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Original Research Article

LOW-DOSE VS STANDARD-DOSE INSULIN IN THE MANAGEMENT OF PEDIATRIC DIABETIC KETOACIDOSIS

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Abstract

Background: The current recommended dosage of insulin in the management of diabetic ketoacidosis (DKA), which is 0.1 U/kg per hour, lacks robust clinical evidence to support its efficacy. Physiological dose-response investigations have determined that even lower doses can effectively restore ketonemia and acidosis to normal levels. Reducing the dosage of insulin may offer benefits during the early stages of treatment, particularly when there is a need for a gradual decline in glucose levels, electrolyte levels. Low-dose vs standard-dose insulin in the management of pediatric diabetic ketoacidosis. **Materials and Methods:** Participants included consecutive children aged 13 years or younger who exhibited diabetic ketoacidosis. The monitoring of blood glucose levels, specifically capillary or venous blood glucose, was conducted at regular intervals of every half hour. Serum electrolytes, blood glucose, urea, calcium, magnesium, phosphate, hematocrit, and venous blood gases, along with corresponding anion gap, were monitored at two-hour intervals during the first five hours and then at four-hour intervals until resolution of ketoacidosis. This study comprised a total of 50 participants diagnosed with diabetic ketoacidosis (DKA). **Result:** This study included a total of 50 children diagnosed with diabetic ketoacidosis (DKA), with 25 children assigned to the low-dose group (Group A) and another 25 children assigned to the standard dose group (Group B). A prevalence rate of 48% was observed in children who presented with diabetic ketoacidosis (DKA) as the initial manifestation of newly developed diabetes. A prevalence rate of 36% was observed in children with severe diabetic ketoacidosis (DKA). The duration required for the resolution of ketoacidosis was 23.11±2.58 hours in the low-dose group and 24.11±2.98 hours in the standard-dose group, with no statistically significant difference observed between the two groups (P=0.44). The duration required for a specific parameter of ketoacidosis to reach the desired endpoints (pH ≥7.30, HCO3 ≥15 mEq/L, BOBH <1 mmol/L, and normal sensorium) was comparable between the two groups. The rate of decline in blood glucose levels per hour and the duration required to reach a level of 250 mg/dL were comparable between the two groups. **Conclusion:** It is determined that the duration of ketoacidosis resolution was comparable between the low-dose and standard-dose insulin infusion methods, while the low-dose insulin approach exhibited a reduced incidence of complications associated with therapy.

INTRODUCTION

Diabetic ketoacidosis (DKA) is responsible for a significant proportion of initial hospitalisations related to diabetes, ranging from 8% to 29%. Consequently, it significantly contributes to the financial burden associated with the management of children diagnosed with type 1 diabetes mellitus.[1] The management of diabetic ketoacidosis (DKA) is primarily centred around fluid correction and insulin therapy. While rehydration alone can lead to partial correction of hyperglycemia, the normalisation of hyperglycemia and the suppression of lipolysis and ketogenesis necessitate the use of insulin.[2] Over

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the course of four decades, there has been significant development in insulin therapy with the objective of determining an optimal dosage that can effectively address ketoacidosis while minimising associated complications. The utilisation of high-dose (1 U/kg per hour) and bolus insulin therapies in the past has diminished in popularity due to research findings suggesting that a comparable therapeutic outcome, while minimising negative effects, can be attained with a dosage of 0.1 U/kg per hour.[3-5] Subsequently, the administration of insulin through continuous infusion at a rate of 0.1 U/kg per hour became the established practise in the treatment of diabetic ketoacidosis (DKA), even though there is limited clinical evidence supporting its superiority over lower doses.[6,7] Several scholarly articles have emphasised the efficacy of administering insulin doses that are lower than the officially recommended standard dosage. The researchers Noyes et al. conducted an observation in which they found that insulin doses of 0.03 and 0.05 U/kg per hour were effective in normalising ketosis in patients with diabetic ketoacidosis (DKA).[8]Puttha et al. and Al Hanshi and Shann, in their respective studies on paediatrics, have documented that a dosage of 0.05 U/kg per hour demonstrated comparable efficacy to the standard dosage in the correction of acidosis.[9,10] The determination of the endpoint of therapy for diabetic ketoacidosis (DKA) is primarily based on the resolution of acidosis rather than the reduction of blood glucose (BG) levels, as widely recognised in the literature. Nevertheless, a significant portion of the discourse surrounding the management of diabetic ketoacidosis (DKA) has revolved around the early stages of treatment, specifically emphasising the role of sodium, water, blood glucose reduction, and their impact on swift changes in osmolality. While the direct association between rapid blood glucose (BG) reduction and cerebral edoema remains inconclusive, certain studies have documented a swift decline in BG levels when administering doses exceeding 0.05 U/kg per hour.[11] Furthermore, it has been observed that children receiving a dosage of 0.05 U/kg per hour of insulin experience a more gradual decrease in plasma osmolality, attributed to a slower reduction in blood glucose levels, in comparison to those receiving a dosage of 0.1 U/kg per hour.[10] The intracellular shift of glucose induced by insulin leads to a non-equimolar increase in serum sodium, with the sodium level experiencing a smaller increase compared to the decrease in blood glucose level. Abrupt reductions in blood glucose levels can lead to a diminished rise in serum sodium levels, resulting in a more pronounced decrease in osmolality than anticipated. Hence, certain authors posit that the reduction or postponement of insulin dosage may result in a gradual decline in blood glucose levels and a gradual adjustment in electrolyte levels. Additionally, it is worth noting that in the context of developing economies, children diagnosed with diabetic ketoacidosis (DKA) may experience potential advantages from a reduced insulin dosage. This is due to the presence of comorbidities, such as malnutrition, which significantly increase the likelihood of therapy-induced hypokalemia and hypoglycemia.[12]

MATERIALS AND METHODS

50 Participants included consecutive children aged 14 years or younger who exhibited diabetic ketoacidosis (DKA), which was defined as having hyperglycemia (blood glucose level >200 mg/dL), acidosis (pH <7.3 or bicarbonate level <15 mEq/L), and ketonemia (beta-hydroxybutyrate level ≥3 mmol/L) or moderate to large ketonuria as indicated by a urine dipstick test.[13] Exclusion criteria encompassed children who presented with septic shock as well as those who had undergone insulin administration prior to enrollment. The first set of instructions indicated that 50 units of regular insulin should be mixed with 50 mL of normal saline, with the conversion rate of 0.1 mL equaling 0.1 U. The second set of instructions specified that 25 units of regular insulin should be mixed with 50 mL of normal saline, with the conversion rate of 0.1 mL equaling 0.05 Unit. The syringes utilised in the trial were assigned a random number and labelled with three alphanumeric codes, as well as the dosage of the study drug (0.1 mL/kg/hour). The study drug was prepared at regular intervals of 5 hours and subsequently administered to the nursing sister who was responsible for medication administration. The administration of continuous insulin infusion was conducted via a dedicated intravenous line utilising an infusion pump. The group assigned to the standard dose received regular insulin at a rate of 0.1 U/kg/hour, while the low-dose group received regular insulin at a rate of 0.05 U/kg/hour. The endpoint of the study was defined as the resolution of ketoacidosis, which was determined by meeting the following criteria: a pH level of 7.30 or higher, a bicarbonate level of 15 mEq/L or higher, and a BOHB level of less than 1 mmol/L. Subsequently, the child's treatment regimen was transitioned to regular subcutaneous insulin administration, with a 30-minute overlap period in conjunction with intravenous insulin. The calculation of fluid volume involved the addition of the deficit (85 mL/kg) and the distribution of 48-hour maintenance fluid over a 48-hour period.[13] During the initial hour of resuscitation, a standard volume of 20 mL per kilogramme of body weight of normal saline was administered to all paediatric patients. An additional 20 mL/kg of normal saline was administered for one hour to children exhibiting signs of hypoperfusion or hypotensive shock. The bolus and other infusions were subtracted from the total calculated volume to be infused. During the initial 5-hour period, a solution of normal saline was administered, which was subsequently replaced with a solution of 0.45%

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saline based on the patient's serum sodium levels and effective osmolality. Dextrose solution with a concentration of 5% was administered to the hydrating fluid when the blood glucose level reached a value of 250 mg/dL or lower. If the blood glucose level reached a value of 100 mg/dL or lower, even with a dextrose concentration of 12.5%, the infusion of insulin was gradually reduced by 0.01 mL/kg/hour every 30 minutes. Following the resuscitation and documentation of urine output, a solution containing potassium chloride at a concentration of 40 milliequivalents per litre (mEq/L) was introduced into the rehydrating fluid. Continuous cardiac monitoring was conducted, and the administration of potassium was adjusted to achieve and maintain a serum level within the range of 3.5-5.5 mEq/L. The monitoring of blood glucose levels, specifically capillary or venous blood glucose, was conducted at regular intervals of every half hour. Additionally, the measurement of beta-hydroxybutyrate (BOHB) levels was performed hourly using a ketone metre, following the necessary calibration process. In instances where glucose readings exceed the upper limit of the glucometer range (greater than 500 mg/dL) or when there is inadequate blood flow in the peripheral regions, capillary blood glucose levels were cross-validated through laboratory analysis utilising the hexokinase method. Hourly monitoring of urine ketone and glucose levels was conducted using the dipstick method. The measurement of glycated haemoglobin (HbA1c) was performed upon the patient's admission. Serum electrolytes, blood glucose, urea, calcium, magnesium, phosphate, hematocrit, and venous blood gases, along with corresponding anion gap, were monitored at two-hour intervals during the first five hours and then at four-hour intervals until resolution of ketoacidosis. Hourly monitoring was conducted to assess vital signs, fluid levels, and the electrocardiogram, as well as to perform neurologic assessments. The assessment of nutritional status was conducted in accordance with the standards established by the World Health Organisation.[14]

The main measure of interest in this study was the duration required for the resolution of ketoacidosis, as indicated by specific biochemical criteria: a pH level of 7.3 or higher, a bicarbonate level of 15 mEq/L or higher, and a beta hydroxybutyrate level below 1 mmol/L. The secondary outcomes assessed in this study included the rate of blood glucose reduction until it reached a level of 250 mg per dL or lower, as well as the occurrence of hypoglycemia, hypokalemia, and cerebral edoema, or any deterioration in cerebral edoema. Hypokalemia is characterised by a serum potassium level below 3.5 mEq/L and/or the presence of electrocardiographic changes that indicate its likelihood. Hypoglycemia was operationally defined as a blood glucose level equal to or less than 60 mg/dL. The diagnosis of cerebral edoema was made based on the criteria outlined by Muir et al.[15]

Statistical Analysis

The data of the patient was analysed based on their assigned group. The chi-square test was utilised to compare the proportion, with the Fisher exact test employed if the cell frequency was less than 5. Additionally, the relative risk with a 95% confidence interval was calculated as appropriate. The data analyses were conducted using SPSS, specifically version 25.0 (SPSS Inc).

RESULTS

This study included a total of 50 children diagnosed with diabetic ketoacidosis (DKA), with 25 children assigned to the low-dose group (Group A) and another 25 children assigned to the standard dose group (Group B). The baseline characteristics of the study participants were found to be similar. A prevalence rate of 48% was observed in children who presented with diabetic ketoacidosis (DKA) as the initial manifestation of newly developed diabetes. A prevalence rate of 36% was observed in children with severe diabetic ketoacidosis (DKA). The duration required for the resolution of ketoacidosis was 23.11±2.58 hours in the low-dose group and 24.11±2.98 hours in the standard-dose group, with no statistically significant difference observed between the two groups (P=0.44).

The duration required for a specific parameter of ketoacidosis to reach the desired endpoints (pH ≥7.30, HCO3 ≥15 mEq/L, BOBH <1 mmol/L, and normal sensorium) was comparable between the two groups. In the subgroup analysis focusing on severe diabetic ketoacidosis (DKA), no statistically significant difference was observed in the duration required for the resolution of ketoacidosis between the two groups. The low-dose group exhibited a significantly lower hazard ratio, indicating a 60% reduction in the resolution of ketoacidosis compared to the standard dose group. The low-dose group exhibited a significantly lower hazard ratio of BOHB resolution (<1 mmol/L) by 64%.

The rate of decline in blood glucose levels per hour and the duration required to reach a level of 250 mg/dL were comparable between the two groups. Nevertheless, the standard-dose group exhibited a greater decline in blood glucose levels at both the 5-hour and 24-hour marks, as indicated by the higher standard error of the mean (SEM), in comparison to the low-dose group.

There was no significant difference observed in the standard error of the mean (SEM) trend between the standard-dose group (0.32±0.07 at 5 hours, P=0.25; 0.21±0.03 at 24 hours, P=0.59) and the low-dose group (0.31±0.07 at 5 hours; 0.18±0.03 at 24 hours). There was no statistically significant difference observed in the proportion of patients who achieved a blood glucose level of 250 mg/dL at the 5-hour mark between the standard-dose and low-dose groups (80% vs 72%). The incidence of a decrease in blood glucose levels exceeding 90 mg/dL per

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hour was found to be higher in the standard-dose group (80%) compared to the low-dose group (60%). The low-dose group exhibited a hazard ratio that was 1.37 times higher than the standard-dose group in achieving a blood glucose level of 250 mg/dL or less by the end of 5 hours (P=0.41). The incidence of hypoglycemia (P=0.42) and at least one episode of hypokalemia (P=0.36) was found to be greater in the standard-dose group when compared to the low-dose group. No hypoglycemia patients experienced two or more episodes of hypoglycemia. The incidence of hypokalemia was observed to be higher in malnourished children belonging to the standard-dose group (P=0.22). Additionally, a greater number of children in the standard-dose group necessitated an increase in the concentration of dextrose and a reduction in the rate of insulin infusion at least once in order to address the declining blood glucose levels. There was no need to administer additional insulin infusion to any of the children.

Table 1: Basic parameter in Children with Diabetic Ketoacidosis

Parameter	Group A=25		Group B=25	
	Number /Mean	Percentage	Number /Mean	Percentage
Age in years	7.14±0.58		8.55±0.74	
Duration of diabetes, mo	29.45±3.85		29.55±3.41	
With previous DKA	18	72	15	60
Duration of symptom	4.59±0.39		4.61±0.42	
Malnutrition	5	20	8	32
New onset DKA	13	52	11	44
Established diabetes mellitus	13	52	13	52
Hemodynamic status, n (%)Compensated shock	3	12	6	24
Hypotensive shock	1	4	1	4
m-GCS 8-14 at admission, n (%)	7	28	8	32
Hemoglobin A1c, %	13.74±2.54		13.66±2.85	
pH	7.14±0.41		7.09±0.33	
Bicarbonate , mEq/L	9.01±1.52		7.22±1.78	
PCO2, mm Hg	21.04±3.91		20.04±3.44	
Capillary BOHB, mmol/L	5.55±0.74		5.41±0.69	
Blood urea nitrogen, mg/dL	11.66±2.22		13.03±2.89	
Creatinine, mg/dL	1.11±0.13		1.21±0.21	
Sodium, mEq/dL	136.98±8.74		138.14±7.89	
Corrected sodium, mEq/L	145.69±7.89		146.99±8.74	
Potassium, mEq/L	4.0±0.66		4.0±0.66	
Urine ketones				
3+ (80 – 160 mg/dL)	16	64	16	64
4+ (>160 mg/dL)	9	36	9	36
Fluid received, mL/kg	15.87±2.67		14.01±3.69	
Blood glucose change, mg/dL	59.97±12.21		29.74±13.44	
Capillary BOHB change, mmol/L	0.31±0.09		0.41±0.09	
Duration of 0.9% saline therapy, h	5.12±1.11		6.54±1.31	
Severity				
Mild	10	40	7	28
Moderate	7	28	8	32
Severe	8	32	10	40

Table 2: Primary outcome

Primary outcome	Group A=25	Group B=25
pH	7.35±0.04	7.31±0.04
Time for bicarbonate≥15 mEq/L, h	15.77±3.74	18.88 ±2.74
Time for resolution of DKA, h	23.11±2.58	24.11±2.98
Time for pH ≥7.30, h	14.11±1.74	17.89±1.44
Bicarbonate, mEq/L	17.01±1.71	16.71±1.37
Time for BOHB <1 mmol/L, h	22.03±2.58	18.16±2.67
Time for resolution of DKA(including normal sensorium), h	22.98±2.52	23.41±2.69
Time for the normal sensorium, h	3.88±0.15	5.89±1.11
BOHB, mmol/L	0.77±0.11	0.74±0.15

Table 3: Secondary outcome

Secondary outcome	Group A=25		Group B=25	
	Number /Mean	Percentage	Number /Mean	Percentage
Hypokalemia	8	32	11	44
Hypoglycemia	1	4	3	12
Tapering of insulin infusion	11	44	12	48
Blood glucose decrease until the level reached ≤250 mg/dL, mg/dL/hour	57.85±5.58		65.69±5.98	
Blood glucose, mg/dL	221.36±12.89		222.74±13.39	

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DISCUSSION

Our study revealed that the duration of ketoacidosis resolution was comparable between the low dose insulin and standard dose insulin cohorts. The low dose group exhibited a 60% reduction in hazard ratio for the resolution of ketoacidosis. The recommended insulin level for the recovery of ketoacidosis ranges from 20 to 200 micro Unit/ml, and it can be attained using a reduced dosage of insulin.[16,17] Previous studies have indicated that the standard dosage of insulin has been found to result in plasma insulin levels that exceed the optimal threshold.[17] In this study, the investigation focused on the reduction of insulin dosage by up to 0.025 U/kg/hour in paediatric patients with diabetic ketoacidosis (DKA), as compared to the standard dosage.[18-20] In their study, Puttha et al,[14] observed that there was a comparable increase in pH at the six-hour mark and a similar median time for resolution of ketoacidosis (pH >7.3) between the low and standard-dose groups. In their study, Kapellen et al. (year) found that the administration of 0.025 U/kg/hour compared to 0.1 U/kg/hour resulted in a comparable duration of acidosis.[20] In a controlled study conducted by Nallasamy et al., it was determined that the efficacy of low-dose insulin was comparable to that of standard dose insulin in the resolution of ketoacidosis. Nevertheless, the monitoring of BOHB was not included as one of the endpoints for ketoacidosis.[19] The standard-dose group exhibited a notable decline in blood group levels within a 24-hour period, although the reduction rate fell within the range reported in previous studies (36 to 90 mg/dL/h).[18,19]Nallasamy et al observed that the rate of decline in blood glucose levels until reaching a threshold of 250 mg/dL was comparable between the low dose and standard-dose groups. Therefore, it can be concluded that the administration of an appropriate dosage of insulin that results in the desired plasma insulin level within the range of 20 to 200 micro unit/mL can effectively produce the desired therapeutic clinical response without causing any disruption to osmotic hemostasis.[19] Although the measurement of plasma insulin levels was not conducted in our study, our findings provide evidence in favour of the utilisation of low-dose insulin for the purpose of achieving clinically significant resolution of ketoacidosis and gradual reduction of blood glucose levels. Previous studies conducted in the field of paediatrics have found that the administration of insulin doses higher than 0.05 units/kg/hour has resulted in a significant decrease in blood glucose levels.[21] Additionally, it has been observed that the gradual reduction in plasma effective osmolality is associated with a slower decrease in blood glucose levels when using an insulin dose of 0.05 U/kg/hour. The association between the initial hour's insulin dosage and the volume of fluid administered over a four-hour period was found to be correlated with the risk of cerebral edoema in the treatment of diabetic ketoacidosis (DKA), even after accounting for the severity of the condition.[22] The complexity of our setting arises from the presence of delayed presentation, severe ketoacidosis, undernutrition, and high effective osmolality upon presentation. As a result, it is crucial to adopt a cautious approach during the initial hours of therapy in order to prevent osmotic disequilibrium and cerebral edoema. It was observed that there was a similarity in fluid administration and the alteration of effective osmolality between the two groups. The incidence of hypoglycemia and the reduction of insulin infusion despite reaching the maximum glucose concentration were more prevalent in the standard dosage cohort. In a study conducted by Nallasamy et al,[19] it was observed that the standard-dose group experienced a higher frequency of episodes where blood glucose levels fell below the desired range (> 90 mg/dL). This finding is consistent with our own study setting. Therefore, the administration of a low dose of insulin following the initial hour of fluid resuscitation is a viable and secure strategy in situations where a gradual reduction in blood glucose levels, effective osmolality, and a smooth resolution of ketoacidosis are sought. The incidence of therapy related complications, hypokalemia, and hypoglycemia was found to be higher in the group receiving the standard dose. In this study group, it is likely that hypokalemia was contributed to by factors such as undernutrition, prolonged illness, severe ketoacidosis, and osmotic diuresis. Furthermore, it is plausible that the administration of insulin could have played a role in the reduction of potassium levels, in addition to the aforementioned factors. In a comparable context, Nallasamy et al,[19] and Moulik et al,[23] observed a greater incidence of hypokalemia in the standard-dose group. Previous studies have reported a higher incidence of hypoglycemia in the standard-dose group compared to our study. The implementation of a monitoring protocol that involved measuring blood glucose levels every half hour may have played a role in the observed decrease in the occurrence of hypoglycemia in our research investigation. Nevertheless, it is imperative to acknowledge the potential advantageous impact of reducing the dosage of insulin. The measurement of blood ketone levels was included as one of the study's endpoints, which differs from the approach taken in previous studies.[18,19] In contrast to previous investigations, our study encompassed the entire duration of ketoacidosis until its resolution, during which we meticulously gathered and examined data spanning a 24-hour period. Additionally, we conducted an analysis of the factors that are specific to limited-resource settings, thereby allowing the findings of the study to be applicable to countries with low and middle income levels.

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CONCLUSION

It is determined that the duration of ketoacidosis resolution was comparable between the low dose and standard-dose insulin infusion methods, while the low-dose insulin approach exhibited a reduced incidence of complications associated with therapy. Therefore, administering insulin through infusion at a rate of 0.05 units per kilogramme per hour is a more secure method for managing diabetic ketoacidosis (DKA) in paediatric patients.

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