RESEARCH PAPER

Low-Dose (0.05 Unit/kg/hour) vs Standard-Dose (0.1 Unit/kg/hour) Insulin in the Management of Pediatric Diabetic Ketoacidosis: *A Randomized Double-Blind Controlled Trial*

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Objective: To compare the efficacy of insulin infusion of 0.05 Unit/kg/hour vs 0.1 Unit/kg/hour in the management of pediatric diabetic ketoacidosis (DKA).

Design: Randomized, double-blind controlled clinical trial.

Setting: Pediatric critical care division of a tertiary care hospital from October, 2014 to July, 2018.

Participants: Children aged 12 years or younger with a diagnosis of DKA. Children with septic shock and those who had received insulin before enrollment were excluded.

Intervention: Low-dose (0.05 Unit/kg/hour) *vs*. Standard-dose (0.1 Unit/kg/hour) insulin infusion.

Outcome measures: The primary endpoint was time for resolution of DKA (pH ≥7.3, bicarbonate ≥15 mEq/L, beta-hydroxybutyrate <1 mmol/L). Secondary outcomes were the rate of fall in blood glucose until 250 mg/dL or less and the rate of complications (hypokalemia, hypoglycemia, and cerebral edema).

Results: Sixty patients were analyzed on an intention-to-treat basis (Low-dose group: *n*=30; Standard-dose group: *n*=30). Mean (SD) time taken for the resolution of ketoacidosis was similar in both groups [22 (12) vs 23 (18.5) hours; *P*=0.92]. The adjusted hazard ratio (95% CI) of the resolution of ketoacidosis was lower in the low-dose group [0.40 (0.19 to 0.85); *P*=0.017]. Mean (SD) rate of blood glucose decrease until 250 mg/dL or less reached [56 (41) vs 64 (65) mg/dL/hour; *P*=0.41] and time to achieve the target [4.2 (3.1) vs 4.8 (3.3) hours; *P*=0.44] were similar in both groups. Hypokalemia [30% vs 43.3%; *P*=0.28] and hypoglycemia [3.3% vs 13.3%; *P*=0.35] were lower in low-dose group. No child had cerebral edema, and no mortality occurred.

Conclusions: Time for resolution of ketoacidosis was similar in the low-dose and standard-dose insulin with a lower rate of therapy-related complications in the low-dose group. Hence, low-dose insulin infusion can be a safer approach in the management of pediatric DKA.

Keywords: *Cerebral edema, Complications, Hypokalemia, Outcome, Safety*.

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Diabetic ketoacidosis (DKA) is a life-threatening complication in pediatric type 1 diabetes mellitus [1] with a mortality rate of up to 13% in developing countries [2-5]. Fluid and insulin are the cornerstones of DKA management. Although rehydration alone can cause a marked decrease in blood glucose, the objectives are to restore circulating volume and replace the electrolytes and the fluid deficits [1]. After the initial fluid resuscitation, insulin is essential to normalize the hyperglycemia, for the correction of acidosis by suppression of the lipolysis, ketogenesis, generation of bicarbonate from ketoacid metabolism, and to restore the normal cellular metabolism [1,6].

High dose (1 Unit/kg/hour) and bolus insulin strategy are no longer practiced after studies found that a similar therapeutic response could be achieved with a dose of 0.1 Unit/kg/hour with lower rates of adverse effects [7-10]. Limited studies have highlighted that lower insulin doses (0.03 to 0.05 Unit/kg/hour) could normalize the raised beta-hydroxybutyrate (BOHB) levels [11-14]. Recent guidelines recommend insulin infusion at a dose of 0.05 to 0.1 Unit/kg/hour, and low-dose insulin is considered safe and effective, despite not proving its superiority with controlled studies [1].

In low-middle income countries, patients may benefit from low-dose insulin because of associated comorbidities, such as malnutrition, high risk of therapy-related hypokalemia, and hypoglycemia [4]. With limited literature available on the effect of low-dose versus standard-dose insulin in the resolution of ketoacidosis, we hypothesized that low-dose (0.05 Unit/kg/hour) would be associated with early resolution of ketoacidosis, gradual decreases in blood

glucose (BG), and lower frequency of complications as compared to the standard-dose (0.1 Unit/kg/hour) insulin.

METHODS

The study was a randomized, double-blind, controlled clinical trial conducted in the division of pediatric critical care of a tertiary care academic institution from October 2014 to July 2018 after institutitional ethics committee approval. Consecutive children 12 years or younger who presented with DKA defined as hyperglycemia (blood glucose >200 mg/dL), acidosis (pH <7.3 or bicarbonate <15 mEq/L), and ketonemia (BOHB ≥3 mmol/L) or moderate or large ketonuria by urine dipstick test were enrolled [1]. Children with septic shock and those who had received insulin before enrollment were excluded. Informed written consent from parents or legally acceptable representative was obtained.

A web-generated, unstratified, block randomization sequence with variable block sizes (*www.sealed envelope.com*) was used to randomize the eligible children into two groups. A person not involved in the study performed the random number allocation. The allocation was concealed in serially numbered opaque, sealed envelopes (SNOSE), with three alphanumerical codes. The study drug was prepared by a nursing staff, who was not involved in patient care and was masked regarding the patient's identity. Each envelope contained a slip showing the instruction for the preparation of insulin (50 units of regular insulin in 50 mL of normal saline, 0.1 mL=0.1 U or 25 U of regular insulin in 50 mL of normal saline, 0.1 mL=0.05 Unit). Trial syringes were labeled with a random number and three alpha-numerical codes and study drug dose (0.1 mL/kg/hour). The study drug was prepared every six hours and given to nursing-sister responsible for medication administration. The participants, the treating team, those administering the medications, investigators, and research personnel who collected data, and study statisticians, were unaware of the treatment assignments. The treatment allocation was disclosed after the first draft of the results was finalized.

Continuous insulin infusion was administrated through a dedicated intravenous line using an infusion pump. The standard-dose group received regular insulin 0.1 U/kg/hour, and the low-dose group received regular insulin at 0.05 U/kg/hour. The resolution of ketoacidosis (pH ≥7.30, bicarbonate ≥15 mEq/L, and BOHB <1 mmol/L) was taken as the endpoint. After that, the child was shifted to regular subcutaneous insulin with an overlap time of 30 minutes with intravenous insulin.

Fluid volume was calculated as a sum of the deficit (85 mL/kg) and 48-hour maintenance fluid spread over 48 hours [1]. All children received 20 mL/kg of normal saline in the first hour of resuscitation. Children with evidence of hypoperfusion or hypotensive shock received an additional 20 mL/kg of normal saline for one hour. The bolus and other infusions were deducted from the total calculated volume to be infused. Normal saline was used for the first six hours and was changed to 0.45% saline based on serum sodium and effective osmolality. Dextrose (5%) was added to the hydrating fluid once the blood glucose level decreased to 250 mg/dL or less. If the blood glucose level approached 100 mg/dL or below despite dextrose concentration of 12.5%, the insulin infusion was tapered at the rate of 0.01 mL/kg/hour every half-hourly. Potassium chloride (40 mEq/L) was added to the rehydrating fluid after resuscitation and documentation of urine output. Continuous cardiac monitoring was done and potassium titrated to maintain a serum level of 3.5-5.5 mEq/L.

Capillary or venous blood glucose was monitored every half-hourly, and BOHB was monitored hourly by (Abbott Optium-H) ketone meter after calibration. Readings above the glucometer range (more than 500 mg/dL) or in the presence of poor peripheral circulation, capillary BG were counter checked by laboratory measurement using the hexokinase method. Urine ketone and glucose were monitored hourly by the dipstick method. Glycated hemoglobin (HbA1c) was done at admission. Serum electrolytes, blood glucose, urea, calcium, magnesium, phosphate, hematocrit, and venous blood gases and corresponding anion gap and effective osmolality were monitored two-hourly first six-hour, subsequently four-hourly till resolution of ketoacidosis. Vital signs, fluid (intake and output), continuous monitoring of the electrocardiogram, and neurologic assessment was performed hourly (or more frequently as indicated). A review of insulin therapy was performed for errors in dose, preparation, and infusion rate six-hourly and as indicated. Nutritional status was assessed using the World Health Organization standards [15].

The primary outcome was the time for resolution of ketoacidosis (pH ≥7.3, bicarbonate ≥15 mEq/L, beta-hydroxybutyrate <1 mmol/L). The secondary outcomes were the rate of decrease in blood glucose until the level reaches 250 mg per dL or less, the incidence of hypoglycemia, hypokalemia, and cerebral edema and/or worsening of cerebral edema. Hypokalemia was defined as serum potassium <3.5 mEq/L and/or suggestive electrocardiographic changes. Hypoglycemia was defined as a blood glucose level ≤60 mg/dL. Cerebral edema was diagnosed as per the criteria given by Muir, et al. [16].

With assumptions of the mean time for resolution of ketoacidosis in the standard-dose group as 20 hours and in the low-dose group as 16 hours [12,17], the sample size

was calculated with a common standard deviation of four hours, a two-sided alpha level of 5%, and 95% power. The sample size was 52 DKA episodes. Considering an attrition rate of 10%, we enrolled 60 participants.

Statistical analysis: The patient's data were analyzed according to their assigned group (Intention to treat). The normality of data was checked with the Kolmogorov-Smirnov *Z* test. Continuous variables between the groups were compared with Student *t*-test if normally distributed or Mann-Whitney *U* test if skewed data. The proportion was compared by the chi-square test (Fisher exact test if cell frequency was <5), and relative risk (95% CI) was calculated as appropriate. Cox proportional model adjusted a prior for age, weight, and severity of ketoacidosis was used to calculate the hazard ratio (95% CI) for resolution of ketoacidosis and blood glucose fall 250 mg/dL or less. Changes in continuous variables up to 24 hours were compared using repeated-measures analysis of variance (RM-ANCOVA), and missed values were handled by Last-Observation-Carried-Forward (LOCF) method. All tests were two-tailed, and a *P* value of less than 0.05 was considered statistically significant. Data analyses were performed using IBM-SPSS, version 20.0 (SPSS Inc) and Epi Info 7 (7.0.9.7, CDC).

RESULTS

The trial flow diagram is depicted in **Fig. 1**. Of the 69 children with DKA screened for eligibility, 60 were enrolled (30 in each group). No protocol violation was noted. Baseline characteristics were comparable (**Table I)**. New onset diabetes presenting as DKA was seen in 48.3% of children. Severe DKA was seen in 38.3% (*n*=23) of children. In all patients data, the mean (SD) blood sugar and BOHB change after the first hour of fluid bolus was –44.8 (72.2) and –0.3 (0.9), respectively. Mean (SD) fluid balance (percentage) at six hours of therapy was similar in the low-dose and standard-dose groups [0.15 (0.14) vs 0.10 (0.1); *P*=0.16].

Mean (SD) time taken for resolution of ketoacidosis was 22 (12) hours in low-dose and 23 (18.5) hours in the standard-dose groups (*P*=0.92) (**Table II**). Time taken for an individual parameter of ketoacidosis to achieve the end-points (pH ≥7.30, HCO3 ≥15 mEq/L, BOBH <1 mmol/L, and normal sensorium) was similar in the two groups (**Table II**). In sub-group analysis (severe DKA), there was no significant difference in mean (SD) time taken for the resolution of ketoacidosis in low-dose group vs standard-dose group [31.4 (11.3) vs 36.3 (21.4) h, *P*=0.52]. The hazard ratio of the resolution of ketoacidosis was significantly lower by 60% in the low-dose group than the standard-dose group [adjusted hazard ratio 0.40, 95% CI: 0.19 to 0.85; *P*=0.017] (**Fig. 2**). The hazard ratio of the resolution of BOHB (<1 mmol/L) was significantly lower by 65% in the low-dose group [adjusted hazard ratio 0.35, 95% CI: 0.17 to 0.74; *P*=0.006].

The mean (SD) rate of blood glucose fall per hour and the time taken until the level was 250 mg/dL was similar in the two groups (**Table II**). However, the mean (SEM) trend in fall of blood glucose until six hours and 24 hours was higher in the standard-dose group [by six hours, 43 (3.4), *P*=0.008; by 24 hours, 12.5 (1), *P*=<0.001] as compared to the low-dose group [by six hours, 29.6 (3.4); by 24 hours, 7.1 (1)]. The mean (SEM) trend in fall of BOHB until six hours and 24 hours was not significantly different between the standard-dose group [by six hours, 0.30 (0.06), *P*=0.81; by 24 hours, 0.17 (0.01), *P*=0.81] and the low-dose group [by six hours, 0.29 (0.06); by 24 hours, 0.16 (0.01)].

There was no difference in the proportion of patients who attained the blood glucose level of 250 mg/dL at six-hour in standard-dose and low-dose groups (76.7% vs 70%, RR=1.10, 95% CI: 0.81 to 1.19; *P*=0.56). The frequency of fall in blood glucose, more than 90 mg/dL/hour, was higher in standard-dose group (76.7%) as compared to low-dose group (60%) (RR=1.28, 95% CI: 0.90 to 1.82; *P*=0.17). The hazard ratio of achieving blood glucose 250 mg/dL or less by the end of six hours was 1.35 times higher in the low-dose group than the standard-dose group (adjusted hazard ratio 1.35, 95% CI: 0.72 to 2.54; *P*=0.35).

Hypoglycemia [RR (95% CI) 4.0 (0.47-33.7); *P*=0.35] and at least one episode of hypokalemia [RR 995% CI) 1.44 (0.73-2.8); *P*=0.28] was higher in the standard-dose group as compared to the low-dose group (**Table II**). None

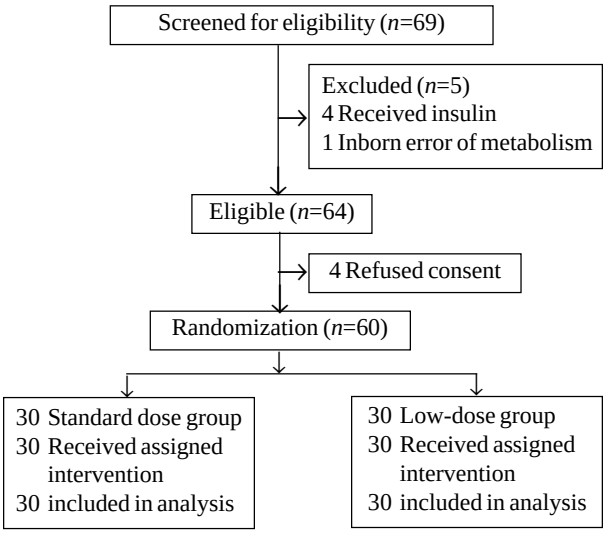

Fig. 1 Study flow chart.

Table I Baseline Characteristics in Children With Diabetic Ketoacidosis

Characteristic	*Low-dose group (n=30)*	*Standard-dose group (n = 30)*
Age, y	7 (3.6)	8.4 (3.2)
Body mass index, *z*-score	– 2.2 (1.6)	– 2.5 (1.5)
Malnutrition, *n* (%)	7 (23.3)	9 (30)
New onset DKA, *n* (%)	15 (50)	14 (46.6)
Established diabetes mellitus, *n* (%)	15 (50)	16 (53.4)
Duration of diabetes, mo	28 (29.6)	28.2 (25.4)
With previous DKA, *n* (%)	11 (73.3)	10 (62.5)
Duration of symptom, d	4.4 (5.7)	4.4 (4.7)
Severity, n (%)		
Mild	12 (40)	8 (26.7)
Moderate	8 (26.7)	9 (30)
Severe	10 (33.3)	13 (43.3)
Hemodynamic status, n (%)		
Compensated shock	3(10)	7 (23.3)
Hypotensive shock	1 (3.3)	1 (3.3)
m-GCS 8-14 at admission, *n* (%)	8 (27)	9 (30)
m-GCS score, median (IQR)	15 (14-15)	15 (14-15)
Hemoglobin A1c, %	13.5 (2.6)	13.3 (2.5)
Blood glucose, mg/dL	465.5 (105.6)	510.3 (113)
pH	7.15 (0.13)	7.10 (0.16)
Bicarbonate , mEq/L	8.9 (4.3)	7.1 (4.3)
PCO_2, mm Hg	20.6 (7.5)	19.2 (7.3)
Capillary BOHB, mmol/L	5.4 (1.4)	5.3 (1.4)
Blood urea nitrogen, mg/dL	11.5 (3.6)	12.8 (5.1)
Creatinine, mg/dL	1.0 (0.3)	1.1 (0.4)
Sodium, mEq/dL	137.5 (6.2)	138 (5.8)
Corrected sodium, mEq/L	143.5 (6.8)	144.6 (5.5)
Effective osmolality, mOsm/kg	292.4 (45.8)	304.4 (11.3)
Potassium, mEq/L	3.9 (0.7)	3.9 (0.7)
Anion gap	26 (7.4)	27.5 (5.6)
Lactate, mmol/L	1.8 (0.8)	2 (1)
Urine ketones, n (%)		
3+ (80 – 160 mg/dL)	19 (63.3)	19 (63.3)
4+ (>160 mg/dL)	11 (36.7)	11 (36.7)
Fluid received, mL/kg[a]	16 (10)	13.7 (5.6)
Blood glucose change, mg/dL[b]	– 61.4 (66)	– 28.3 (75.4)
Capillary BOHB change, mmol/L[b]	– 0.2 (1.0)	– 0.3 (0.9)
Duration of 0.9% saline therapy, h	5 (2.7)	6.3 (3.9)

Data presented in mean (SD) or as stated (%). DKA-diabetic ketoacidosis; m-GCS-modified Glasgow Coma Scale score; PCO_2 – partial pressure of carbon dioxide; BOHB – beta hydroxy hydroxybutyrate. [a]before starting insulin infusion; [b]after the initial hour of fluid resuscitation before starting insulin infusion. All P>0.05.

of the hypoglycemia patients encountered more than or equal to two episodes of hypoglycemia. The hypokalemia was more in malnourished children in the standard-dose group (*P*=0.31), and more children in the standard-dose group required a higher concentration of dextrose and tapering of insulin infusion at least once to counter the falling blood glucose **(Table II)**. None of the children required the increment of insulin infusion.

The mean (SEM) trend of fall in effective osmolality until six hours [0.53 (0.37) vs 0.70 (0.37); *P*=0.33] and 24 hours [0.54 (0.14) vs. 0.27 (0.14), *P*=0.45] was not significantly different between the standard-dose group and the low-dose group. No child had cerebral edema, and no mortality occurred in the study.

DISCUSSION

We found that the time taken for the resolution of ketoacidosis was similar in the low-dose insulin and standard-dose insulin groups. The hazard ratio of the resolution of ketoacidosis was lower by 60% in the low-dose group. The optimal insulin level for recovery of ketoacidosis is 20 to 200 micro Unit/ml, and it could be

Table II Outcome Measures in the Two Study Groups

Characteristic	*Low dose group (n=30)*	*Standard dose group (n=30)*
Primary outcome		
Time for resolution of DKA, h	22 (12)	23 (18.5)
Time for pH ≥7.30, h	13.4 (11.5)	17.1 (17.6)
pH	7.33 (0.02)	7.32 (0.03)
Time for bicarbonate ≥15 mEq/L, h	15.5 (11.7)	18.6 (18.7)
Bicarbonate, mEq/L	16.4 (1.4)	16.1 (1.3)
Time for BOHB <1 mmol/L, h	21.6 (11.8)	17.8 (9.8)
BOHB, mmol/L	0.76 (0.16)	0.73 (0.19)
Time for resolution of DKA (including normal sensorium), h	23 ((12.8)	23.1 (18.5)
Time for the normal sensorium, h	3.7 (11.1)	6 (17.4)
Secondary outcome		
Blood glucose decrease until the level reached ≤250 mg/dL, mg/dL/hour	56 (41)	64 (65)
Time to achieve blood glucose ≤250 mg/dL, h	4.2 (3.1)	4.8 (3.3)
Blood glucose, mg/dL	217 (29.8)	218.8 (32)
Hypokalemia[a]	9 (30)	13 (43.3)
Hypoglycemia[a]	1 (3.3)	4 (13.3)
Tapering of insulin infusion[a]	13 (43.3)	14 (46.7)

Data presented as mean (SD) *except [a]no. (%). DKA-diabetic ketoacidosis; BOHB-beta hydroxy hydroxybutyrate. All P>0.05.*

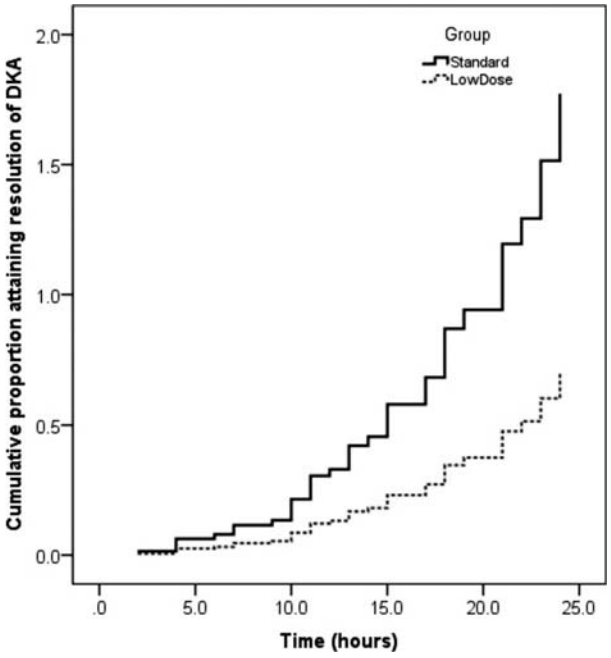

Fig. 2 Hazard curves plot for resolution of diabetic ketoacidosis (DKA).

achieved with a lower dose of insulin [18]. The standard-dose of insulin has been reported to achieve higher than optimal plasma insulin requisite level [6,18]. With this justification, lowering of insulin dose up to 0.025 U/kg/hour as compared with standard-dose was studied in pediatric DKA [12,14,19]. Puttha, et al. [12] found that a rise in pH at six hours and the median time for resolution of ketoacidosis (pH >7.3) was similar in the low and standard-dose groups [12]. Kapellen, et al. [19] reported that 0.025 vs 0.1 U/kg/hour was associated with a similar duration of acidosis [19]. A controlled study by Nallasamy, et al. [14] found that low-dose was not inferior to standard-dose insulin in the resolution of ketoacidosis. However, BOHB was not monitored as one of the endpoints of ketoacidosis [14].

The trend of fall in blood group up to 24-hour was significantly higher in the standard-dose group, although the reduction rate was within the reported range (36 to 90 mg/dL/h) as with other studies [12-14]. Nallasamy, et al. [14] reported that the rate of fall in BG until ≤250 mg/dL was similar in low and standard-dose groups [14]. Hence, any effective dose of insulin which achieves the optimal plasma insulin level (20 to 200 micro-unit/mL) could exhibit the desired therapeutic clinical response without affecting osmotic hemostasis [6,14]. Though we could not measure plasma insulin levels in our study, our results support the use of low-dose insulin to achieve clinically effective resolution of ketoacidosis and gradual reduction of BG.

Retrospective pediatric studies have reported rapid BG decrease with the use of insulin dose higher than 0.05 units/kg/hour [20] and the gradual decrease in plasma effective osmolality due to slower decrease in BG by using insulin dose of 0.05 U/kg/hour [13], despite the well-established fact that resolution of ketoacidosis and not BG determine the endpoint of DKA management [1]. The amount of insulin administrated in the first-hour and volume of fluid administrated over four-hour were associated with the risk of cerebral edema after adjusting for the severity of ketoacidosis in the management of DKA [21]. Our setting is complicated by delayed presentation, severe ketoacidosis, undernutrition, and high effective osmolality at presentation, where initial hours of therapy warrant a more cautious approach to preventing osmotic disequilibrium and cerebral edema. We found that fluid administration and change of effective osmolality was similar in both the groups. The frequency of fall of BG and tapering of insulin infusion despite maximum glucose concentration was higher in the standard-dose group. Nallasamy, et al. [14] found that more episodes of out of range fall of BG (> 90 mg/dL) in the standard-dose group in a study setting similar to ours. Hence, low-dose insulin after the first hour of fluid resuscitation is a safe approach in a setting where a gradual decrease in BG, effective osmolality and smooth resolution of ketoacidosis is desired.

Therapy-related complications, hypokalemia, and hypoglycemia were higher in the standard-dose group. Undernutrition, prolonged duration of illness, severe ketoacidosis, and osmotic diuresis likely contributed to hypokalemia in this study group. In addition to these factors, insulin dose also could have contributed to the lowering of potassium levels. In a similar setting, Nallasamy, et al. [14] and Moulik, et al. [22] reported the frequency of occurrence of hypokalemia was higher in the standard-dose group. Hypoglycemia was reported in higher proportion by previous authors [14,22] in the standard-dose group as compared to our study. Half-hourly monitoring of blood glucose could have contributed to the lower incidence of hypoglycemia in our study. However, the potentially beneficial effect of lowering the insulin dose cannot be ignored entirely.

We monitored the blood ketone (BOBH) as one of the endpoints of the study, which is in contrast to previous studies [9,12,14]. Unlike other studies, we followed until the resolution of ketoacidosis and collected and analyzed the 24 hours data. We also analyzed the factors unique to limited-resource settings, enabling the available study results to apply to the low and middle-income countries. The limitation of our study is that we could not enroll adolescents with DKA due to hospital admission policy during the study period.

WHAT IS ALREADY KNOWN?

- Insulin infusion at 0.05 Unit/kg/hour was comparable to 0.1 Unit/kg/hour with respect to a decrease in blood glucose and resolution of acidosis.

WHAT THIS STUDY ADDS?

- Low-dose (0.05 Unit/kg/hour) insulin infusion was comparable to 0.1 Unit/kg/hour insulin infusion for the resolution of ketoacidosis, decrease in blood glucose, and therapy-related complications in pediatric diabetic ketoacidosis.

We conclude that the time for resolution of ketoacidosis was similar in the low-dose and standard-dose insulin infusion, with a lower rate of therapy-related complications in low-dose insulin. Hence, insulin infusion at 0.05 Unit/kg/hour is a safer approach in the manage-ment of pediatric DKA.

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Ethics approval: Institute Ethics Committee of JIPMER, Puducherry; No. JIP/IEC/2014/4/308, dated 27 June, 2014.

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REFERENCES

1. Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes. 2018;19:155-77.
2. Kanwal SK, Bando A, Kumar V. Clinical profile of diabetic ketoacidosis in Indian children. Indian J Pediatr. 2012;79:901-4.
3. Tiwari LK, Jayashree M, Singhi S. Risk factors for cerebral edema in diabetic ketoacidosis in a developing country: Role of fluid refractory shock. Pediatr Crit Care Med. 2012;13:e91-6.
4. Jayashree M, Singhi S. Diabetic ketoacidosis: Predictors of outcome in a pediatric intensive care unit of a developing country. Pediatr Crit Care Med. 2004;5:427-33.
5. Poovazhagi V. Risk factors for mortality in children with diabetic keto acidosis from developing countries. World J Diabetes. 2014;5:932-8.
6. Luzi L, Barrett EJ, Groop LC, Ferrannini E, DeFronzo RA. Metabolic effects of low-dose insulin therapy on glucose metabolism in diabetic ketoacidosis. Diabetes. 1988;37: 1470-7.
7. Alberti KG, Hockaday TD, Turner RC. Small doses of intramuscular insulin in the treatment of diabetic "coma". Lancet. 1973;2:515-22.
8. Kitabchi AE, Ayyagari V, Guerra SM. The efficacy of low-dose versus conventional therapy of insulin for treatment of diabetic ketoacidosis. Ann Intern Med. 1976;84:633-8.
9. Burghen GA, Etteldorf JN, Fisher JN, Kitabchi AQ. Comparison of high-dose and low-dose insulin by continuous intravenous infusion in the treatment of diabetic ketoacidosis in children. Diabetes Care. 1980;3:15-20.
10. Dunger DB, Sperling MA, Acerini CL, et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child. 2004;89:188-94.
11. Noyes KJ, Crofton P, Bath LE, et al. Hydroxybutyrate near-patient testing to evaluate a new end-point for intravenous insulin therapy in the treatment of diabetic ketoacidosis in children. Pediatr Diabetes. 2007;8:150-6.
12. Puttha R, Cooke D, Subbarayan A, et al. Low dose (0.05 units/kg/h) is comparable with standard dose (0.1 units/kg/h) intravenous insulin infusion for the initial treatment of diabetic ketoacidosis in children with type 1 diabetes-an observational study. Pediatr Diabetes. 2010;11:12-7.
13. Al Hanshi S, Shann F. Insulin infused at 0.05 versus 0.1 units/kg/hr in children admitted to intensive care with diabetic ketoacidosis. Pediatr Crit Care Med. 2011;12:137-40.
14. Nallasamy K, Jayashree M, Singhi S, Bansal A. Low-dose vs standard-dose insulin in pediatric diabetic ketoacidosis: A randomized clinical trial. JAMA Pediatr. 2014;168:999-1005.
15. de Onis M, Blossner M. The World Health Organization Global Database on Child Growth and Malnutrition: methodology and applications. Int J Epidemiol. 2003;32:518-26.
16. Muir AB, Quisling RG, Yang MC, Rosenbloom AL. Cerebral edema in childhood diabetic ketoacidosis: natural history, radiographic findings, and early identification. Diabetes Care. 2004;27:1541-6.

17. Kurup PM, Rameshkumar R, Soundravally R, Satheesh P. Capillary versus Serum b-hydroxybutyrate in Pediatric Diabetic Ketoacidosis. Indian Pediatr. 2019;56:126-9.
18. Soler NG, FitzGerald MG, Wright AD, Malins JM. Comparative study of different insulin regimens in management of diabetic ketoacidosis. Lancet. 1975;2: 1221-4.
19. Kapellen T, Vogel C, Telleis D, Siekmeyer M, Kiess W. Treatment of diabetic ketoacidosis (DKA) with 2 different regimens regarding fluid substitution and insulin dosage (0.025 *vs*. 0.1 units/kg/h). Exp Clin Endocrinol Diabetes. 2012;120:273-6.
20. Bradley P, Tobias JD. Serum glucose changes during insulin therapy in pediatric patients with diabetic ketoacidosis. Am J Ther. 2007;14:265-8.
21. Edge JA, Jakes RW, Roy Y, et al. The UK case-control study of cerebral oedema complicating diabetic ketoacidosis in children. Diabetologia. 2006;49:2002-9.
22. Moulik NR, Jayashree M, Singhi S, Bhalla AK, Attri S. Nutritional status and complications in children with diabetic ketoacidosis. Pediatr Crit Care Med. 2012;13:e227-33.