Original article

https://doi.org/10.6065/apem.2448086.043
Ann Pediatr Endocrinol Metab 2025;30:95-101

Annals of Pediatric Endocrinology & Metabolism
apem

Assessment of the use of long-acting insulin in management of diabetic ketoacidosis in pediatric patients: a randomized controlled trial

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Purpose: We evaluated the effectiveness of early start of long-acting insulin during management of diabetic ketoacidosis (DKA) in pediatric patients.
Methods: Patients with DKA were randomly assigned to receive either a traditional DKA management protocol or concurrent administration of subcutaneous (SC) long-acting insulin alongside intravenous insulin during DKA treatment. The primary outcomes were duration of insulin infusion and adverse effects of the intervention, mainly hypoglycemia and hypokalemia.
Results: For this study, 100 pediatric patients with DKA were enrolled, 50 in each group (group I received the conventional DKA management and group II received conventional DKA management plus SC long-acting insulin once daily). Patients in group II showed a significant reduction in both duration and dose of insulin infusion compared to group I, with a median (interquartile range) of 68.5 hours (45.00–88.25 hours) versus 72 hours (70.25–95.5 hours) (P=0.0001) and an insulin dose of 3.48±1.00 units/kg versus 4.04±1.17 units/kg (P=0.016), respectively. Concurrent administration of SC long-acting insulin with intravenous insulin during DKA treatment was associated with a decreased risk of hypoglycemia (number of hypoglycemia events: group I, 22 events; group II, 12 events, P=0.029), with no increased risk of hypokalemia compared to the control group (number of hypokalemia events: group I, 12 events; group II, 19 events, P=0.147).
Conclusion: The current study showed that coadministration of SC long-acting insulin in addition to the usual insulin infusion during DKA management in the pediatric population can lead to a shorter duration of insulin infusion. In addition, this approach is not associated with increased risk of hypoglycemia or hypokalemia. Moreover, coadministration of long-acting insulin may be associated with a decreased incidence of hypoglycemia.

Keywords: Diabetic ketoacidosis, Insulin, Long-acting, Child

Received: 15 April , 2024
Revised: 23 October, 2024
Accepted: 12 November, 2024

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Highlights

- A randomized controlled trial assessed long-acting insulin in managing pediatric diabetic ketoacidosis (DKA).
- Long-acting insulin demonstrated effective and safe glycemic control during DKA management.
- Findings support integrating long-acting insulin into standard DKA treatment protocols.

Introduction

Diabetic ketoacidosis (DKA) is a common acute complication of type 1 diabetes in children

ISSN: 2287-1012(Print)
ISSN: 2287-1292(Online)

and adolescents [1]. An increasing prevalence of DKA at diagnosis of type 1 diabetes in children has been recently reported [2].

DKA is a serious condition that can lead to death in up to 13% of patients in developing countries [3,4]. In addition, DKA can cause permanent neurological sequelae, and, more frequently, memory deterioration [5], as well as several other renal and metabolic complications [6-8].

The management of DKA in children involves mainly intravenous (IV) insulin infusion and IV fluid therapy [9]. Most commonly, insulin is administered through the IV route throughout DKA management, followed by a transition to SC insulin after improvement and resolution of ketosis [10]. However, shifting the patient from IV insulin to an SC regimen can be complicated and time consuming [11].

Alternatively, concurrent administration of SC long-acting insulin with IV insulin during DKA treatment may facilitate a shift in insulin regimen [12] and is considered a safe approach [13]. However, the effectiveness of this intervention is not known [11].

This randomized controlled study aims to evaluate the effectiveness and safety of early start of SC long-acting insulin during IV management of DKA in pediatric patients.

Materials and methods

This study is a randomized controlled trial that took place in the Pediatric Endocrinology Unit of Mansoura University Children's Hospital, Mansoura, Egypt, from October 2020 to October 2021. It was approved by the Ethical Committee of Mansoura Faculty of Medicine, Egypt. (MS.19.04.561) Written informed consent was obtained from caregivers of all patients.

1. Included subjects

We included children aged 6 years to 18 years with pre-existing type I diabetes who presented with DKA, defined as plasma glucose level ≥250 mg/dL, arterial pH ≤7.30, and serum bicarbonate level ≤15 mmol/L [14].

2. Excluded subjects

Children newly diagnosed with type I diabetes, initiation of IV insulin before admission, associated DM complications like nephropathy and neuropathy, associated hematological or rheumatologic disorders, vasculitis, need for emergency surgery, or malignancy were excluded from the analysis.

3. Patient groups

The enrolled patients were randomly assigned to 2 treatment groups, each containing 50 patients. Group I received a standard treatment regimen for DKA as in the International Society of Pediatric and Adolescent Diabetes (ISPAD) guidelines including continuous short-acting insulin infusion and IV fluids [14]. Group II received a standard treatment regimen for DKA in addition to SC long-acting insulin using the same type and dose as before development of DKA, with 43 patients using glargine and 7 patients using degludec.

4. Randomization

Randomization was performed using a computer-generated random table technique with sealed envelopes.

5. Sample size

The sample size was calculated using PASS ver. 15.0.5 for Windows (2017) based on the results published by Houshyar et al. [15]. The efficacy of long-acting insulin in management of DKA patients was the primary outcome measured by duration to control acidosis. Patients were allocated into 2 groups: groups I and II. Houshyar et al. [15] reported the mean duration to control acidosis as 13.77±6.10 hours for the study group compared to 16.91 for controls, with a standard deviation of 6.49. The null hypothesis was the absence of difference between the groups regarding the efficacy of long-acting insulin in management of DKA patients. A sample size of 50 patients in each group was needed to achieve 80% power (1-β or the probability of rejecting the null hypothesis when it is false) using a 2-sided independent samples *t*-test with a significance level (α or the probability of rejecting the null hypothesis when it is true) of 5% and hypothesized common standard deviation of 5 in both groups.

6. Study intervention

Detailed history collection and examination were performed for all participants in the study. History regarding potential risk factors for DKA, including recent infections, missed doses, and use of possible hyperglycemia-inducing medications, was documented.

Missed dose was defined as every instance where patients failed to take their prescribed rapid-acting insulin during the week prior to admission. Puberty was assessed using the Tanner stage. We defined nonpubertal as Tanner stage 1. Delayed puberty was defined as the absence of signs of puberty by age 13 in girls or 14 in boys, while pubertal children were defined as Tanner stages 2–5, indicating the onset and progression of puberty [16,17]. Biochemical measurements were conducted for all cases during admission, including random blood glucose at baseline and every hour until resolution of DKA using a glucometer (Accu Check Advantage; Roche, Indianapolis, IN, USA) calibrated according to the manufacturer's instruction. Urine ketones were measured at presentation and every 4 hours until DKA resolution. Capillary blood gases and electrolyte levels, including potassium and sodium, were assessed at presentation and every 2 hours using a Modular Analytics E170 system (Roche Diagnostics) until resolution of DKA. All

patients received IV fluid therapy according to clinical status following ISPAD guidelines [14] as follows: mild DKA received maintenance IV fluids plus a 50-mL/kg deficit correction over 48 hours; moderate DKA received maintenance IV fluids plus a 70-mL/kg deficit correction over 48 hours; and severe DKA received maintenance IV fluids plus a 100-mL/kg deficit correction over 48 hours. Group I received the standard treatment regimen for DKA, including continuous short-acting insulin infusion and IV fluids. Group II received the standard treatment regimen for DKA in addition to their usual type and dose of SC long-acting insulin, administered during the first night within 6 hours of admission while receiving insulin infusion. All patients were started on insulin infusion at 0.05 IU/kg/hr according to the severity of the condition and the patient response. The type of fluids was decided based on the blood glucose level as follows: if glucose was >300 mg/dL, no dextrose was added; for glucose levels between 150 mg/dL and 300 mg/dL, 5% dextrose was added; and for glucose levels below 150 mg/dL, 10% dextrose was added. Potassium chloride (KCl) was added to the IV fluids according to serum potassium levels as follows: if serum potassium was >6 mEq/L, no KCl was added; for serum potassium between 5–6 mEq/L, 20 mEq/L of KCl was added; for serum potassium between 4–5 mEq/L, 30 mEq/L of KCl was added; and for serum potassium between 3–4 mEq/L, 40 mEq/L of KCl was added.

Recovery from DKA was documented by laboratory findings of blood sugar <250 mg/dL, serum bicarbonate >15 mmol/L, and pH >7.3 [14]. The time of recovery from DKA and complications such as hypoglycemia and hypokalemia were assessed and compared between the 2 study groups. Hypoglycemia was defined as a blood glucose level below 4.0 mmol/L [18]. Hypokalemia was defined as serum potassium equal to or less than 3.0 mEq/L [19].

7. Statistical analysis

IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis of the collected data. Normally distributed continuous variables are expressed as mean±standard deviation (SD), while categorical and abnormally distributed continuous variables are expressed as median and interquartile range or number and percentage (as appropriate). Student *t*-test and Mann-Whitney *U*-test were used for normally and abnormally distributed continuous data, respectively. The chi-square test was used for categorical data. *P*-value <0.05 was considered statistically significant.

Results

During the current study, 110 pediatric patients with DKA were recruited. Ten were excluded from the study according to the exclusion criteria: patients who had already started treatment (n=6) and those who declined to participate (n=4). The remaining 100 patients were randomized into 2 groups. Demographic and anthropometric data between the 2 groups, as well as risk factors for developing DKA, were matched (Table 1). A comparison of basic laboratory data between the groups showed no significance nor did the degrees of acidosis and hyperglycemia on presentation (Table 2). The amount of IV fluids administered to the groups showed no significant

Table 1. Demographic and anthropometric data of the studied diabetic ketoacidosis cases

Variable	Group I (N=50)	Group II (N=50)	*P*-value
Age (yr)	11.76±3.30	12.28±2.78	0.396
Sex			
Male	26 (52.0)	32 (64.0)	0.224
Female	24 (48.0)	18 (36.0)	
Weight (*z*-score)	0.04 (-2.8 to 1.9)	-0.65 (-2.6 to 1.6)	0.281
BMI (*z*-score)	0.01 (0.7–0.5)	0.10 (-0.2 to 0.3)	0.110
Height (z-score)	0.03 (-3.5 to 1.4)	-0.75 (-2.4 to 1.3)	0.291
Tanner staging			0.083
Nonpubertal	8 (16.0)	17 (34.0)	
Delayed	8 (16.0)	4 (8.0)	
Pubertal	34 (68.0)	29 (58.0)	
Duration of diabetes (yr)	4.86±2.81	4.55±3.31	0.612
Type of long-acting insulin			0.784
Glargine	42 (84.0)	43 (86.0)	
Degludec	8 (16.0)	7 (14.0)	
Dose of long-acting insulin units/kg, median (IQR)	0.33 (0.29–0.37)	0.33 (0.30–0.35)	0.486
Infection	13 (26.0)	9 (18.0)	0.334
Missed doses	7 (14.0)	13 (26.0)	0.134
Use of other hyperglycemic medications (n)	0 (0)	0 (0)	0.000

Values are presented as mean±standard deviation, number (%), or median (range) unless otherwise indicated.
Group I, conventional DKA management; group II, conventional DKA management plus subcutaneous long-acting insulin once daily; DKA, diabetic ketoacidosis; BMI, body mass index; IQR, interquartile range.

Table 2. laboratory data of the studied diabetic ketoacidosis cases

Variable	Group I (N=50)	Group II (N=50)	*P*-value
PH	7.09±0.10	7.08±0.09	0.189
Initial RBG (mg/dL)	426.06±91.77	440.72±87.98	0.417/t=0.815
Bicarbonate level (mEq/L)	9.6±5.6	9.4±5.3	0.195
Serum potassium (mEq/L)	3.93±0.64	3.98±0.69	0.657
Serum sodium (mEq/L)	137.28±4.94	136.88±3.78	0.652
Hemoglobin (g/dL)	12.42±1.16	12.82±1.10	0.656
Serum creatinine (mg/dL)	1.04±0.23	0.93±0.31	0.060
HbA1c (%)	10.03±1.30	9.70±1.21	0.194
Corrected sodium (mEq/L)	141.5 (139.0–144.8)	142.0 (140.0–147.8)	0.241
Corrected osmolarity (mOsm/L)	296.5 (291.7–301.8)	297.7 (291.6–309.7)	0.197
Urinary ketones			0.178
+1	7 (14.0)	2 (4.0)	
++2	18 (36.0)	17 (34.0)	
+++3	25 (50.0)	31 (62.0)	
Degree of acidosis			0.715
Mild	12 (24.0)	10 (20.0)	
Moderate	28 (56.0)	32 (64.0)	
Severe	10 (20.0)	8 (16.0)	

Values are presented as mean±standard deviation, median (range), or number (%) unless otherwise indicated.
Group I, conventional DKA management; group II, conventional DKA management plus subcutaneous long-acting insulin once daily; DKA, diabetic ketoacidosis; RBG: random blood glucose; HbA1c, glycosylated hemoglobin.
t=Student *t*-test.

Table 3. Comparison of IV fluids, insulin infusion duration, and insulin infusion dose between studied groups

Variable	Group I (N=50)	Group II (N=50)	*P*-value
Duration of IV fluids & insulin infusion (hr)			0.067
24–36	32 (64)	21 (42)	
36–48	14 (28)	24 (48)	
>48	3 (6)	5 (10)	
Duration of IV insulin infusion (hr)	72 (70.25–95.5)	68.5 (45.00–88.25)	<0.001
Total amount of insulin infusion administered units/kg	4.04±1.17	3.48±1.00	0.016

Values are presented as number (%), median (interquartile range), or mean±standard deviation.
Group I, conventional DKA management; group II, conventional DKA management plus subcutaneous long-acting insulin once daily; DKA, diabetic ketoacidosis; IV, intravenous.

Table 4. Comparison of complications between studied groups

Variable	Group I (N=50)	Group II (N=50)	*P*-value
No. of hypoglycemia events	23 (46.0)	12 (24)	0.029
Level of BG during hypoglycemia	57.9±4.48	57.7±4.87	0.929
No. of hypokalemia events	12 (24.0)	19 (38.0)	0.147
Level of potassium during hypokalemia	2.90±0.09	2.87±0.10	0.452
No. of cerebral edema events	0 (0)	0 (0)	0.000

Values are presented as number (%) or mean±standard deviation.
Group I, conventional DKA management; group II, conventional DKA management plus subcutaneous long-acting insulin once daily; DKA, diabetic ketoacidosis; BG, Blood Glucose.

difference (*P*=0.067) (Table 3), although the duration of insulin infusion was significantly shorter in group II (median [interquartile range, IQR]: 72 (70.25–95.5) vs. 68.5 (45.00–88.25), *P*<0.001). Similarly, group II needed significantly lower doses of insulin infusion (Table 3) and showed a decreased risk of hypoglycemia, with no increased risk of hypokalemia between the groups (Table 4).

Discussion

IV infusion of regular insulin is currently the preferred method for managing DKA in children [14]. Coadministration of SC long-acting insulin alongside IV insulin has been suggested as an alternative approach to accelerate the resolution of DKA [20]. However, this is not yet the standard of care due to

insufficient supporting data [21].

Thus, our study aimed to evaluate the use of long-acting insulin in the management of DKA in pediatric patients and its impact on recovery time and complications. We included 100 children with pre-existing type 1 diabetes who presented with DKA and divided them into 2 groups. Group I received the standard DKA treatment regimen, which included continuous short-acting insulin infusion and IV fluids. Group II received the standard treatment regimen along with their usual dose of SC long-acting insulin.

Our study demonstrated that children with DKA who received a concomitant dose of SC long-acting insulin, in addition to the IV insulin regimen, experienced a shorter duration of insulin infusion and required a lower total dose of insulin. Similarly, a recent retrospective study involving 190 pediatric patients with DKA investigated the coadministration of SC long-acting insulin alongside IV insulin. The study found that patients who received an early dose of SC long-acting insulin (0.2 units/kg) had a significantly shorter duration of IV insulin administration compared to those who received standard therapy alone (17.0 [IQR, 14–22.8] hours vs. 22.9 [IQR, 4.3–29.3] hours; $P<0.001$). Additionally, the coadministration of SC long-acting insulin resulted in a lower total dose of IV insulin required for DKA resolution (total units of IV insulin infused, mean±SD, units/kg: 1.74±0.64 vs. 2.32±1.34; $P=0.002$) [21]. In another retrospective study by Shankar et al. [13], the authors compared early coadministration of SC glargine (0.3 units/kg) with standard DKA therapy alone. They concluded that the addition of SC glargine was associated with a significantly shorter mean time to acidosis resolution (12.4±2.9 hours vs. 17.1±6.2 hours, $P<0.001$) and a reduced duration of insulin infusion (14.8±6.0 hours vs. 24.4±9.0 hours, $P<0.001$). Importantly, these 2 studies included both newly diagnosed and pre-existing type 1 diabetes mellitus (T1DM) patients; however, they did not compare the outcomes between these groups. A few adult studies investigated coadministration of long-acting insulin with standard DKA management. In 2022, in a randomized controlled trial involving 60 adults with DKA, Thammakosol and Sriphrapradang [12] compared the early coadministration of glargine with IV insulin to standard IV insulin infusion and concluded that glargine coadministration (0.3 units/kg) resulted in more rapid resolution of DKA (9.89±3.81 hours vs. 12.73±5.37 hours, $P=0.02$). Furthermore, a meta-analysis of studies comparing the coadministration of long-acting insulin with standard DKA management versus standard management alone concluded that the coadministration significantly accelerated DKA (mean difference: -4.19 hours; 95% CI, -7.81 to -0.57; $P=0.02$) [22]. The duration of DKA resolution in the present study was longer compared to other studies, such as the one by Harrison et al. [23], which examined the effect of coadministration of long-acting insulin alongside standard therapy in pediatric DKA. This difference may be attributed to the greater number of severe DKA cases in this study, which may increase the time needed for DKA resolution. Additionally, in this study, we followed a more conservative approach to the insulin infusion dose, using a lower dose of 0.05 IU/kg/hr compared to the higher dose of 0.1 IU/kg/hr used in the study of Harrison et al. [23], which may also have influenced the duration of infusion.

Observing adverse effects, the current study showed that coadministration of SC long-acting insulin with insulin infusion was associated with a statistically significant lower incidence of hypoglycemic events. In addition, this study found no increased risk of hypokalemia between the studied groups. No events of cerebral edema were documented among the studied groups. The lower rates of hypoglycemia observed in group II can be attributed to the stabilizing effect of long-acting insulin, which reduces the need for higher total doses of insulin infusion (as shown in Table 3). This reduction in insulin infusion decreases the risk of hypoglycemia associated with higher insulin doses. In a prospective randomized study, Hsia et al. [24] studied the coadministration of long-acting SC insulin (0.25 U/kg) with insulin infusion in 61 patients with diabetes. They concluded that adding one dose of SC long-acting insulin to insulin infusion was not associated with hypoglycemia; furthermore, the addition of SC long-acting insulin was associated with a decreased incidence of rebound hyperglycemia. Similarly, in a study by Harrison et al. [23], coadministration of long-acting SC insulin with insulin infusion was examined in 149 DKA admissions. Their results showed that this coadministration did not significantly increase the risk of hypoglycemia, with an incidence of 29% compared to 20% in the standard therapy group ($P=0.4$). In line with these findings, a recent retrospective study by Welter et al. [21] involving 190 pediatric patients with DKA evaluated early coadministration of long-acting insulin during DKA management. The authors concluded that this approach did not increase the risk of hypoglycemia, as indicated by similar means of lowest blood glucose levels (104±39.9 mg/dL vs. 105±35.8 mg/dL, $P=0.834$), nor did it increase the risk of hypokalemia, with comparable lowest median serum potassium concentrations (3.3 [IQR, 2.8–3.8] mEq/L vs. 3.3 [IQR, 2.6–3.9] mEq/L, $P=0.10$). Similar results were found by Thammakosol and Sriphrapradang [12]. Contrary to the results of this study, Harrison et al. [24] found that coadministration of long-acting insulin with insulin infusion during DKA treatment can be associated with an increased risk of hypokalemia. This contradiction can be explained by the differing definitions of hypokalemia used in the 2 studies. In this study, hypokalemia was defined as a serum potassium level of 3.0 mEq/L or less [19], while that in the study of Harrison et al. [23] was defined as a serum potassium level less than 3.5 mEq/L. This difference in definition could lead to a higher number of patients being diagnosed with hypokalemia.

In the current study, group I exhibited a marginal increase in serum creatinine compared to group II, suggesting that group I suffered from more dehydration. Previous studies suggested that severe dehydration can exacerbate the metabolic stress of DKA, potentially leading to longer recovery times [25,26]. However, in the current study, the difference in the duration of IV fluid administration was not significant. Additionally, the degrees of acidosis and ketosis in the 2 groups showed no significant difference, with group II showing marginally more acidosis as

lower PH and bicarbonate levels and higher urinary ketones. This finding suggests that the initial marginal difference in serum creatinine did not influence the duration of insulin infusion. Moreover, supporting this explanation, Sottosanti et al. [27] pointed out that the rapidity of recovery from DKA was not correlated with the degree of dehydration. Rather, the level of acidosis was a stronger predictor of the duration of treatment than hydration status alone.

The current study has several limitations, including a relatively small sample size, a lack of documentation for rebound hyperglycemia, and the absence of records regarding the duration of hospital stay for the patients. Furthermore, the type of long-acting insulin given to group II was not standardized, the study was not blinded, and it exclusively focused on patients with pre-existing T1DM.

In conclusion, the current study demonstrated that coadministration of SC long-acting insulin in addition to the usual insulin infusion during DKA management in the pediatric population can lead to a shorter duration of insulin infusion. In addition, this approach is not associated with increased risk of hypoglycemia or hypokalemia. Moreover, coadministration of long-acting insulin may be associated with a decreased incidence of hypoglycemia.

Notes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability: The data that support the findings of this study can be provided by the corresponding author upon reasonable request.

Author contribution: Conceptualization: MHA, AE; Data curation: AS, GG; Formal analysis: AE, AS; Methodology: MHA, AE, AS; Project administration: MHA, GG; Visualization: AS, GG; Writing – original draft: MHA, AE; Writing – review & editing: AE, AS, AES, GG

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