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Original Article

Insulin infusion responses in diabetic ketoacidosis alone and with a mixed hypochloremic alkalosis

Deepashree Gupta [a], Anju Prasad [b], Faisal Siddiqui [b], Sujata Sitaula [b], Stewart G. Albert [b,*]

[a] Division of Endocrinology, University of California, Los Angeles, United States
[b] Department of Internal Medicine, Division of Endocrinology, Saint Louis University School of Medicine, United States

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ABSTRACT

Aims: Although diabetic ketoacidosis (DKA) commonly presents as a pure diabetic ketoacidosis (PDKA), up to 30% of cases may be associated with a mixed hypochloremic metabolic alkalosis (HMA). It is unknown whether there is a difference in treatment outcomes between these two entities. We evaluated an insulin infusion protocol (IIP), previously validated for hyperglycemia management in ICU's, for the management of PDKA and HMA.

Materials and methods: A retrospective case series/cohort study of 41 DKA admissions was further characterized as having PDKA or HMA. HMA was defined in those having an elevated delta-delta gradient (ΔAG-ΔHCO3) $\geq$ 5 mmol/L and base excess chloride (BE_{Cl}) > 2.7 mmol/L. The main outcome measures were times to recovery of glucose levels to $\leq$250 mg/dL and of anion gap to $\leq$12 mmol/L.

Results: The initial serum glucose was 553 ± 265 mg/dL, serum bicarbonate of 8.8 ± 5.1 mmol/L, and venous pH 7.13 ± 0.2). Recovery of glucose occurred in 5 h: 25 min (±3 h:39min), and for anion gap in 11 h:25 min (±6 h:56min). HMA compared with PDKA had a delayed recovery of serum glucose (7 h: 23min ± 3 h: 35min vs. 4 h: 31min ± 3:h:21min, p = 0.017), which was due to the higher initial level of glucose (p = 0.02) rather than level of BE_{Cl} (p = 0.17). There was no difference in time to anion gap closure between the PDKA and HMA.

Conclusions: Correction of hyperglycemia and acidosis in PDKA as well as in HMA was managed through the IIP. The simultaneous fluid and electrolyte management corrected the hypochloremic alkalosis.

1. Introduction

Diabetic ketoacidosis (DKA) commonly presents as a pure diabetic ketoacidosis (PDKA), however up to 30% of cases may be associated with mixed acid-base abnormalities (HMA) [1,2]. Recently, it has been shown that the concomitant HMA hypochloremic alkalosis may be independent of vomiting, but related to the level of total serum ketones [3]. Pathogenesis of this alkalosis is not established but it has been suggested that the hypochloremia may be caused by a chloride shift into intracellular compartments [4] or due to enhanced renal chloride excretion [3]. It was not clear from these studies [3] whether PDKA or HMA differed in response to standard insulin therapy for DKA.

A new unified insulin infusion protocol (IIP) was instituted at Saint Louis University Hospital in 2014 and made available [5] to treat DKA well as patients with hyperglycemia in the intensive care units [6–9] or in the postoperative cardiac care units [10,11]. The protocol was developed to eliminate complexity of some insulin infusion protocols [10,12] and to mitigate hypoglycemia found in others [6,13–16]. While the IIP was identical for the management of hyperglycemia and DKA, fluid and electrolyte management were tailored for specific abnormalities encountered in DKA [17]. We therefore sought to determine whether 1) this combined IIP was comparable to existing protocols for DKA, and 2) whether the IIP was effective in treating both PDKA as well as HMA.

2. Materials and methods

A retrospective case series/cohort study of patients admitted to the intensive care units of St Louis University Hospital was evaluated from January through June 2016. Retrospective anonymous data was collected from standard electronic medical records and was considered exempt by the institutional review board of the

* Corresponding author. Division of Endocrinology, Saint Louis University School of Medicine, 1402 South Grand Blvd, St. Louis, MO, 630104, United States.
E-mail address: stewart.albert@health.slu.edu (S.G. Albert).

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university. Patients were considered to have diabetic ketoacidosis if they presented with hyperglycemia (blood glucose $\geq$250 mg/dL), venous pH $\leq$ 7.30, serum HCO3 $\leq$18 mmol/L and a serum beta hydroxybutyrate $\geq$ 2 mmol/L.

The IIP derivation and assumptions were described previously [5]. Briefly, the rate of insulin infusion is a weight based protocol. At very high serum glucose levels the insulin infusion rate is 0.18 units/kg/h (which eliminates the need for insulin boluses) [17,18]). The infusion rate decreases proportionately with decreasing serum blood glucose values, and the rate abruptly declines at blood glucose levels less than 160 mg/dL to avoid hypoglycemia. The insulin infusion rate is pre-calculated and stored in the electronic medical record system (EPIC Systems Corporation, Verona, WI) in weight-based columns (ranging from 40 kg through 150 kg with increments of 10 kg) and the insulin infusion rates are titrated according to the current blood glucose (in rows with increments of blood glucose of 10 mg/dL). EPIC allows nurses to see only the patient admission weight specific columns in order to avoid confusion. When the protocol is utilized for DKA, all other fluid and electrolyte aspects of the DKA protocols are maintained [17]. (A simplified version of the protocol may be described as: for blood glucose <160 mg/dL: insulin infusion rate $_{\text{Units/kg/hr}}$ = 0.0003*(blood glucose $_{\text{mg/dL}}$)- 0.0275; for blood glucose 161–400 mg/dL: insulin infusion rate $_{\text{units/kg/hr}}$ = 0.0006*(blood glucose $_{\text{mg/d}}$L) −0.0458. Blood glucose values > 400 mg/dL are considered due to volume contraction for the sake of the insulin infusion and the insulin infusion rate not adjusted further upwards. Blood glucose values >400 mg/dl are considered as the upper limit for insulin infusion titration due to concern about volume contraction, which can improve relatively rapidly with simultaneous intravenous fluid administration.

Subjects were characterized as having PDKA or HMA. There are at least two methods of analyzing complex mixed acid-base conditions, the physiologic approach (the delta-delta gradient) [1,19] and the physicochemical approach (also called the Stewart method) [3,20,21]. The patient laboratory data was first screened for a concomitant mixed acidosis/alkalosis with the physiologic approach which specifically calculates the delta-delta gradient (ΔAG-ΔHCO3) [1,19]. This method postulates that the ketoacids that cause the increase in anion gap (greater than the normal gap of 12 mmol/L) will cause a direct 1:1 decrease in the concentration of bicarbonate (from the normal expected serum level of 24 mmol/L). In PDKA, the ΔAG-Δ(HCO3) would be 0 ± 5 mmol/L. However, a difference $\geq$5 mmol/L suggests that there is a concomitant metabolic alkalosis such as due to a co-existing hypochloremic metabolic alkalosis [19]. The analysis was then followed with the physicochemical approach [20,21] as modified using the formulas of Yasuda et al. [3] such that the modified base excess (BE_{xa}) can be calculated as $BE_{xa} = BE\text{-}BE_{fw}\text{-}BE_{Cl}\text{-}BE_{alb}$ where $BE_{free\ water}$ =(0.3*(Na-142), BE_{cl}=(104-(Cl*142/Na), and BE_{alb}= (0.34*(4.4-albumin). Routine blood chemistry and venous blood gas analysis were performed in the clinical laboratory. The normal BE_{Cl} range was defined from standard laboratory evaluation of patients with diabetes in the stable state, as −1.8 mEq/L (95% CI; −4.1 to 2.70}, and hypochloremic alkalosis was defined as BE_{Cl} > 2.7 mmol/L.

3. Statistical analysis

Demographic and clinical data are reported as mean and standard deviation (±SD). Parametric group mean data were analyzed by non-paired Student's test or analysis of variance (ANOVA) for non-paired comparisons. When there was a significant difference by ANOVA, post hoc analyses were performed by Fisher's LSD procedure for subgroup analysis. Correlation and regression analyses were performed with the statistical software Statistica for Windows (Version 5, StatSoft Inc, Tulsa OK). Significance was defined as a P < 0.05 by two-tailed testing.

4. Results

4.1. Assessment of insulin infusion protocol in diabetic ketoacidosis

There were 41 admissions for DKA amongst 18 men and 17 women during the evaluation period, with 6 readmissions. The mean age was 43 (SD ± 17) years. They presented with hyperglycemia (serum glucose 553 ± 265 mg/dL), acidosis (pH 7.13 ± 0.2), low serum bicarbonate (8.8 ± 5.1 mmol/L), elevated anion gap (26.4 ± 6.8 mmol/L), elevated beta-hydoxybutyrate (8.6 ± 3.6 mmol/L) and elevated lactic acid levels (3.76 ± 3.84 mmol/L). They would be classified as having severe DKA in 11 episodes by pH (pH < 7.00) and in 30 episodes by low serum bicarbonate (<10 mmol/L). There was no difference between men and women in age or metabolic parameters.

They were admitted to the intensive care units and received the St. Louis University unified insulin infusion protocol with adjustments with intravenous insulin, potassium and phosphate per standard DKA protocol [13]. The patient glucose levels were lowered from admission with the insulin infusion and then stabilized in the intensive care units until the patient was able to eat. During the stabilization phase, the blood sugar was maintained at 193 ± 56 mg/dL at an insulin infusion rate of 4.1 ± 2.8units per hours, Fig. 1. There were two episodes of hypoglycemia with a blood glucose values < 70 mg/dL (one with a blood glucose of 63 mg/dL and one with a blood glucose of 30 mg/dL) for a combined overall rate of hypoglycemia of 0.24%. Both episodes occurred during an interruption of a glucose infusion during the stabilization period, and both resolved with intravenous glucose and subsequent resumption of the insulin infusion.

The glucose levels were lowered to $\leq$250 mg/dL in 5H:25 min (±3 h:39min), and correction of anion gap to $\leq$12 mmol/L occurred at 11 h:25 Min (±6 h:56min). Resumption of subcutaneous was usually delayed until the patient was able to eat (total infusion time 25 h: 00 min ± 15 h:32min) and the insulin infusion continued (total infusion time 26 h:43 min ± 16 h:38 min) during the transition from intravenous to subcutaneous insulin. The time to recovery did not differ, when compared to that previously published, for serum glucose $\leq$250 mg/dL (5.4 ± 3.6 h, p = 0.38) [17,18]) and for anion gap $\leq$12 mmol/L in one series (11.4 ± 6.9 h, p = 0.46) [18]) and (13.6 ± 11.8 h < p = 0.28) [22,23]). in another series with a proprietary computer generated protocol.

There was a direct correlation of initial serum glucose with time to correction of serum glucose to $\leq$250 mg/dL (Fig. 2) and similarly a correlation of the initial serum bicarbonate to the time of closing the anion gap to less than 12 mmol/L (Fig. 3). The time to achieve the blood glucose goal of $\leq$250 mg/dL increased at approximately 1 h for each elevation of 140 mg/dL. Similarly, there was an inverse relationship of the initial serum bicarbonate to the time of closing the anion gap, with a prolongation of 2 h for each 5 mmol/L decrease in initial serum HCO3 level.

4.2. Relationship of correction of acid-base balance with regard to mixed ketoacidosis/hypochloremic alkalosis

There were 28 episodes considered to be PDKA and 13 episodes considered to have HMA (BE_{Cl} > 2.7 mmol/L). There were 17 women and 18 men, with one man and one women each having recurrent hypochloremic alkalosis. Three of the 13 episodes of HMA were associated with acute pancreatitis and vomiting, while the remainders of the presentations of HMA were not attributed to vomiting. The demographics are shown in Table 1. There was no difference between those who had HMA compared to those with

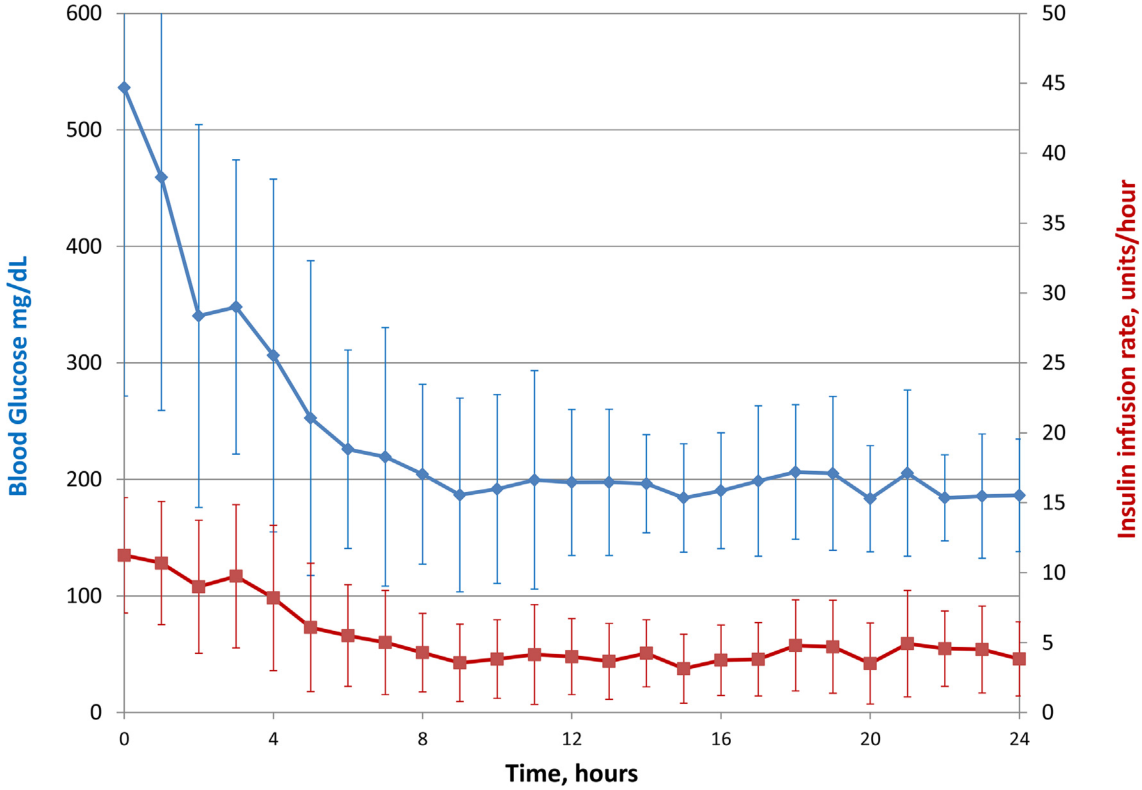

Fig. 1. Time course of blood glucose and insulin infusion value during the insulin infusion protocol for diabetic ketoacidosis. (Values are mean and SD).

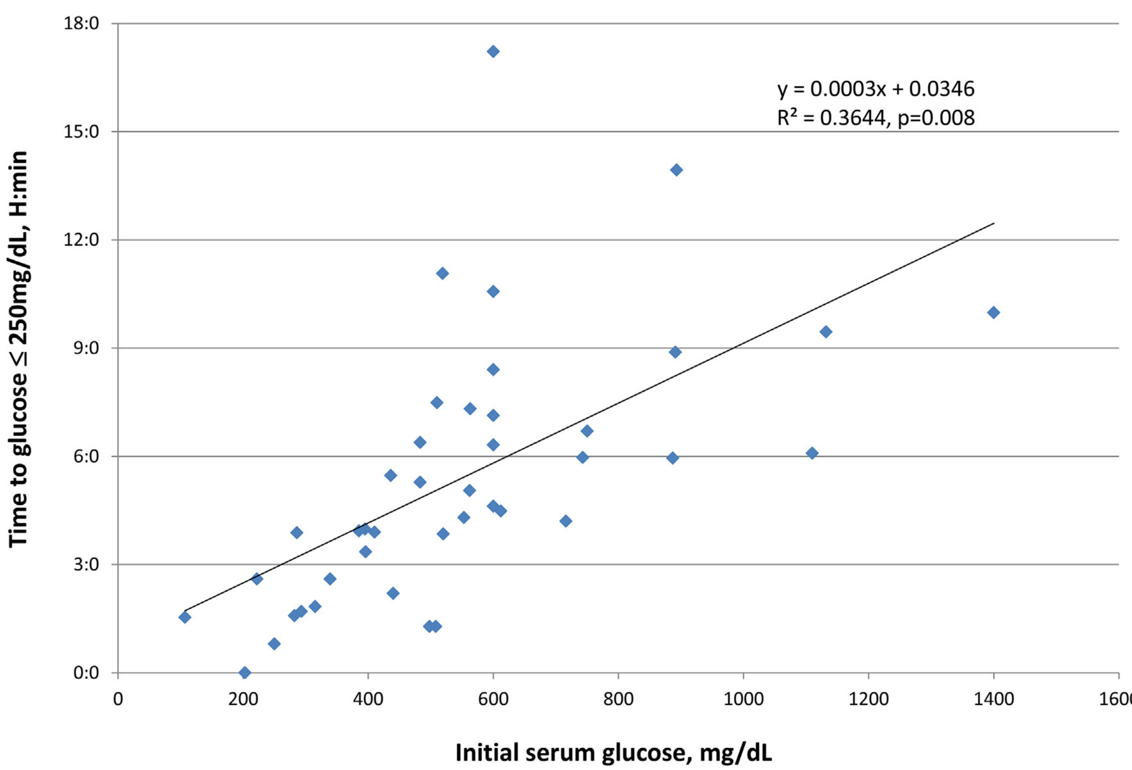

Fig. 2. Time to correction of blood glucose to ≤250 mg/dL depending upon initial blood glucose level on admission.

PDKA with regard to age, weight, A1c, initial venous pH, and levels of serum lactic acid, beta-hydroxybutyrate and modified calculated base excess (BE_{xa}). Those with HMA did appear to have a greater severity of illness compared with those with PDKA as manifested by elevated initial levels of glucose (712 ± 334 mg/dL vs 480 ± 191 mg/d, $p = 0.0075$), higher anion gap (31 ± 8 mmol/L vs.

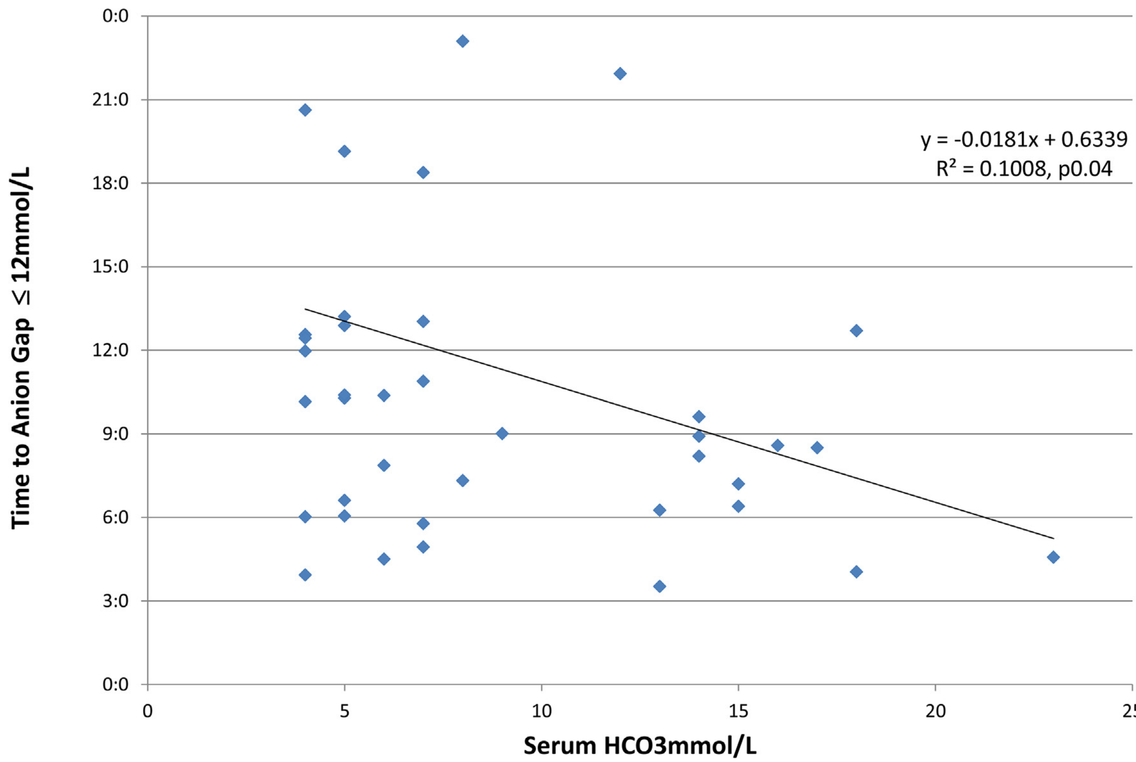

Fig. 3. Time to correction of anion gap to ≤12 mmol/L depending upon initial serum bicarbonate level on admission.

Table 1
Demographics and treatment outcomes of patients with PDKA and HMA.

Table	All	PDKA N = 28	HMA N = 13	Comparison PDKA vs HMA, p
Baseline Characteristics				
Age, years	44.5 (17.1)	43.3 (18.4)	47.4 (13.9)	0.5208
Weight, kg	80.7 (26.9)	80.1 (29.5)	82.5 (18.5)	0.8191
Recent A1c,%	12.4 (2.4)	12.7 (2.3)	11.5 (2.8)	0.2249
Recent A1c, mmol/mol	112 (3)	115 (3)	102 (7)	
Venous pH	7.13 (0.19)	7.10 (0.20)	7.20 (0.2)	0.1241
BE, mmol/L	−17.4 (10.5)	−20.4 (8.0)	−11.3 (12.7)	0.0090
Lactate, mmol/L	3.8 (3.8)	4.0 (2.7)	3.3 (2.7)	0.6653
Beta hydroxy butyric acid, mmol/L	8.6 (3.6)	8.8 (3.3)	8.3 (4.2)	0.6446
Glucose, mg/dL	553 (265)	480 (191)	712 (334)	0.0075
Sodium, mmol/L	133 (8)	134 (5)	129 (11)	0.0421
Potassium, mmol/L	5.2 (1.2)	5.0 (0.9)	5.7 (1.7)	0.0712
Chloride,mmol/L	98 (10)	102 (6)	87 (10.7)	0.0000
Bicarbonate,mmol/L	9 (5)	8 (4)	11 (6)	0.0266
Anion gap,mmol/L	26 (7)	24 (5)	31 (8)	0.0039
Delta-Delta,mmol/L	−1.9 (6.1)	−4.1 (4.2)	6.0 (2.8)	0.0000
Albumen, g/dL	3.5 (0.8)	3.5 (0.8)	3.5 (0.9)	0.8906
BE (free water),mmol/L	−2.8 (2.3)	−2.3 (1.5)	−3.9 (3.2)	0.0421
BE (Cl),mmol/L	−0.21 (7.4)	−4.2 (4.3)	8.5 (4.8)	0.0000
BE (alb),mmol/L	0.31 (0.28)	0.31 (0.27)	0.32 (0.31)	0.8906
BE (xa),mmol/L	−17.5 (11.4)	−16.6 (9.5)	−19.4 (15.0)	0.4774
Post treatment				
Time to glucose ≤250 mg/dL	5:26 (3:38)	4:31 (3:21)	7:23 (3:35)	0.0174
Time to anion gap ≤ 12 mmol/L	11:25 (6:56)	12:05 (7:49)	10:00 (4:28)	0.3799
Time to subcutaneous insulin	13:00 (15:32)	26:44 (13:41)	21:16 (19:00)	0.3008
Time on insulin infusion	26:44 (16:38)	27:59 (14:36)	24:02 (20:46)	0.4859
Change in serum Chloride, mmol/L	12.9 (10.0)	9.2 (7.3)	20.9 (10.7)	0.0002
Change in serum HCO3,mmol/L	9.4 (4.7)	8.5 (3.3)	11.3 (6.7)	0.0811
Change in serum anion gap, mmol/L	16.4 (7.0)	14.5 (5.4)	20.5 (8.3)	0.0079
Change in BE (Free water), mmol/L	1.8 (2.4)	1.0 (1.7)	3.5 (2.9)	0.0010

24 ± 5 mmol/L,p = 0.004) and by BE $_{\text{free water}}$ (-3.9 ± 3.2 mmol/L vs-2.3 ± 1.5 mmol/L,p = 0.042). By definition of hypochloremic alkalosis, those with HMA compared to PDKA had lower serum chloride (87 ± 11 mmol/L vs. 102 ± 6 mmol/L, p < 0.0001, and higher positive delta-delta gap (6.0 ± 2.8 mmol/L vs. −4.1 ± 4.2 mmol/L, p < 0.0001).

With regard to clinical treatment outcomes (Table 1), those with HMA compared with those with PDKA had a delay in time for recovery of serum glucose ≤ 250 mg/dL (7H:23min ± 3 h:35min vs. 4H:31min ± 3:h:21min, $p = 0.017$), which was predominantly due to the higher initial level of glucose ($p = 0.02$) rather than the level of BE_{Cl} ($p = 0.17$) (by analysis of covariance). There was no difference in the time to recovery of the anion gap between the HMA and PDKA groups. There were greater changes after treatment in the HMA compared with the PDKA groups in serum chloride (change in chloride 20.9 ± 10.7 mmol/L vs 9.2 ± 7.3 mmol/L, $p < 0.001$), in $BE_{free\ water}$ (change in $BE_{free\ water}$ 3.5 ± 2.9 vs 0.96 ± 1.71 mmol/L, $p = 0.001$), and in BE_{Cl} (change in BE_{Cl} −11.5 ± 8.3 vs −2.26 ± 6.60, $p < 0.001$), presumably due to the retention of sodium and chloride with the standard intravenous NaCl infusions for DKA.

5. Discussion

The management of diabetic ketoacidosis is well established [17]. There are two major components, the reversal of the ketosis with insulin supplementation, and the correction of the volume and electrolyte disturbances with fluid adjustments. We recently devised a unified insulin infusion protocol (IIP) with the goals of managing hyperglycemia and postoperative hyperglycemia. The IIP was designed to have high insulin infusion rates at very elevated blood glucose levels in order to reverse ketoacidosis and abruptly decreased insulin infusion rates as the blood sugar approaches the desired goal in order to limit hypoglycemia [5]. Recently, it has been confirmed that in diabetic ketoacidosis there is a high prevalence of simultaneous hypochloremic alkalosis [3]. What was not answered was whether these two conditions, PDKA or HMA differed in response to therapy. We therefore undertook two-fold analyses of the effectiveness of this insulin infusion protocol in comparison to existing protocols for DKA, and in the effectiveness of the protocol in PDKA and with HMA.

The insulin infusion protocol was effective in reversing the DKA. The patients evaluated were representative of previous studies with regard to hyperglycemia at onset and severity of the diabetic ketosis. The times to correction of glucose levels to ≤250 mg/dL and correction of the anion gap to ≤12 mmol/L were comparable to exiting protocols [18,23]. However, the lack of significant difference between these studies and the current study may be associated with a type 2 error, as the differences were not pre-specified.

In this convenience series, HMA occurred in 13 out of 28 cases, 46%. Those patients with HMA had a greater severity of illness compared with those with PDKA as manifested by elevated initial glucose of glucose, greater anion gap, and greater volume depletion as estimated by $BE_{free\ water}$. By definition, they had a higher positive delta-delta gap as screening test of a mixed acid-base disturbance, which was confirmed by the lower serum chloride and calculation of BE_{Cl} for hypochloremic alkalosis. They responded in a similar manner to the IIP with regard to time to correction of the anion gap. The delay in correction of serum glucose to ≤250 mg/dL apparently was due to the higher level of serum glucose levels.

The second component of treatment of the DKA is through the correction of the underlying fluid and electrolyte disturbances. This protocol used the standard fluid management of volume, intravenous saline and electrolytes [17]. There was no delay in the correction for the increased anion gap due to the hypochloremic alkalosis as there was increased retention of volume (as calculated with $BE_{free\ water}$), and chloride (BE_{Cl}) with the standard fluid and electrolyte infusions.

There are limitations of this study. It was a retrospective analysis of our current protocol, though it was compared with existing protocols. We did not specifically limit inclusion of those with hypochloremic alkalosis without vomiting because we wanted to ascertain the effectiveness of the total management protocol in all patients.

In summary, the insulin infusion protocol which was designed to manage postoperative hyperglycemia, stress induced hyperglycemia and ketoacidosis, was comparable to protocols in the literature in time and effectiveness to correct the metabolic abnormalities of diabetic ketoacidosis. The protocol had a very low incidence of hypoglycemia. In this convenience sample there was a high incidence of concomitant HMA which may be screened by an elevated delta −delta gradient. It appears that the insulin infusion corrects the excessive ketotic acidosis while the fluid and electrolyte management simultaneously corrected the hypochloremic alkalosis.

Disclosure statement

The authors have nothing to disclose.

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Drs DG and SGA designed, supervised and wrote the manuscript. Dr. SGA performed the statistical analysis. Drs. AP, FS and SS performed the data collection. The guarantor Dr. SGA takes responsibility for the contents of the article, conflict of interest statement, and reference to prior publication of the study.

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