ml/kg/h) (mean ± SD) | 99.93 ± 26.88 | 94.16 ± 31.13 | 0.34 |
| Actual fluid intake (L) (median)               | 4.73                  | 4.45                   | 0.39    |
| Patients received bicarbonate therapy n (%)    | 13 (18.1%)            | 11 (22.4%)             | 0.36    |
| Mean insulin dose (IU/kg/h) mean ± SD          |                       |                        |         |
| 1st 6 h                                        | 0.11 ± 0.02           | 0.1 ± 0.01             | 0.80    |
| After 1st 6 h                                  | 0.11 ± 0.03           | 0.1 ± 0.02             | 0.48    |
| Duration of DKA resolution (hours) (median, range) | 14 (6–40)           | 10 (6–38)              | 0.43    |
| Glucose (mg/dl) (mean ± SD)                    | 532.67 ± 157          | 550.14 ± 139.64        | 0.53    |
| Serum Na (meq/L) (mean ± SD)                   | 133.58 ± 4.56         | 134.16 ± 4.24          | 0.47    |
| Corrected Na (meq/L) (mean ± SD)               | 142.4 ± 4.54          | 143.12 ± 4.75          | 0.40    |
| Serum CL(meq/L) (mean ± SD)                    | 102.67 ± 5.02         | 102.91 ± 4.49          | 0.81    |
| CL:Na ratio (mean ± SD)                        | 0.77 ± 0.03           | 0.77 ± 0.18            | 0.97    |
| BHOB (mmol/L) (mean ± SD)                      | 5.44 ± 1.13           | 5.43 ± 1.55            | 0.95    |
| PH (mean ± SD)                                 | 7.08 ± 0.099          | 7.06 ± 0.12            | 0.39    |
| HCO3 (meq/L) (mean ± SD)                       | 5.8 ± 2.5             | 6 ± 2.7                | 0.65    |
| Anion gap (mean ± SD)                          | 25.9 ± 4.4            | 24.6 ± 3.5             | 0.12    |
| Creatinine (mg/dl) (mean ± SD)                 | 0.75 ± 0.24           | 0.76 ± 0.31            | 0.81    |
| Effective osmolality (mosmol/L) (mean ± SD)    | 297.1 ± 11.9          | 300.9 ± 11.3           | 0.07    |
| Severity of DKA n (%)                          |                       |                        |         |
| Moderate (n=49)                                | 29 (40.3%)            | 20 (40.8%)             | 0.95    |
| Severe (n= 72)                                 | 43 (59.7%)            | 29 (59.2%)             |         |
Precipitating factors for DKA were similar in both groups with infections representing 46.7% in NS group and 44% in 0.45% saline. There was no discernible precipitant in 46.7% of NS group and none in 52% of the other group.

Significantly more patients in the NS group needed shock therapy (79.2% versus 49% in 0.45 saline group, \( P = 0.001 \)). Rates of fluids, total fluid intake, severity of DKA, mean insulin doses/hour, and number of patients needing sodium bicarbonate were comparable (Table 1).

The initial laboratory data at the time of recruitment (serum glucose, corrected serum Na, serum Cl, Cl:Na ratio, PH, HCO3, creatinine, effective osmolarity, and anion gap) were comparable between two groups (Table 1). Corrected serum sodium was comparable in both groups throughout the study period. Serum chloride and Cl/Na ratios were significantly higher in NS group at 4 and 8 h after initiation of therapy. Serum chloride levels rose significantly by 2.1 mmol/L between hour 4 and hour 8 in NS group \( (P = 0.007) \) and by 1.7mmol/L in 0.45% group \( (P = 0.37) \). The NS group (I) had significantly higher proportion of hyperchloremia at 4 and 8 h \( (P \text{ value}, 0.002, 0.02 \text{ respectively}) \). On the other hand, the anion gap was significantly higher at 4 and 8 h in 0.45% saline-receiving patients with \( (P \text{ values}, 0.006, 0.000 \text{ respectively}) \). At the start, BHOH levels in both groups had a mean value of 5.5 ± 1.1 vs 5.4 ± 1.5 \( (P \text{ value}=1.000) \). Differences continued to be insignificant throughout the study period (Table 2). Concerning the course of blood glucose during correction, there was no significant difference between two groups at 4 and 8 h \( (P \text{ value}=0.45, 1.00 \text{ respectively}) \). Effective serum osmolarity was comparable during the study period. Figures 1, 2, 3 and 4 show blood chloride, glucose, anion gap, and bicarbonate trends in the two groups throughout the study period.

| Table 2 | The course of PH, HCO3, corrected Na, CL, Cl:Na ratio, capillary BHOH, anion gap, glucose, and effective osmolarity at 4 and 8 h among both groups. |
|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Laboratory variables | Timing (hours) | Group 1 0.9% NS (N=72) Mean ± SD | Group 2 0.45% NS (N=49) Mean ± SD | \( P \) value |
| PH | 4 | 7.16 ± 0.1 | 7.14 ± 0.13 | 0.37 |
| | 8 | 7.23 ± 0.09 | 7.20 ± 0.1 | 0.55 |
| | At recovery | 7.35 ± 0.04 | 7.36 ± 0.05 | 0.21 |
| HCO3 (meq/L) | 4 | 7.34 ± 3.4 | 6.98 ± 3.18 | 0.56 |
| | 8 | 9.8 ± 3.6 | 8.8 ± 3.5 | 0.5 |
| | At recovery | 16.9 ± 1.37 | 17.02 ± 1.96 | 0.82 |
| Serum Na (meq/L) | 4 | 136.28 ± 4.94 | 135.94 ± 4.64 | 0.70 |
| | 8 | 137.3 ± 5.4 | 138.4 ± 6.6 | 0.98 |
| | At recovery | 140.7 ± 6.5 | 140.3 ± 5.4 | 0.69 |
| Corrected Na (meq/L) | 4 | 142 ± 4.8 | 143.1 ± 4.6 | 0.18 |
| | 8 | 141 ± 6 | 143.4 ± 6.2 | 0.12 |
| | At recovery | 140.7 ± 6.5 | 140.3 ± 5.4 | 0.69 |
| CL (meq/L) | 4 | 106.28 ± 5.1 | 103 ± 3.6 | 0.002 |
| | 8 | 108.4 ± 5.6 | 104.7 ± 6.1 | 0.06 |
| CL:Na ratio | 4 | 0.78 ± 0.03 | 0.76 ± 0.02 | 0.001 |
| | 8 | 0.79 ± 0.02 | 0.76 ± 0.03 | 0.000 |
| Anion gap | 4 | 22.8 ± 5.1 | 26.1 ± 5 | 0.002 |
| | 8 | 18.5 ± 4.5 | 25.8 ± 5.6 | 0.000 |
| BHOH | 4 | 4.6 ± 1.1 | 4.9 ± 1.5 | 0.97 |
| | 8 | 4.05 ± 1.1 | 4.09 ± 1.4 | 0.88 |
| Plasma glucose (mg/dl) | 4 | 389 ± 166 | 433 ± 145 | 0.35 |
| | 8 | 307.3 ± 134 | 324.8 ± 124.5 | 0.51 |
| Effective serum osmolality (mosmol/L) | 4 | 293 ± 12.4 | 296 ± 12.7 | 0.21 |
| | 8 | 291 ± 12.5 | 295 ± 13 | 0.22 |
| Hyperchloremia \( n \) (%) | 0 | 9 (15.3%) | 4 (11.1%) | 0.4 |
| | 4 | 16 (28.6%) | 2 (4.9%) | 0.002 |
| | 8 | 15 (34.9%) | 4 (12.5%) | 0.02 |
Although the median duration of correction of ketoacidosis was longer among normal saline group than 0.45% saline (14 versus 10 h), it did not reach statistically significant difference ($P$ value= 0.43). None of recruited patients developed brain edema or renal dysfunction. All recruited patients were discharged without any alteration in their neurological status compared to the previous status before DKA development.

Comparison between patients who did not receive any shock therapy in both groups (0.9% versus 0.45%) was shown in Table 3. The comparison revealed statistically significant difference between both groups regarding CL:Na ratio and anion gap at 8 h ($P$ values, 0.007, 0.000) respectively. However, the other compared parameters did not show significant difference.

Discussion

The management of DKA should be aimed at restoration of normal homeostasis and tissue perfusion with a gradual reduction of acidosis and blood glucose to avoid possible complications. Isotonic (normal saline NS) is the fluid most commonly used for resuscitation initiation of rehydration during DKA management in pediatric and adult guidelines. Recently, however, there has been increasing awareness that the non-physiological nature can lead to hyperchloremic metabolic acidosis and acute renal injury as a result of renal vasoconstriction [15]. Other investigators have not found a detrimental effect of NS on overall mortality or renal functions [16]. The debate for replacing NS by other solutions with different Na concentrations persists till the moment. In our study, we compared the use of two solutions in the rehydration of children with moderate and severe DKA (NS which contains Na 154 meq/L) and (0.45% NS which contains Na 75 meq/L).

In the current study, the serum bicarbonate level and PH were comparable between both groups at the time of start of management and throughout the study with no significant difference between both groups. This is in agreement to what reported by Savas-Erdeve et al. that the use of an isotonic solution did not create a difference in HCO3 or PH levels when compared to hypotonic solution with lower Na concentration [3].

The primary cause of acidemia in DKA is thought to be ketoacidosis, lactic acidosis, and renal dysfunction can be contributing factors [13]. Hyperchloremia predominates instead in the recovery phase. Misinterpretation of hyperchloremic acidosis may obscure the detection of ketoacidosis resolution [8]. A simple bedside test with detection of BOHB levels can solve the
problem, unfortunately this test is not always available in limited resource settings. Although both groups of patients in our study presented with comparable chloride levels (102.7 vs 102.9mmol/L) on admission, differences became evident as early as 4 h into the study when both groups had been receiving NS and before rehydration fluids for the second group were changed (106.3 vs 103mmol/L). It is important to note that more patients in group 1 had received anti-shock treatment with NS boluses (79.2% vs 49%) and this had already impacted on their serum chloride levels. Additionally, comparison between patients who did not receive any shock therapy in both groups (0.9% versus 0.45%) revealed no significant difference regarding chloride levels. Previous studies have found the highest chloride levels to occur with periods of rapid rehydration with large amounts of normal saline [17]. However, anti-shock treatment can be lifesaving in some situations for restoring perfusion and improving glomerular filtration.

Eight hours into the study (4 h after group 2 had been switched 0.45% saline) serum chloride levels had climbed a further 2.1mmol/L in group 1 and 1.7mmol/L in group 2 (108.4 vs 104.7mmol/L). The NS group had significantly higher proportion of patients with hyperchloremia at 4 and 8 h. Concerning the chloride, sodium ratio, the NS group had significantly higher ratio at 4 and 8 h than those in the 0.45% saline group. In contrast, such frequency of patients with hyperchloremia was not seen in the 0.45% NS group which suggests that the choice of rehydration fluid might be an important factor for the development of hyperchloremia. This comes in line with several studies that showed that patients who received normal saline had significantly higher incidence of hyperchloremic acidosis [18–20].

The median duration of management till DKA resolution was longer among the group of NS (14 h) versus (10 h) among 0.45% saline group but it did not reach statistical significance (P value=0.43). We speculate that
the prolonged duration of insulin infusion among normal saline group due to misinterpretation of hyperchloremic acidosis as ongoing ketoacidosis but unfortunately lack of availability of chloride levels after 8 h was a limitation in this study.

Basnet et al. found hyponatremia to be induced in patients receiving 0.45% from the start of DKA management. This did not occur in patients switching to 0.45% after an initial period of NS treatment [18]. Our findings concur with those of that study since we found no significant differences in serum sodium levels between the two groups throughout the course of DKA management. This is also in line with Rother et al. who found that rehydration using 75 mmol/L of Na did not lead to decline in the serum Na level [21]. However, this contradicts Toledo et al. who reported a higher plasma Na level with the use of an isotonic perfusate than that achieved with a perfusate with a lower Na content [22]. Savas-Erdeve et al. did not find any difference in plasma Na and plasma corrected Na between patients who received rehydration solutions containing 75mEq/L and patients received 100 mEq/L of Na. Gosmanov et al. recommend in adult DKA management that if patients are to be switched to 0.45% saline after an initial 4-h resuscitation

| Laboratory variables | Timing (hours) | Group 1 (0.9% NS (N=15)) Mean ± SD | Group 2 (0.45% NS (N=25)) Mean ± SD | P value |
|----------------------|---------------|-----------------------------------|-----------------------------------|--------|
| PH                   | 0             | 7.14 ± 0.07                       | 7.13 ± 0.06                       | 0.60   |
|                      | 4             | 7.21 ± 0.09                       | 7.22 ± 0.05                       | 0.62   |
|                      | 8             | 7.29 ± 0.09                       | 7.26 ± 0.04                       | 0.42   |
|                      | 12            | 7.32 ± 0.04                       | 7.34 ± 0.04                       | 0.56   |
| HCO3 (meq/L)        | 0             | 8.4 ± 1.6                         | 8.02 ± 1.8                        | 0.49   |
|                      | 4             | 10.05 ± 2.8                       | 9.41 ± 2.1                        | 0.42   |
|                      | 8             | 13.3 ± 3.01                       | 11.4 ± 1.9                        | 0.07   |
|                      | 12            | 13.25 ± 2.8                       | 12.6 ± 1.3                        | 0.67   |
| Serum Na (meq/L)    | 0             | 133.8 ± 3.8                       | 134 ± 4.2                         | 0.85   |
|                      | 4             | 136.3 ± 5.7                       | 135.4 ± 5.3                       | 0.62   |
|                      | 8             | 136.3 ± 4.6                       | 136.3 ± 6.6                       | 0.98   |
| Corrected Na (meq/L)| 0             | 141.8 ± 4.7                       | 142 ± 4.6                         | 0.91   |
|                      | 4             | 140.8 ± 5.2                       | 142.3 ± 5.1                       | 0.37   |
|                      | 8             | 141.1 ± 6.1                       | 136.3 ± 4.6                       | 0.40   |
| CL (meq/L)          | 0             | 102.4 ± 4.9                       | 102.7 ± 4.3                       | 0.86   |
|                      | 4             | 104.7 ± 3.8                       | 102.6 ± 3.5                       | 0.12   |
|                      | 8             | 107.6 ± 4.8                       | 103.6 ± 4.2                       | 0.08   |
| CL:Na ratio         | 0             | 0.77 ± 0.03                       | 0.76 ± 0.02                       | 0.94   |
|                      | 4             | 0.76 ± 0.01                       | 0.75 ± 0.02                       | 0.21   |
|                      | 8             | 0.79 ± 0.01                       | 0.76 ± 0.03                       | **0.007** |
| Anion gap           | 0             | 23.6 ± 2.9                        | 22.8 ± 2.9                        | 0.48   |
|                      | 4             | 21.4 ± 5.02                       | 23.7 ± 4.03                       | 0.16   |
|                      | 8             | 13.8 ± 2.03                       | 11.4 ± 1.9                        | **0.000** |
| BHOH                | 0             | 4.8 ± 0.94                        | 5.32 ± 1.6                        | 0.26   |
|                      | 4             | 3.9 ± 1.1                         | 4.2 ± 1.3                         | 0.48   |
|                      | 8             | 3.07 ± 0.88                       | 3.4 ± 1.1                         | 0.43   |
| Hyperchloremia n (%)| 0             | 2 (13.3%)                         | 2 (8%)                            | 0.63   |
|                      | 4             | 2 (13.3%)                         | 1 (4%)                            | 0.22   |
|                      | 8             | 2 (13.3%)                         | 2 (8%)                            | 0.63   |
| Duration of DKA resolution (hours) | 9.87 ± 3.58 | 8.80 ± 3.317 | 0.34 |
with NS, patients must be both hemodynamically stable and have a normal to high corrected serum sodium level. If patients subsequently become hyponatremic, treatment should revert to NS [23].

Concerning the course of glycemia, the initial glucose level and its rate of decline did not show any significant differences between the two studied groups. This is noted also in other studies using rehydration solutions with different Na concentrations [3, 18, 20]. In addition, there was no significant difference between the two studied groups as regards the rate of insulin infusion. This is in line with what was reported by Yung et al. [20]. This denotes that insulin infusion dose is not affected by the change in Na concentration in the rehydration fluids during DKA management.

Capillary BHOH levels did not differ between the two groups throughout the study period but the anion gap dropped faster in the group receiving NS, significantly lower levels being demonstrable as early as 4 h into the management of DKA. It is speculated that since BHOH levels were equal in both groups throughout, it was the higher levels of serum chloride in the NS patients that narrowed the gap in this group.

Limitations of the study
The retrospective nature of the study is the main limitation. Future prospective studies with larger number of participants with more emphasis on determination of brain injuries associated with DKA management and its risk factors are needed.

Conclusion
There is an unavoidable iatrogenically induced rise in serum chloride with the use of normal saline in the initial resuscitation of children presenting in DKA and shock. The incidence of hyperchloremia is significantly less with the use of half normal saline. Half normal saline is not associated with a decline in the corrected serum sodium concentration and does not affect the rate of correction of acidosis or rate of drop in blood glucose or duration of DKA resolution when compared to normal saline solution as post-bolus rehydration fluid therapy in pediatric patients with DKA.

Abbreviations
DKA: Diabetic ketoacidosis; IV: Intravenous; ISPAD: International Society for Pediatric and Adolescent Diabetes; DEMPU: Diabetes, Endocrine, and Metabolism Pediatric Unit; GCS: Glasgow Coma Scale; ABG: Arterial blood gases; β-HOH: β-Hydroxybutyrate; NS: Normal saline

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Authors’ contributions
Dr. MH shared in study design, interpretation of data, statistical analysis, drafting and writing manuscript, and final revision of the version to be published. Dr. NB revised the results and participated in writing the manuscript. Dr. HSE did the laboratory work up. Dr. MI was the consultant who directly oversaw the progress of the cases. Drs. HM and SA shared in design of study, data collection, interpretation of data, drafting of the article, and final revision for publication. Dr. NA participated in data collection and sorting for statistical analysis, drafting of the article, writing the manuscript, and final revision for publication. All authors have read and approved the manuscript.

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Data is available with the authors on request.

Declarations
Ethics approval and consent to participate
Received approval from Research Ethics Committee of Kasr Alainy, Faculty of Medicine, Cairo University (number: E141014); consent to participate was not applicable.

Consent for publication
Not applicable.

Competing interests
All authors declare no conflict of interest.

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