Original Article

Efficacy and Safety of Insulin degludec/aspart (RyzoDeg) in Type 2 Diabetes Mellitus in Pakistan: Real-Life Experience

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ABSTRACT

Background: Insulin Degludec/Aspart (IDeg/Asp) is a novel insulin co-formulation launched in Pakistan in 2018 containing Insulin Degludec and aspart in a 70/30 ratio that can be given once daily or twice daily.
Objectives: This study aimed was to look at the efficacy and safety of IDeg/Asp in real-life Pakistani population with Type 2 Diabetes mellitus in a secondary care setting in Islamabad, Pakistan.
Methods: A 12-week multi-centric observational cohort study was performed at different hospitals in Islamabad, Pakistan with 105 patients who were prescribed IDeg/Asp. The data was collected from T2DM patients having HbA1C ≥ 7.0% and aged between 40-70 years. The primary of the study was a decrease in HbA1C from the base-line and secondary end-points include change in body weight, fasting plasma glucose level, postprandial glucose level, hypoglycemic episodes and adherence to the treatments. The statistical analysis was carried out through a paired T-test.
Results: Baseline HbA1c, fasting glucose, post-prandial glucose and weight were 8.48±1.27%, 201.05±44.41 mg/dl, 266.67±58.45 mg/dl and 79.18±17.69 kg respectively. At the end of 12 weeks, there was a mean reduction in HbA1c by 1.79% to 6.69±0.52%, fasting glucose reading by 78 mg/dl to 123.33±24.68 mg/dl and post-prandial glucose by 95 mg/dl to 171.62±30.73 mg/dl. There was minimal weight loss with the weight coming down by a mean of 1.62 kg to 77.56±16.13 kg. There was only 1 patient who experienced hypoglycemia. Similarly, All the participants were well adhered to their treatments throughout the study duration as per the Morisky-Green-Levine test.
Conclusion: This real-life observational study on the use of IDeg/Asp in a Pakistani population with Type 2 Diabetes mellitus have shown that once or twice daily IDeg/Asp is significantly more effective in hyperglycemia management with lesser side effects in people with uncontrolled Type 2 Diabetes mellitus.

KEY WORDS: Insulin Degludec/Aspart (IDeg/Asp), Type 2 diabetes, Post prandial glucose.

INTRODUCTION

The Prevalence of diabetes mellitus is increasing worldwide with an estimated 537 million people now living with diabetes mellitus according to the 2021 International Diabetes Federation atlas and this figure is predicted to rise to 783 million by 2045.[1] Pakistan has the highest comparative diabetes prevalent rates (30.8%) and now stands third behind China and India in terms of a number of people with diabetes

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mellitus currently amounting to 33 million.[1] However, despite such a large number of people in Pakistan diagnosed with diabetes mellitus, there is a dearth of studies regarding the efficacy and safety of newer hypoglycemic agents and second-generation insulin analogues in real-life clinical settings in Pakistan.

Insulin Degludec/Aspart (Ryzodeg) is a novel insulin co-formulation launched in Pakistan in 2018. It is a combination of second-generation ultra long-acting insulin analogue degludec with insulin aspart. Insulin degludec forms multiple soluble and stable di hexamers in the body that increase its half-life to 25 hours and duration of action to 42 hours.[2] It gives a flat action profile and flexibility of dosing with decreased risk of nocturnal hypoglycemia as compared to other basal insulin such as insulin glargine.[2] The chemical nature of insulin degludec allowed a stable co-formulation with rapid-acting insulin aspart (insulin degludec 70% / aspart 30%). This combination provides basal coverage for more than 24 hours along with one time-post-prandial maintenance of glucose levels[3] mimicking the human insulin as it directly binds to the insulin receptors on the muscle and fat cells and establishes its anti-hyperglycemic effects.[4]

To date, there is no study conducted in Pakistan to look at the efficacy, safety and tolerability of insulin degludec/aspart in real-life clinical settings. So in current study we aimed to evaluate the effects of insulin degludec/insulin aspart in the management of type 2 diabetes concerning glycemic control, weight change of the patients, side effects and patient's adherence to the treatment.

METHODOLOGY

Study design and participants:

This study was a twelve-week follow-up, multi-centred observational longitudinal cohort, prospective non-randomized study design that was conducted in two phases a) pre-treatment data collection phase and b) post-treatment follow-up phase. Follow-up was conducted after three months of the first phase. The study was conducted at six different specialized diabetes clinics and hospitals in Rawalpindi and Islamabad comprising the diabetic population of these cities over eight months from October 2018 to June 2019. The study was approved from the Bio-Ethics Committee (BEC) of Quaid-i-Azam University Islamabad with the protocol number (BEC-FBS-QAU2019-150) as well as respective ethical review boards of participating centres i.e. Shifa International Hospital Islamabad Pakistan (Ref. No. IRB#221-711-2019) and the Pharmacy Department of Quaid-i-Azam University with the protocol number (NO.PHM/2019/285-289). All enrolled subjects signed informed consent before starting of the interview. This study includes patients diagnosed with type-II diabetes between age 40-60 years with HbA1C ≥ 7% having uncontrolled diabetes. The exclusion criteria include patients with other types of diabetes such as Type 1 diabetes mellitus and gestational diabetes. The primary end point of the study was a decrease in HbA1c from baseline and secondary endpoints include change in body weight, fasting plasma glucose level, post-prandial glucose level, hypoglycemic episode and adherence to the treatment.

Procedure:

A convenient sampling technique was followed in recruiting patients. The data was collected from 105 ambulatory patients from all the selected centres. Before starting insulin degludec/aspart, a complete education session was given to all the participants on the lifestyle modifications and insulin technique by the certified diabetes educator present at the centre along with a brochure. The following parameters were collected at baseline and after 12 weeks and recorded on a data collection form: age, sex, duration of diabetes, concurrent diabetes medications, HbA1c, weight, fasting plasma glucose level, post-prandial glucose level and hypoglycemic episodes. Medication adherence was assessed by a self-reported Morisky Levine Green adherence questionnaire. It is a 4-item questionnaire with high reliability and validity, which has been particularly useful in chronic conditions like hypertension and other cardiovascular diseases.

Statistical Analysis:

Data analysis was accompanied using statistical tools. A *P* value of 0.05 or less was considered significant. One-way ANOVA tests were employed to measure the significance of pre and post-variables separately; post-hoc Bonferroni test was performed for pairwise comparison of the primary outcome. Chi-square tests and paired sample T-tests were employed to compare treatment baseline characteristics and for before and after treatment comparison. Frequencies and percentages of categorical variables were determined, mean and standard deviation of numerical values were also calculated.

RESULTS

Out of 105 participants, there was a male preponderance (52%, N= 55) and most of the participants were less than 60 years old (73%, N=77) (Table-I).There was a reduction in HbA1c by 1.79% from a baseline HbA1C value of 8.48±1.27% to 6.69±0.52% after 12 weeks and was statistically significant with a *P* value of <0.001 (Fig.1d). Fasting plasma glucose level values before treatment was 201.05±44.41 mg/dl at baseline dropping by 78 mg/dl to 123.33±24.68 mg/dl that was again statistically significant (*P* value <0.001) (Fig.1b). Similarly, there was a drop of 95 mg/dl in post-prandial glucose reading from a baseline value of 266.67±58.45 mg/dl to 171.62±30.73 mg/dl (P<0.001) (Fig.1c)

Surprisingly there was a weight reduction of 1.62 kg at the end of three months with baseline mean weight values of 79.18±17.69 kg coming down to 77.56±16.13 kg (Fig.1a). There were negligible hypoglycemic

Table-I: Difference in treatment groups by sample characteristics.

Variables	*Degludec/Aspart 70/30*
Gender	
Male	55 (35.6)
Female	50 (27.8)
Age	
40-50	38 (21.1)
51-60	39 (21.7)
>60	28 (15.7)
Hypoglycemia	
Yes	1 (1%)
No	104 (99%)
Body weight (kg)	
Pre-treatment	79.18±17.6
Post-treatment	77.56±16.13
HbA1c	
Pre-treatment	8.48±1.27
Post-treatment	6.69±0.52
Fasting plasma glucose (mg/dl)	
Pre-treatment	201.05±44.41
Post-treatment	123.33±24.68
Postprandial plasma glucose	
Pre-treatment	266.67±58.45
Post-treatment	171.62±30.73

events observed in our cohort with only 1 person experiencing minor hypoglycemia. There were no severe hypoglycemic episodes reported in our cohort over 12-weeks. Four participants who were injecting Insulin degludec/aspart noticed other adverse events such as injection site reactions.

All the participants (N=105) were well adhered to their treatments throughout the study duration due to several reasons such as prior treatment counselling, once or twice daily administration of injection, ease in the administration of the injection and lesser side effects such as hypoglycemia for insulin Degludec/ Aspart as per Morisky Green Levine test.

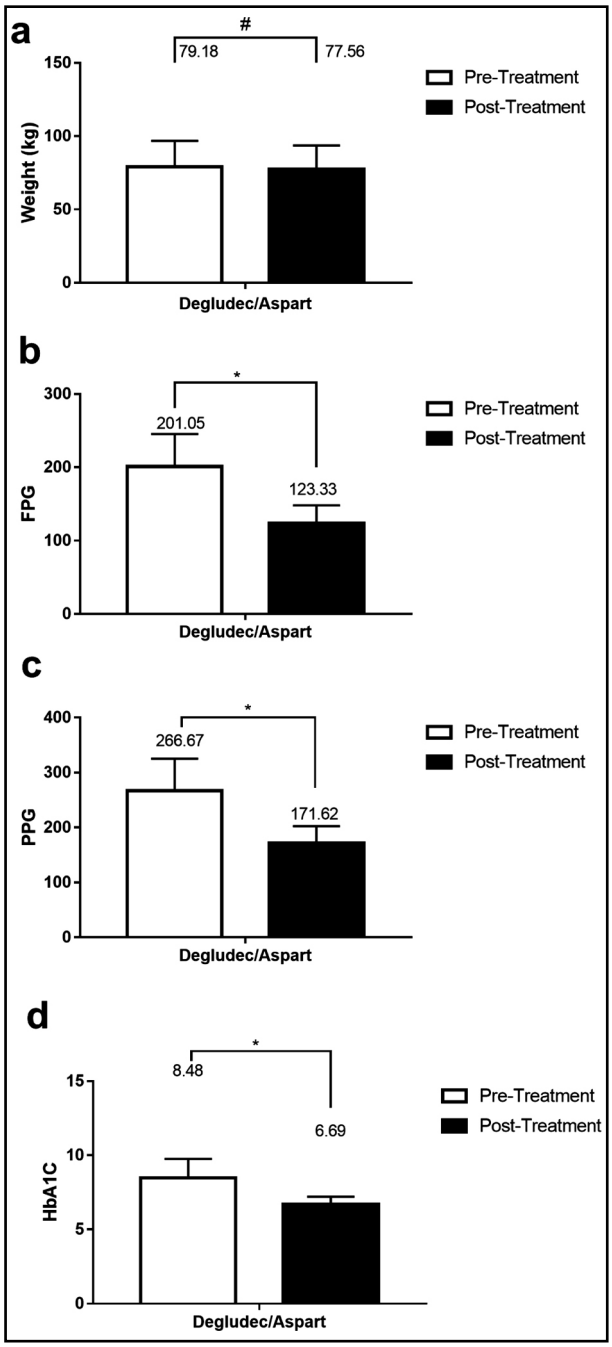

Fig.1: (a) Change in weight before and after the treatments (b)Change in fasting plasma glucose levels before and after treatments (c) Change in post-prandial glucose levels before and after the treatments (d) Change in HbA1C levels before and after the treatments.

DISCUSSION

This 12-week multi-centric observational cohort the study incorporates five different parameters against which insulin degludec/aspart was evaluated including reduction in HbA1c levels, change in fasting

plasma glucose and post-prandial glucose levels before and after use of insulin degludec/aspart, weight changes, side effect profile and adherence with treatments. Our study has shown that once or twice daily insulin degludec/aspart is significantly more effective in reducing not only fasting blood sugar readings with a mean reduction of 78 mg/dl but also post-prandial blood glucose reduction with a mean reduction of 95 mg/dl resulting in a significant HbA1c drop of 1.79% over 12 weeks. This is associated with minimal hypoglycemic risk as only 1 patient in our cohort experienced a minor hypoglycemic episode over 12-week.

In comparison, phase 3 randomized controlled STEP BY STEP trial comparing insulin degludec/aspart once daily co-formulation with once-daily insulin glargine and once daily insulin aspart with largest meal have shown insulin degludec/aspart combination to be non-inferior to insulin glargine and insulin aspart with HbA1c reduction of 1.01% and 1.17% by 26 and 38 weeks respectively.[5] This is associated with significantly less symptomatic hypoglycemia with insulin degludec/aspart with a relative risk reduction of 0.86 (0.65-1.14) over 38 weeks.[5] Similarly, a post hoc analysis of elderly patients in 2 phase 3 randomized controlled BOOST trial (INTENSIFY PREMIX 1 & INTENSIFY ALL) comparing insulin degludec/aspart twice daily with twice daily BiAsp 30 have shown insulin degludec/aspart to be non-inferior to BiAsp 30 with fasting blood glucose reduction of 92 mg/dl and HbA1c reduction of 1.3% over 26 weeks with lower risk of both nocturnal and overall hypoglycemia in the elderly population.[6]

However, it will be more appropriate to compare our study with the ARISE study which is a prospective, non-interventional, single-arm study assessing insulin degludec/aspart in 1112 patients with type 2 diabetes mellitus over 26 weeks period in real-world setting across six countries.[7] The ARISE study has shown an HbA1c reduction of 1.4% over 26 weeks with fasting glucose reduction of 48 mg/dl and significantly reduced non-severe and severe hypoglycemia.[8] Our study has shown a comparable reduction in HbA1c and fasting glucose levels with fewer hypoglycemic episode over 12 week.

In addition, there was a minimal weight loss of 1.62 kg over 12 week in our study with insulin degludec/aspart. In comparison, the ARISE study also showed a weight loss of 1 kg over 26-week period.[8] This finding of weight neutrality or minimal weight loss with insulin degludec/aspart combination seen in our study as well as ARISE study can be explained by unique pharmacokinetic and pharmacodynamics characteristic of insulin degludec with a flatter profile resulting in less glycemic variability and hence lesser overall insulin units to be used with insulin degludec/aspart co-formulation. The phase 3 trial studies of insulin degludec/aspart have also shown reduced insulin units to be used with insulin degludec/aspart when compared with either insulin glargine or BiAsp 30 insulin.[5,6] Another alternative explanation can be lesser overall hypoglycemic episodes with insulin degludec/aspart which will help people with type 2 diabetes to avoid overcorrection of hypoglycemia leading to weight gain. Whatever the mechanism of action, these findings from both real-world studies regarding insulin degludec/aspart have strengthened the evidence regarding insulin degludec/aspart to be used as the insulin of choice to start when considering overweight patients who will prefer to choose insulin with neutral or less weight gain properties.

The limitation of our study is similar to other real-life observational studies including an observational study conducted in a real-life clinical setting and, therefore, affected by uncontrollable variables. There will also be some recall bias specifically about hypoglycemic episodes, as some minor and nocturnal hypoglycemic episodes will not be remembered or noticed by the patients while investigating these episodes. Nevertheless we believe that there were no severe hypoglycemic episodes in our cohort over 12 weeks as these would have been remembered and documented by the patients. The strength of our study lies in the fact that this is the first study looking not only at the efficacy and safety but also at treatment adherence of a novel insulin co-formulation in real-life setting in Pakistan. Also, our study results are broadly similar to the ARISE study which is one of the largest real-life studies of insulin degludec/aspart containing well over 1100 patients across six countries[7] indicating that insulin degludec/aspart is an effective insulin option in patients with type 2 diabetes mellitus in Pakistani type 2 diabetes mellitus cohort.

CONCLUSION

Our study has shown that the use of once or twice daily insulin degludec/aspart is safe and efficacious in real-life clinical settings in the Pakistani population with significant reduction in HbA1c, fasting and post-prandial glucose level with weight neutrality and minimal risk of hypoglycemia. All the patients enrolled in the study showed excellent adherence to this treatment. However, prospective observational studies must be designed in a Pakistani set-up to validate the results of this study incorporating insulin degludec/aspart.

Conflict of interest: None.

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Author Contribution:

MES was responsible for topic conception, data collection, analysis and write up of draft;
UYR was involved in data analysis and writing up draft;
MS, FD, AI, GMK & AS involved in data analysis and statistical input. All authors have agreed to final draft.

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