ORIGINAL ARTICLE

OPTIMIZING THE DAILY UNITS OF INSULIN; INSULIN DEGLUDEC ASPART VERSUS PREMIXED INSULIN ASPART IN THE STANDARD OF CARE REGIMEN FOR TYPE 2 DIABETICS

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Background: This study aimed to evaluate the impact of Insulin Degludec Aspart on daily insulin dose in comparison with premixed insulin aspart. **Methods:** It was a Quasi-Experimental study conducted in the Department of Pharmacology, Army Medical College, National University of Medical Sciences, Rawalpindi and the Department of Medicine, Pak Emirates Military Hospital, Rawalpindi. One hundred and twenty participants with documented type 2 diabetes, taking premixed insulin aspart therapy were enrolled in the study. Sixty participants were substituted with insulin degludec aspart from premixed insulin aspart. Daily units of insulin were recorded for 12 weeks and compared for both groups. SPSS version 26 was used for analysing the study results. **Results:** Participants of the insulin degludec aspart group showed a significant reduction in the daily insulin dose compared to the premixed insulin aspart group. Fifty-two units per day were administered in the participants of the premixed insulin aspart patients while insulin degludec aspart participants received 40 units of median daily insulin dose (p-value<0.001).

Conclusion: Insulin degludec aspart proved superior to premixed insulin aspart in a reduction in the daily dose of insulin with insulin degludec aspart

Keywords: Biphasic insulin aspart; Glycaemic control; Insulin degludec aspart; Type 2 diabetes mellitus

Citation: Malik KM, Farhat K, Ali S, Noor M, Ahmad B. Optimizing the daily units of insulin; insulin degludec aspart versus premixed insulin aspart in the standard of care regimen for type 2 diabetics. J Ayub Med Coll Abbottabad 2023;35(2):294–7.

DOI: 10.55519/JAMC-02-11674

INTRODUCTION

An effective and early glycaemic control to achieve sustained and long-term reductions in complications associated with type 2 diabetes mellitus as well as maintenance of a suitable daily range of glycaemia, can produce an impact beyond the duration of the intervention. For treating type 2 diabetes mellitus, the role of lifestyle interventions and pharmacological modalities is synchronous and vital.[1] Maintaining an optimal quality of life in diabetics is the target of antidiabetic therapy, with the aim to slow the progression of the disease.[2] Type 2 diabetes mellitus is a disease of the pancreas, involving a gradual beta (β) cell failure, resistance to insulin and progressive worsening of the glycaemic regulation of the body.[3] Once the diagnosis of diabetes is established, lifestyle moderation and initiation of oral antidiabetic drug therapy is recommended.[4] Despite these measures, a progressive worsening of glycaemic control ensues owing to the progressive nature of the disease, making the initiation of insulin inevitable in these patients as the course of the disease progresses. Insulin is initiated when the glycaemic target is not met, even after combination therapy with three oral agents.[5] Once daily basal insulin injection has been recommended by a collaborative statement from the American Diabetes Association and the European Association, as a first choice for the commencement of insulin treatment in patients having type 2 diabetic mellitus.[6] Basal insulin ensures optimal control of glycaemia and shows a reduced incidence of hypoglycaemic episodes.[7] However, the Postprandial control of glucose levels requires additional bolus doses as basal plus one bolus or basal plus two bolus doses, with breakfast, lunch and dinner meals.[8] Substituting a multiple oral drug regimen with a multiple injectable drug regimen is burdening for the patients and a challenge in ensuring patient compliance with insulin. Switching to premixed insulin regimens from the basal bolus therapies has been a better alternative practised worldwide, providing basal as well as mealtime coverage in one injection.[9] However, these insulins have associated limitations in their pharmacokinetic and pharmacodynamic profiles.[10] These limitations may manifest as variability in glycaemic control from day to day, insufficient 24-hour coverage and an increased frequency of hypoglycaemic episodes with premixed insulin in comparison with the basal and basal-bolus regimens.[11] In light of this limitation with conventional insulin therapies, a newer co-formulation of insulin has been formulated. Insulin degludec aspart is the first soluble co-formulation of ultra-long acting and a rapid acting insulin analogue, insulin degludec and insulin aspart, respectively. The non-necessity for resuspension and an extended duration of action, permitting once-daily dosing, make insulin degludec aspart a choice in

patients unable to comply with conventional therapies.[12] Previous studies have established the role of insulin degludec aspart in maintaining better glycaemic control. In this study, we evaluated the impact of insulin degludec aspart on the daily requirement of insulin, in comparison with the conventional twice daily premixed insulin aspart therapy, included in the standard of care regimen of type 2 diabetics. In conjunction with lifestyle modifications and oral antidiabetic drug therapies, the aim of this study was to establish an ameliorated antidiabetic regimen with improved documented outcomes among the Pakistani population.

MATERIAL AND METHODS

This quasi-experimental study was conducted in joint collaboration with the Department of Pharmacology, Army Medical College, National University of Health Sciences, Rawalpindi and the Department of Medicine, Pak Emirates Military Hospital Rawalpindi (PEMH), from September to December 2021. Using the World Health Organization calculator, a sample size of 34 was obtained. We increased the sample size to 120 to enhance the impact of the study. Patients with documented type 2 diabetes mellitus, ≥18 years of age, taking premixed insulin aspart therapy without treatment change in the last 8 weeks were included in the study.[13] Patients with underlying thyroid or cortisol hormonal imbalance, Modified Onset Diabetes of the Young, chronic liver/renal disease, pregnancy or taking GLP-1 receptor agonists were excluded.[14] Ethical approval was acquired for the study from the institutional review board of Army Medical College and PEMH Rawalpindi (ERC/ID/150).

Patients presenting to the medical outpatient department of PEMH were briefed regarding the study protocol. Duly signed informed consent was acquired from all participants who gave consent for the study. Brief history and demographic profile were obtained from the participants in the outpatient department. In 60 participants taking premixed insulin aspart therapy, treatment was switched to insulin degludec aspart. All participants were counselled regarding dietary modifications by a registered diabetes educator and as per the recommendations from the expert panel of diabetes regarding the use of once daily insulin degludec aspart, the morning meal was kept as the main meal of the day. The remaining meals were divided into smaller and frequent meals instead of two big meals of the day. No change in the oral antidiabetic drug therapy was made, in participants of both groups and the oral therapy was continued as before.

Daily units of insulin administered by the participants of both groups were recorded for 12 weeks. The dose of insulin for the participants switched to insulin degludec aspart was determined by the prescribing physician based on recently evaluated HbA1c levels. Units of insulin before enrolment in the study were considered as baseline for participants of both groups. Any increments or reductions made in the units of insulin, based on fasting and post-prandial plasma glucose concentrations, recorded by the participants were also noted. The median daily insulin dose was calculated for both groups at the end of 12 weeks. Data was analysed using Statistical Package for social sciences (SPSS) version 26. Male and female participants of both groups are presented as frequency and percentage and analysed using the Chi-square test. Age is presented as mean ± standard deviation. Median daily insulin dose is presented as median with interquartile ranges and intergroup comparison was done using the Mann-Whitney U test for comparing medians. A *p*-value of ≤0.05 has been considered statistically significant.

RESULTS

Out of the 120 participants enrolled in the study, there were 34 male and 26 female patients in the premixed insulin aspart group. 38 male and 22 female participants were present in the insulin degludec aspart group. The approximate mean age for group A participants was 57 years and for group B participants was 58 years. During the 12-week study period, the units of insulin were adjusted in all the participants, as increments or reductions in the units of insulin, according to the individual needs, based on the target glycaemic control and response to therapy, for every patient (Table-1).

At baseline, before the treatment switch, participants of both groups received equal units of insulin. Units of insulin were significantly lowered in the insulin degludec aspart group after 12-week treatment. Participants who switched to the insulin degludec aspart required a substantially lower dose of insulin as compared to the biphasic insulin aspart group (Table-2 and Figure-1 and 2).

Table-1: Demographic attributes and baseline daily insulin dose among participants of premixed insulin aspart and insulin degludec aspart groups

Characteristics	Insulin Degludec Aspart Group n = 60	Premixed Insulin Aspart Group n = 60	*p*-value
Age (years)	57.23 ± 9.38	57.63 ± 9.40	0.81
Gender			
Males, *n* (%)	34 (56%)	38 (63%)	
Females, *n* (%)	26 (44%)	22 (34%)	0.5
Median Insulin Dose Before Treatment Switch	52 (44–56)	52 (46–54)	0.8

Table-2: Summary of daily insulin dose among participants of premixed insulin aspart and insulin degludec aspart groups

	Premixed Insulin Aspart Group	Insulin Degludec Aspart Group	*p*-value
Median Insulin Dose Before Treatment	52 (44–56)	52 (46–54)	0.8
Median Insulin Dose After Treatment	52 (44–56)	40 (38–42)	<0.001

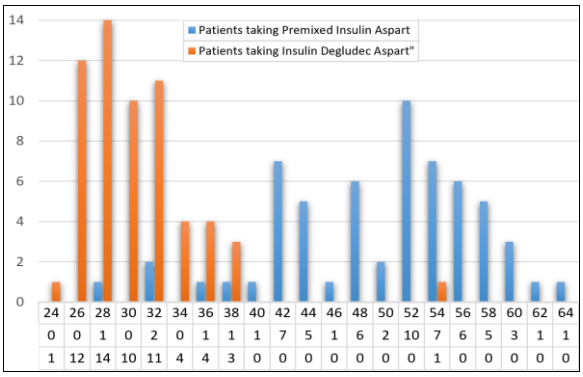

Figure-1: Daily insulin units administered in participants of premixed insulin aspart group and Insulin degludec aspart group

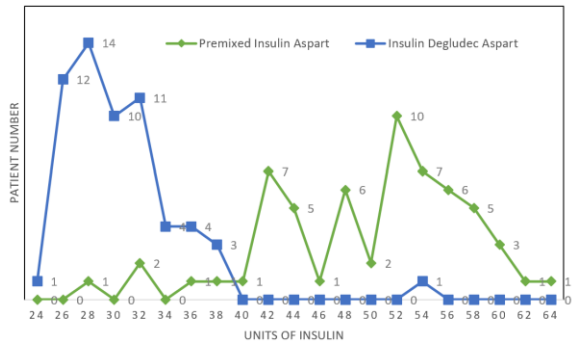

Figure-2: Trend-line showing the reduction in the requirement of insulin units in the Insulin Degludec Aspart group as compared to the incremented requirements in the premixed insulin aspart group

DISCUSSION

The present study observed the outcomes of substituting treatment with insulin degludec aspart from premixed insulin aspart on the median daily insulin dose. Initiating treatment with insulin degludec aspart produced statistically significant results in our study, in comparison with premixed insulin aspart. A substantial reduction in the units of insulin administered per day in the insulin degludec aspart group was noted. A number of studies have proven the role of insulin degludec aspart in improving glycaemic outcomes in diabetics with a lower dose requirement than premixed insulin aspart.

The ultra-long duration of action of the degludec component of insulin degludec aspart, for more than 30 hours makes once daily dosing of insulin possible. The prandial control of glycaemia is provided by the rapid acting aspart component. As recommended by the Food and Drug Authority (FDA), the minimum starting dose of insulin degludec aspart is 10 units per day, which can be incremented based on the patient's glycaemic status. Units of insulin are administered as either once daily dose or divided into two equal doses, given with two carbohydrate rich meals.[15]

Expert panel on diabetes have recommended the administration of insulin degludec aspart with the main carbohydrate-rich meal of the day. Twice daily administration of insulin degludec aspart requires two carbohydrate rich meals, for optimal glycaemic control. For administrating insulin degludec aspart as once daily injection, as in our study, the morning meal can be kept as the main meal of the day, dividing the rest of the meals into smaller meals, taken at increased frequency.[16]

After initiating therapy with insulin degludec aspart, the steady state is reached within 2–3 days. Once the steady state is attained, administration of equal units of insulin per day results in an optimal control of glycaemia. This pharmacokinetic property of insulin degludec aspart was implied in our study for commencing insulin degludec aspart therapy in a once daily dose.[17]

A single-centre, open-label, single-arm study was carried out on twenty-two subjects receiving once-daily insulin degludec for five consecutive days (with separate bolus insulin aspart as needed for safety and glycaemic control), to achieve a clinical steady state of the basal component. On Day 6, they received a single injection of insulin degludec aspart. using a 30-h euglycemic glucose clamp, with blood glucose stabilized at a target of 5.5 mmol/L, the pharmacodynamic response was assessed. the peak action of insulin aspart followed by a stable descent of the basal glucose levels by insulin degludec were retained in all the participants. It took 2–3 days of once daily insulin degludec administration to achieve the steady state, confirming the radically long duration of action of insulin degludec and the effectivity of a single daily dose to be similar to the administration of insulin degludec aspart twice per day.[18]

Takahisa Hirose and his colleagues in 2018 summarized the findings of a pharmacodynamic analysis of insulin degludec aspart carried out in various pre-clinical and clinical studies. They concluded that insulin degludec aspart undergoes a distinct pharmacodynamic pattern, producing a peak action

rapidly due to the aspart component, followed by a stable and flat basal effect produced by the degludec component, supporting the once daily dosing regimen.[19]

Fujioto with his colleagues carried out a post hoc analysis to examine the safety and efficacy of insulin degludec aspart versus premixed insulin aspart in elderly patients with type 2 diabetes. The mean insulin dose at the end of the trial was significantly lower for patients treated with insulin degludec aspart than for patients treated with premixed insulin aspart (p <0.0001). Similar and significant results were produced in Japanese patients (p=0.0121).[20]

CONCLUSION

A reduction in the dose requirement of insulin was observed in the participants of the insulin degludec aspart group, in comparison with the biphasic insulin aspart group.

AUTHORS' CONTRIBUTION

KMM: Conceptualization of study design, data collection, literature search, data analysis, data interpretation, write-up. KF: Conceptualization of study design, data interpretation, proof reading, approval of manuscript. SA: Proof reading, approval of manuscript. MN: Proof reading, data interpretation, approval.

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Submitted: January 4, 2023	*Revised: March 2, 2023*	*Accepted: March 6, 2023*

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