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A STUDY TO EVALUATE THE REQUIREMENT OF HIGHER THAN RECOMMENDED DOSES OF SUBCUTANEOUS INSULIN AFTER RESOLUTION OF DIABETIC KETOACIDOSIS IN CHILDREN

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A B S T R A C T

Objective: To evaluate the effect of higher than recommended initial subcutaneous regular insulin dosage on glycemic control in the first 48 hours of therapy after resolution of diabetic ketoacidosis (DKA).

Methods: Records of patients with DKA, hospitalized in the past 3 years [n=72, median age=8.0 (IQ 6.0-10.0 years), male:female ratio 1:0.75] were analyzed. The patients were designated into two groups according to the starting doses of subcutaneous regular insulin after resolution of DKA. Group 1 (n=26) received a median dose of 1.4 U/kg/day (1.3-1.5) and group 2 (n=46) received a median dose of 0.92 U/kg/day (0.8-1). Clinical and laboratory data were compared using standard statistical methods.

Results: The number of patients who experienced hypoglycemia (<50 mg/dL) were 2 (9.67%) in group 1 and none had symptomatic hypoglycemia. Episodes of blood glucose in the target range (100-200 mg/dl) were significantly higher in group1 than in group 2 (p=0.001) and the number of hyperglycemic episodes were significantly lower in group1 (p=0.001). The incidences of hypoglycemia and hyperglycemia between the two groups were not related to the age of presentation or the severity of disease at onset. Comparison of the glycemic variability indices between the 2 groups revealed the standard deviation to be 78.7 and 75.8 and coefficient of variation to be 0.36 and 0.29 respectively.

Conclusion: After resolution of DKA, a higher initial dose of 1.3-1.5 U/kg/day subcutaneous regular insulin is associated with better glycemic control in children without an increase in risk of hypoglycemia.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease caused by T cell-mediated pancreatic β cell impairment (1). When diagnosed with T1DM, patients are immediately treated with insulin to avoid metabolic decompensation, diabetic ketoacidosis (DKA), and long-term chronic complications (2, 3). DKA is the presenting manifestation of diabetes in 25% (15-83%) of children with T1DM and in 5-33% children with T2DM (4, 5).The risk of DKA in established T1DM is 1-10% per person per year (6). Incorrect dosage or omission of insulin is one of the factors precipitating DKA in 75% of the cases. Keeping pancreatic β cell function in T1DM patients could result in better glycemic control, decrease glycosylated hemoglobin (HbA1c) levels, minimize blood glucose fluctuations, and risks of long- term complications, such as risk of retinopathy and kidney disease (7,8). Keenan (9) reported that there was residual endogenous insulin secretion in 67.4% T1DM patients with disease duration of 50 yrs or longer, and in nine post-mortem examinations of pancreatic tissue, insulin positive cells were found. Rother (10) also reported residual insulin secretion by pancreatic β cells in cases of long-standing T1DM that was suppressed by exogenous insulin, which suggests that pancreatic β cells are protected by exogenous insulin. After resolution of DKA, there is a transition to subcutaneous insulin therapy. Several factors influence the

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initial subcutaneous daily insulin dose. It is known that the required initial daily insulin dose may vary according to many factors including age, body weight, stage of puberty, duration and phase of diabetes (11). An excellent initial subcutaneous insulin dose estimate is one that provides tight blood glucose control and minimizes the risk of hypoglycemia. The dose is usually higher in pubertal children. On the other hand, most children with new onset diabetes have some residual beta cell function (the honeymoon period), which reduces exogenous insulin needs. The recommended regimen of subcutaneous insulin dosing according to age (12) is presented in table 1.

Table 1

Age(yrs)	Target glucose(mg/dl)	Total daily insulin(U/kg/day)
0-5	100-200	0.6-0.7
5-12	80-150	0.7-1
12-18	80-130	1-1.2

The recommended total daily insulin requirement gradually increases with age. The optimal insulin dose can only be determined empirically, with frequent self monitored blood glucose levels and insulin adjustment by the diabetes team (12). Regular insulin is soluble crystalline zinc insulin, an essential component of most daily replacement regimens (13). Due to its chemical structure, it has a wide peak and a long tail for bolus insulin, and thus cannot mimic the activity of the β cell, but is available to initiate treatment after resolution of DKA and serves to determine the daily insulin dose before basal-bolus insulin regimen. The ideal time to begin administration of subcutaneous insulin is just before a meal. In order to avoid rebound hyperglycemia, rapid acting insulins (lispro or aspart) are administered subcutaneously 15-30 minutes prior and regular insulin 1-2 hour prior to stopping insulin infusion (12).

It has previously been reported that intensive insulin therapy would improve endogenous insulin secretion, consequently leading to better glycemic control. Thus, one of the aims of therapy following DKA is to control blood glucose levels as early as possible. Higher initial insulin doses could rapidly decrease blood glucose levels, but their effect on blood glucose fluctuations has not been extensively investigated (14). Therefore, this first study from India, aims to investigate the requirement of higher than recommended doses of subcutaneous insulin for optimal control of blood glucose after resolution of DKA in children with newly diagnosed type 1 diabetes mellitus in a tertiary care hospital.

METHODS

This study was conducted in Dr B C Roy Post Graduate Institute of Paediatric Sciences in Kolkata after hospital ethics committee approval. Hospital records of patients who presented in the last 3 years (March 2014-February 2017) were analyzed. Diagnosis of T1DM and DKA were made according to the 2014 International Society for Paediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines for Diabetes in Childhood and Adolescence (15).

Children ≤12 yrs of age presenting with DKA were included in this study. However infants, patients having additional endocrine diseases, severe liver or kidney damage, chronic cardiac insufficiency, chronic systemic diseases like asthma, children consuming drugs that cause hyperglycemia and those with inadequate hospital records were excluded from this study. Data regarding severity of DKA (Table 2), starting subcutaneous total daily dose of insulin, number of hypoglycemic events (blood glucose levels ≤50 mg/dl), number of hyperglycemic events (blood glucose >200 mg/dl), glycosylated haemoglobin (HbA1c) levels at presentation, arterial blood gas values, blood glucose values at presentation and before start of subcutaneous insulin therapy were collected. Finally the patients were divided into 2 groups, group 1 consisted of patients who received ≥1.20U/kg/day subcutaneous insulin [n=26] and Group2 consisted of those who received <1.20U/kg/day [n=46]. Glycemic variability indices [standard deviation (SD), coefficient of variation (CV), maximum blood glucose, minimum blood glucose] were calculated and compared between the two groups. All blood glucose measurements were performed by the same capillary blood glucose monitoring machine (SD check glucometer with SD check gold glucostrips, SD Biosensor Inc, Republic of South Korea**),** an electronic glucometer using the modified glucose oxidase method, calibrated monthly by electronic calibrators. Clinical and laboratory data were collected and analysed. Laboratory data included complete blood counts, blood culture, and liver and renal function tests. 5 patients in group 1(19.23%) and 7 patients in group 2(15.21%) had leucocytosis (p=0.746); haemoglobin and platelet counts being normal. The median leucocyte count in group 1 was 12,000 and in group 2 was 14,000. 4 patients in group 1(15.38%) and 3 patients in group 2 (6.52%) had positive blood cultures (p=0.244) and were treated with intravenous antibiotics according to their antibiograms.

Table 2 Classification of severity of DKA (12)

Parameters	Normal	Mild	Moderate	Severe
CO2(mEq/L,venous)	20-28	16-20	10-15	<10
pH(venous)	7.35-7.45	7.25-7.35	7.15-7.25	<7.15
Clinical	No change	Oriented, alert but fatigued	Kussmaul respirations; oriented but sleepy; arousable	Kussmaul or depressed respirations; sleepy to depressed sensorium to coma

After resolution of DKA, we advanced oral feeds, reduced intravenous fluids and subsequently stopped them and shifted from insulin infusion to subcutaneous therapy. Before transition to basal bolus regimen, we started all patients on regular insulin every 6 hours to determine the daily insulin requirement. Pre meal blood glucose measurement was performed before each insulin injection 30 minutes before the meals and the insulin dose was determined according to the blood glucose levels: 100-200 mg/dL, same as the previous dose; >200 mg/dL, 110% of the previous dose; <100 mg/dL, 90% of the previous dose (12). A professional dietician planned the patients' diet which contained carbohydrates providing approximately 50-55%, fat up to 30-35%, and protein 10-15% of daily energy requirements (17). Four meals and three snacks were given a day and no additional food was consumed unless hypoglycemic events occurred. Blood glucose levels were measured more frequently in patients who suffered from any signs of hypoglycemia or hyperglycemia.

Statistics

Data was presented as median (25%-75%) or n (%), along with SDs. We used Mann-Whitney U-test and chi-square test to compare numerical and categorical variables respectively between groups. A p-value of <0.05 was chosen to represent statistical significance.

RESULTS

Table 3 Descriptive data between the 2 groups

Parameters	Group 1(n=26)	Group 2(n=46)	p-value
Age(years)	9.5 (6-11.5)	8 (5.4-10)	0.5
Male	14 (53.8%)	27 (58.6%)	0.805
Blood glucose on admission(mg/dl)	462 (365-576)	464 (392-571)	0.925
pH	7.17 (7.05-7.23)	7.16 (7.02-7.23)	0.877
Bicarbonate (mmol/ml)	9.5 (7.2-11.5)	8.7 (5.4-12)	0.7
HbA1C	8.5 (7.1-9.3)	8.2 (6.3-9.2)	0.726
Dose of insulin infusion (U/kg/hr)	0.1 (0.1-0.1)	0.1 (0.1-0.1)	0.995
Blood glucose at start of subcutaneous insulin (mg/dl)	157 (122-191)	154 (121-198)	0.974
Starting insulin dose (U/kg/day)	1.40 (1.3-1.5)	0.92 (0.8-1)	0.003
Insulin dose on 1st day (U/kg/day)	1.5 (1.42-1.58)	0.98 (0.92-1.03)	0.0007

Thus, the initial insulin requirement and the dose given on the first day after resolution of DKA were significantly higher in Group 1, rest all the parameters of the two groups were comparable.

Table 4 Comparison between the blood glucose measurements between the 2 groups

	Group 1(n=26)	Group2(n=46)	p-value
No. of patients who experienced episodes <50 mg/dl	2 (7.69%)	0	
Percentage of episodes between 100-200 mg/dl	36.5 (25-50)	11.5 (3.11-24)	0.001
Percentage of episodes >200 mg/dl	49 (24-74)	82.1 (62.1-87.4)	0.001

2 patients in group1 experienced hypoglycemia, these were mild events without neuroglycopenic symptoms (confusion, seizure or coma) and were treated with oral glucose solutions. Hyperglycemic episodes were significantly lower and normoglycemic episodes were significantly higher in group 1.

Table 5 Incidence of hypoglycemia and hyperglycemia with respect to age, HbA1c levels and pH at presentation.

Parameters	Incidence of hypoglycaemia		p-value	Incidence of hyperglycemia		p-value
Age≤5 yrs	Group1 (n=2)	Group2 (n=0)		Group1 (n=13)	Group2 (n=38)	
	1	0	P=1	2	12	P=0.4723
Age>5 yrs	1	0		11	26	
HbA1c≤8	2	0	P=1	1	8	P=0.416
HbA1c >8	0	0		12	30	
pH≤7.1	1	0	P=1	8	26	P=0.739
pH>7.1	1	0		5	12	

The incidences of hyperglycemia in children of older age group (>5 yrs), with higher HbA1c levels (HbA1c>8) and lower pH (≤7.1) at presentation were greater, but not significant. There was no significant difference between the 2 groups with respect to hypoglycemia.

Table 6 Glycemic variability indices of the two groups

	Group 1(n=26)	Group 2 (n=46)	p-value
Minimum BG (mg/dL)	96 (84.3-119)	138 (99-194)	0.209
Maximum BG (mg/dL)	334 (288-366)	374 (340-437)	0.301
Standard deviation	78.7 (55.9-91.5)	75.8 (60.8-96.1)	0.504
Coefficient of variation	0.36 (0.27-0.42)	0.29 (0.22-0.37)	0.408

In order to compare the additional glycemic variability indices of the 2 groups, we further included minimum and maximum blood glucose levels, standard deviation (SD) and coefficient of variation (CV) of blood glucose between them (Table 6); difference between the two groups were not significant.

DISCUSSION

T1DM is a serious childhood health problem, DKA being one of its most grave complication. It may present for the first time in emergency or develop some time later after initial diagnosis. Once DKA has resolved in the newly diagnosed child, therapy is transitioned to that described for nonketotic onset. Children with previously diagnosed diabetes who develop DKA are usually transitioned to their previous insulin regimen (12).The available guidelines do not take into account the difference in blood glucose dynamics that occurs at different insulin doses. Insulin regimens for treatment of type1 diabetes should be highly individualised. There are different approaches to initiate subcutaneous insulin after resolution of DKA, partly influenced by practice style and health care economics. In some institutions, basal-bolus insulin regimen is initiated immediately after resolution of DKA and the patient is discharged from hospital and further managed as an outpatient. However, many physicians prefer to start with subcutaneous regular insulin prior to discharge and determine the daily insulin requirement for the individual patient. Whichever regimen is followed, our main concern is to maintain euglycemia while avoiding hypoglycemia. Early control of blood glucose with insulin therapy might be associated with improved long-term glycemic control and higher endogenous insulin production (16, 18). In practice, subcutaneous insulin doses of 0.6-1.2 U/kg/day are typically chosen at T1DM onset and the dose is then adjusted on a daily basis to achieve the targeted glycemia (12).

It is well-known that the metabolic abnormalities occurring in the diabetic state, in particular hyperglycemia, cause mitochondrial superoxide overproduction, which leads to activation of major pathways involved in the pathogenesis of complications of diabetes (19). Thus, the primary goal of treatment in children and adolescents with T1DM is to maintain near-normoglycemia as far as possible (20,21). In our study, the incidence of hyperglycemia was significantly lower in group 1 than in group 2 (Table 4), thereby demonstrating that regular insulin at a dose higher than the standard recommended dose (>1.2U/kg/day) is associated with a lower risk of hyperglycemia in the early period. Wang (14) in their study on influence of initial insulin dosage on blood glucose dynamics of children with type 1 DM also found that the initial high insulin dosage (1.4±0.2

U/kg/day) decreased blood glucose significantly more rapidly than the low dosage (0.6±0.2U/kg/day). Lemieux (21) in their study on starting subcutaneous insulin doses in paediatric population with newly diagnosed type 1 diabetes divided their study group into a lower dose insulin group (prescribed 0.5 units/kg/day or less) and a higher dose insulin group (prescribed >0.5 unit/kg/day). He found significant difference between the intended total daily dose (TDD) of subcutaneous insulin as recorded in physicians note to what was actually administered to the patient based on nursing records. To control blood glucose levels, significantly higher dose was actually given than what was intended. This reflects the dynamic nature of diabetes management, in which insulin doses are adjusted according to the presence of hyper/ hypoglycemia. Based on the significant upward trend, it is likely that children prescribed a lower TDD of insulin experienced ongoing hyperglycemia, indicating a higher insulin need than predicted.

Several studies have shown that the most prominent barrier for tight glycemic control is the fear of hypoglycemia (22, 23). In our study, there was no significant difference between the two groups with respect to hypoglycemia (Table 4). In group 1, only 2 patients had suffered hypoglycemia (each with 1 blood glucose episode of <50 mg/dL) which was treated with oral glucose solutions. None of our patients experienced neuroglycopenic symptoms. Our findings conform to the study of Schneider (24) who examined management of newly diagnosed paediatric diabetes and found that an initial average dose of regular insulin of 0.3U/kg/day yielded no hypoglycemic events in the first 24 hrs of treatment. Similar findings were also demonstrated by the study done by Lemieux (21) which revealed no difference in the incidence of hypoglycemia between the 2 groups receiving high and low total daily dose insulin within 48 hrs of initiation of subcutaneous insulin. In both groups more than 85% patients had no documented hypoglycemia, mild events being treated with oral glucose. Our study however differed from another recent study (25), using data from Paediatric Quality Initiative, which reviewed the rates of hypoglycemia in the first two weeks after diagnosis in 1680 children with type 1diabetes. They found that rates of hypoglycemia rose constantly from 4.8% to a maximum of 11.2% between day 2 and day 5, and then remained stable. The average daily insulin dose on day 2 was 0.79 U/kg/day. The highest average daily insulin dose was 0.91 U/kg/day on day 5, coinciding with the highest rate of hypoglycaemia. However, this study did not provide rates of hypoglycemia within the first 48 hrs and the starting doses of insulin. Similar findings were described in the study done by Wang (14) in which equal number of patients were placed in 3 groups receiving low (0.6±0.2, group 1); medium (1±0.2, group 2) and high (1.4±0.2, group 3) doses of starting subcutaneous insulin; the higher doses induced more hypoglycemic events than the lower doses. At the end of one week of treatment, the insulin dosage of group 1 and group 2 remain unchanged, but four patients in group 3 were adjusted to the group 1 dosage and two were adjusted to the group 2 dosage due to increased incidence of hypoglycemia.

Our study shows that the incidence of hyperglycemia or hypoglycemia between the two groups were not significant when analysed with respect to age (below or above 5 years), higher HbA1c (>8) and lower pH (<7.1) at presentation (Table 5). These findings however differ from those by Schneider (24) where younger age, more severe disease at onset (higher HbA1c, higher blood glucose and lower pH) and higher daily insulin doses were associated with a higher risk of hypoglycemia from day 2-day 14. Lemieux (21) also showed that there is a relation between incidence of hypoglycemia and younger age at presentation. Children ≤6 years age were nearly two times more likely than those 6-10 years of age (24.1% versus 10.9%, respectively) and five times more likely than those ≥10 years of age (24.1% versus 4.5%, respectively) to experience a hypoglycemic event. Studies (26) have shown association between age and beta-cell function, with older children demonstrating a longer course of preserved beta-cell function.

The study is limited by a relatively small sample size, and a retrospective design that led to exclusion of subjects whose data were incomplete. The results of our study suggest that while current practice in children with newly diagnosed type 1 diabetes following resolution of DKA allows for a range of starting insulin doses from 0.6 U/kg/day to 1.2 U/kg/day, there is no higher incidence of hypoglycemia with higher range insulin doses upto 1.4-1.5 U/kg/day. In conclusion, we suggest that an initial dose of 1.4-1.5 U/ kg/day regular insulin may safely be used after resolution of DKA in children with new-onset T1DM with decreased incidence of hyperglycemic events, well controlled blood glucose levels and with no increase in risk of hypoglycemia.

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