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Original Research Article

Fast-acting insulin aspart in pediatric type 1 diabetes mellitus patients in a tertiary care center: Indian experience

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ABSTRACT

Background: The objective of this retrospective study was to evaluate the effectiveness and safety of fast-acting insulin aspart with additional drug excipients (L-arginine and niacinamide) in the Indian pediatric population.
Methods: Data of pediatric type 1 diabetes mellitus (T1DM) outpatients in the age group of 1 to 18 years on treatment with injection degludec as long-acting Insulin OD and faster aspart as rapid-acting mealtime insulin 5-minutes before the meal for 20-weeks, was collected from the medical records of subjects. The primary endpoint was the mean change in glycated hemoglobin (HbA1c) and the secondary endpoints were mean changes in fasting plasma glucose (FPG) and 1 and 2-hour postprandial glucose (PPG), from baseline to 20-weeks post-treatment. The safety of treatment was also evaluated.
Results: Data of 30 pediatric patients (Male: Female-14:16) with a mean age of 7.98 years was considered for this retrospective data analysis. Compared to baseline, there was a significant decline ($p<0.001$) in mean HbA1c levels by -0.72, in FPG by -32.87 mg/dl, in 1-hour PPG levels by -8.57 mg/dl, and 2-hour PPG levels by -11.3 mg/dl, after 20-weeks of treatment. Three and two patients reported symptomatic undocumented hypoglycemia and symptomatic documented hypoglycemia respectively, and one patient each reported local site reaction, and lipodystrophy. No episodes of nocturnal hypoglycemia were reported.
Conclusions: In Indian pediatric T1DM patients 20-weeks mealtime faster aspart along with insulin degludec provided effective glycemic control, and treatment resulted in lower HbA1c, FPG, and 1 and 2-hour PPG levels.

Keywords: Pediatric, Type 1 diabetes, T1DM, Insulin therapy, Aspart, Glycemic control

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a prominent chronic disease showing an increasing trend amongst the pediatric and adolescent age group, globally as well as in India.[1,2] Current trends indicate that globally there are more than 1.1 million children and adolescents with T1DM and with more than 128 thousand new cases are added every year. In India, approximately 16,000 new cases of T1DM are diagnosed every year in the age group of 0-14 years.[3]

It has been proved that the acute and chronic complications of T1DM can be prevented or delayed only with optimal glucose control. To achieve this feat, one has to strike a fine balance taking into account the erratic eating pattern and the progressive growth and pubertal changes which are inseparable parts of the pediatric age group.[4,5] Diabetes management aims to optimize glycemic control. Hemoglobin A1c (HbA1c) is an indicator of control of blood glucose level over a period of time. Achieving target HbA1c is dependent on both fasting and postprandial glycemic control. Current guidelines on the management

of T1DM recommend target HbA1c to be ≤7%.[6] Intensive insulin therapy is required to achieve this target.

The basal-bolus regimen involving multiple daily injections is presently an effective approach for the therapeutic management of T1DM.[7] Even though it closely resembles the physiological secretion of insulin in a normal individual, there is an emergent need for better and faster-acting insulins to reduce post-meal glycemic excursions.[7] When it comes to the Indian diet pattern, many studies have shown that in India people tend to eat a carbohydrate-rich diet comprising almost 65 to 70% carbohydrate content.[8,9] Thus, in the Indian population it seems that there is higher postprandial glucose (PPG) excursions with relatively early PPG peaks, and this is also shown in multiple studies.[10] This mandates the need for faster-acting postprandial insulin.

Fast-acting aspart insulin formulation includes two additional drug excipients, niacinamide, and L-arginine, which accelerate absorption and stabilize the formulation, respectively. Additionally, both excipients are characterized as safe ingredients for injectable drug products by the US FDA.[11] Although, innovative in formulation, fast-acting aspart includes insulin aspart-a molecule that has an established safety profile with more than 17 years of clinical experience. In a pooled analysis of six PK/PD trials, the onset of exposure was earlier for Faster aspart compared with insulin aspart.[12] Additionally, the time to early half-maximal concentration was reduced by 10-minutes. Both insulin formulations had similar total and maximal exposures; however, the Faster aspart has a shortened t_{Cmax} (approximately 7-minutes shorter). The onset of appearance in the bloodstream was reduced from 9 to 4-minutes, demonstrating that faster aspart is twice as fast as insulin aspart. This results in better glycemic control and prevents post-meal hyperglycemia.[12-14] The present retrospective study aims to describe the experience with fast-acting insulin aspart in the Indian pediatric T1DM population.

METHODS

Study design

This retrospective study collected data of pediatric T1DM outpatients in the age group of 1 to 18 years, who attended the pediatric endocrinology department of Indraprastha Apollo hospital, Delhi, India, between March 2019 to December 2019. The data was collected from the medical records of the subjects.

These pediatric patients were on treatment with injection degludec as long-acting Insulin once a day and faster aspart as rapid-acting mealtime insulin 5-minutes before the meal for at least 20-weeks and maintained blood glucose diary with at least 4-point self-monitoring of blood glucose (SMBG) daily and had continuous glucose monitoring system (CGMS) data using medtronic iPro2 professional CGM. Latter was used initially after the start of insulin for 7-days and 7-days before the end of the 20-weeks treatment period.

The data was collected from the medical records of subjects and included demographic (age, sex), and anthropometric data (BMI, weight, height, standard deviation score [SDS] as per standard growth charts [WHO for <5 years, IAP or 5-18 years]), basal and bolus insulin doses, SMBG data (FPG) taken as an average of 7-days FPG reading, and 1 and 2-hour PPG), at baseline and post 20-weeks treatment period. Safety data included episodes of hypoglycemia (defined as blood glucose <70 mg/dl regardless of symptoms), lipodystrophy, and local site reactions.

Ethical clearance

The study was conducted in conformity with the principles of the declaration of Helsinki, international council for harmonization-good clinical practices (ICH-GCP) guidelines, Indian council of medical research, Indian GCP guidelines, and as per the approved protocol. The process of data analysis was only initiated after approval from the institutional ethics committee of institutional ethics committee-BioMedical research, Indraprastha Apollo Hospital, Delhi, India. Since this was a retrospective data collection study, informed consent was not required. Patient confidentiality was maintained during the data entry and analysis process.

Endpoints

The primary endpoint was a mean change in HbA1c and the secondary endpoints were mean changes in FPG and 1 and 2-hour PPG from baseline to week 20 post-treatment. Safety endpoints were adverse effects, episodes of hypoglycemia, insulin dose, or change in body weight.

Statistical analysis

Qualitative and quantitative variables are presented using descriptive statistics. Quantitative variables were evaluated using a paired t-test at a 5% level of significance and the corresponding p value is presented. Data were analyzed using SPSS® statistics software, version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Data of 30 pediatric patients (Male: Female-14:16) with a mean (SD) age of 7.98 (xx.x) years was considered for this retrospective data analysis. Demographic and baseline characteristics of patients are summarized in Table 1.

The study data revealed that compared to baseline there was a significant decline ($p<0.001$) in HbA1c levels by -0.72, in FPG by -32.87 mg/dl, in 1-hour PPG levels by -8.57 mg/dl, and 2-hour PPG levels by -11.3 mg/dl, after 20-weeks of treatment. It was observed that after 20-weeks of treatment the dose of bolus insulin decreased

significantly (p<0.001) by -0.10 U/kg/day and the dose of basal insulin decreased by -0.05 U/kg/day, but this change was not significant. Mean changes in glycemic parameters along with basal and bolus insulin doses after 20-weeks of treatment compared to baseline are presented in Table 2.

Table 1: Patient characteristics at baseline, (n=30).

Parameters		Overall, n (%)	
Sex, n (%)			
Male		14 (46.7)	
Females		16 (53.3)	
Sex distribution			
Age group (Years)	**Male, n (%)**	**Female, n (%)**	**Total**
≤5	5 (55.6)	4 (44.4)	9
5-10	6 (54.5)	5 (45.5)	11
>10	5 (50)	5 (50)	10
Age (Years), mean		7.98	
Height (cm), mean		122.72	
Height (SDS)		-0.42	
Weight (kg), mean		24.92	
Weight (SDS)		-0.30	
BMI (kg/m^2), mean		15.88	
BMI (SDS)		15.88	
FPG (mg/dl), mean		136.47	
HbA1c (%), mean		8.61	
Insulin dose (U/kg/day), mean			
Basal		0.48	
Bolus		0.52	

Table 2: Mean change in glycemic parameters after 20-weeks of treatment compared to baseline, (n=30).

Variables	Week 0 Mean ± SD	Week 20 Mean ± SD	Diff.	P value[a]
HbA1c	8.61± 0.63	7.89± 0.38	-0.72	<0.001
FPG	136.47± 19.19	103.6± 18.76	-32.8	<0.001
1 hr PPG	165.57± 8.27	157.00± 5.57	-8.57	<0.001
2 hr PPG	158.8± 10.31	147.5± 10.75	-11.3	<0.001
Insulin basal (U/kg/d)	0.48± 0.17	0.43± 0.14	-0.05	>0.05
Insulin bolus (U/kg/d)	0.52± 0.23	0.42± 0.19	-0.10	<0.001

HbA1c-Glycated hemoglobin; FPG-Fasting plasma glucose; PPG-Postprandial plasma glucose.

Safety and tolerability

Seven (23.3%) patients reported of adverse events. Three (10%) patients reported symptomatic undocumented hypoglycemia, 2 (6.7%) patients had symptomatic documented hypoglycemia, and one (3.3%) patient each reported local site reaction, and lipodystrophy. No episodes of nocturnal hypoglycemia were reported. The safety data are presented in Table 3.

Table 3: Safety assessment, (n=30).

Adverse events	N	Percentage (%)
Lipodystrophy	1	3.3
Local site reaction	1	3.3
Symptomatic documented	2	6.7
Symptomatic undocumented	3	10

DISCUSSION

The present retrospective data analysis aimed to study the efficacy, and safety of fast-acting aspart, newer rapid-acting insulin used at mealtime, along with long-acting basal insulin. It was an observational study where data was collected, retrospectively, from 30 patients of T1DM who were on treatment with degludec and faster-acting insulin aspart, for a period of 20-weeks.

Results of this retrospective analysis showed that HbA1c was reduced significantly after 20-weeks indicating good glycemic control with treatment. The result was consistent with previous trials.[15] FPG also showed a significant decline after 20-weeks. Similarly, 1-hour PPG declined significantly after treatment with faster aspart. These results were in line with the previous study in adults, conducted by Russel et al which tested the efficacy of faster aspart. The authors concluded that mealtime faster aspart reduced HbA1c significantly as compared to insulin aspart.[16] Similarly, 1-hour PPG was statistically significantly lower (ETD -1.18 mmol/L [95% CI-1.65; -0.71], -21.21 mg/dL [-29.65; -12.77]; p<0.0001). It also showed that better 2-hour PPG values were achieved with faster aspart (-0.67 mmol/L [-1.29; -0.04], -12.01 mg/dL [-23.33; –0.70]; p=0.0375).[16] In the present study, too, results show a significant reduction in 2-hour PPG similar to other studies.[15,16]

Recurrent episodes of hypoglycemia may lead to significant neurocognitive outcomes in the pediatric age group.[17] This study did not report any case of nocturnal hypoglycemia which was monitored on CGM between 00 to 06. Episodes of hypoglycemia and other side effects were also comparable to the previous studies.[18,19] Faster-acting aspart is new rapid-acting insulin given at mealtime, as a part of basal-bolus therapy, along with long-acting insulin to treat T1DM. Due to rapid absorption, it helps mimic the physiological insulin secretion hence improving glycemic control without a significant increase in hypoglycemic episodes. Faster aspart shows greater early insulin exposure than insulin aspart, approximately 2-fold greater within the first 30-minutes, amounting to a glucose-lowering effect that is 74% greater than that of aspart.[12] During the late phase, the left shift in insulin

exposure for the faster aspart resulted in a shorter time to late half-maximal concentration (approximately 12 minutes shorter).[13,14,20]

The results of this retrospective analysis show that this newer insulin could be a breakthrough in pediatric diabetes management because the patient in the pediatric age group have erratic eating habits and ill-defined meal sizes and times. The rapid absorption can even allow insulin administration after the child starts taking a meal to prevent the danger of hypoglycemia if the child refuses the meal after insulin administration which is common in the pediatric population. Faster aspart has shown similar efficacy and safety profile even when given up to 20-minutes after the start of the meal.[16]

There were a few drawbacks of this study. First, the sample size was statistically powered and confined to a single center. Secondly, there was no blinding. it was an observational study where the treatment was already given and data analyzed retrospectively, leading to confounding and bias. Thirdly there was no comparison with any other group on a different treatment regimen. Lastly, the duration of treatment studied was short not allowing the study of the long-term effect of therapy.

CONCLUSION

Treatment of T1DM aims to provide an insulin regime that is closer to the normal physiological response of the body to carbohydrates. An intensive insulin regime is presently the best therapy available. Newer drugs are being introduced time and again to achieve the target of good glycemic control. One such drug is faster acting aspart. This study shows the drug to be safe and effective in the pediatric population after 20-weeks of treatment but large prospective, multicentric studies will need to be conducted to confirm the findings of our retrospective analysis and the long-term effects of the treatment with faster-acting aspart.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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