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Hypoglycemia in Type 2 Diabetes Patients Substituted with Insulin Degludec Aspart from Premixed Insulin Therapy: A Quasi Experimental Study

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ABSTRACT

***Objective*:** To determine whether Insulin Degludec Aspart is associated with a reduced risk of hypoglycemia as compared to premixed Insulin aspart therapy in type-2 diabetes mellitus patients.

Study Design: Quasi-experimental study

***Place and Duration of Study*:** Department of Pharmacology, Army Medical College, National University of Medical Sciences, Rawalpindi and Department of Medicine, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Sep to Dec 2021.

Methodology: One hundred twenty participants with documented type 2 diabetes, taking premixed Insulin Aspart therapy, were enrolled in the study. The participants were divided into two groups. Group-A participants were continued on Premixed Insulin Aspart therapy, and Group-B participants were substituted with Insulin Degludec Aspart. The symptomatic hypoglycemic episodes were recorded for 12 weeks as confirmed hypoglycemia, nocturnal hypoglycemia, and severe hypoglycemia.

***Results*:** Among the Premixed Insulin Aspart-Group, 49(81.6%) participants and in the Insulin Degludec Aspart-Group, 26(43.3%) participants reported 160 and 40 episodes of confirmed total hypoglycemia, respectively (p-value<0.001). 43(71.6%) participants in the Premixed Insulin Aspart-Group and 11(18.3%) participants in the Insulin Degludec Aspart-Group reported 73 and 12 episodes of confirmed nocturnal hypoglycemia, respectively (p-value<0.001). No severe hypoglycemic episodes were recorded in both groups after 12 weeks.

***Conclusion*:** The use of Degludec Aspart is associated with a reduced incidence of hypoglycemia, offering improved treatment compliance among the Pakistani population with type 2 diabetes.

Keywords: Biphasic Insulin Aspart, Glycemic Control, Insulin Degludec Aspart, Type 2 Diabetes Mellitus.

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INTRODUCTION

Maintaining a well-regulated glycemic control is the mainstay in managing diabetes mellitus.[1] In Pakistan, the incidence of diabetes is rising rapidly. Increased inclination towards sedentary lifestyles, unhealthy dietary habits, environmental factors and stress in the Pakistani population have caused this incidence to rise rapidly in the past decades.[2] Early management halts the progression of diabetes. However, the irreversible nature of the disease makes the initiation of Insulin inevitable in these patients.[3] The significance of maintaining eminent glycemic control in reducing the complications associated with diabetes is well documented. Insulin has been established as the most effective blood glucose-lowering remedy as the course of the disease progresses.[4,5] Hypoglycemia is a prominent effect of Insulin therapy and is considered a main restraining factor in achieving tight glycemic control. An increased incidence of hypoglycemia has been observed in the literature and clinical practice, with basal-bolus and premixed Insulin therapies, the analogues of Insulin predominantly used for Insulin initiation worldwide.[6]

A newer co-formulation of Insulin, Insulin Degludec Aspart, has been formulated to reduce the incidence of hypoglycemia in people with diabetes, provide effective glycemic control, and improve the overall quality of life for people with diabetes.[7] Longer duration of action simplifies dosage frequency and, thus, treatment compliance. A rapidly acting and ultra-long acting Insulin, Insulin Aspart and Insulin Degludec, in a 30:70 ratio, respectively, in a single injection have provided post-meal as well as basal glycemic control, without the requirement of resuspension, as with the premixed Insulin.[8] After subcutaneous injection, Insulin Aspart, the rapidly absorbed component, provides post-prandial glycemic control, while Insulin Degludec is absorbed slowly over 24

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hours, providing basal glycemic control throughout the day.[9] These attributes make Insulin Degludec Aspart a preferable choice in people with diabetes experiencing daytime as well as nocturnal hypoglycemia with the basal-bolus and premixed Insulin therapies and improve therapeutic compliance.[10] Among the physicians in Pakistan, the inclination towards the use of Insulin Degludec Aspart has risen for the past two years. This study has been designed to evaluate the impact of Insulin Degludec Aspart on hypoglycemic episodes in type 2 diabetics in Pakistan, observed as confirmed total hypoglycemic episodes and nocturnal hypoglycemic episodes compared with the conventional premixed Insulin therapy.

METHODOLOGY

The quasi-experimental study was conducted at the Department of Pharmacology, Army Medical College, National University of Health Sciences (NUMS) Rawalpindi Pakistan, in collaboration with the Department of Medicine, Pak Emirates Military Hospital, Rawalpindi Pakistan, from September to December 2021, after acquiring approval from the Institutional Review Board (ERC/ID/150). The sample size was calculated using a World Health Organization calculator, taking reference fasting plasma glucose concentrations of 238.7±75.8 mg/dl and 165.8±56.9 mg/dl in Premixed Insulin Aspart and Biphasic Insulin Aspart groups, respectively.[11]

Inclusion Criteria: Documented type 2 diabetes patients of either gender, aged ≥18 years, taking Premixed Insulin Aspart therapy without treatment change in the last eight weeks were included.

Exclusion Criteria: 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 from the study.

Informed consent from the participants were taken. Study participants were divided into two groups using random table (Figure).

There were 60 participants in each group. Group-A was continued on Premixed Insulin Aspart therapy, and Group-B was substituted with Insulin Degludec Aspart, administered with breakfast and kept as the main meal of the day. The principal investigator obtained a brief history and demographic profile of the participants in the outpatient department. Participants were briefed about the study procedure and educated about the symptoms of hypoglycemia. Symptom charts were provided to all participants to aid in the diagnosis of hypoglycemia at home. Participants were advised to measure their blood glucose levels with the help of a glucometer when the hypoglycemia was suspected based on the symptoms. A plasma glucose concentration of less than 70mg/dl was considered hypoglycemia. A plasma glucose concentration of less than 56mg/dl was considered severe hypoglycemia. Hypoglycemia during the night, from 12am to 6am, was considered as nocturnal hypoglycemia. Participants were advised to record the hypoglycemic episodes for 12 weeks. At the end of 12 weeks, the data was collected and analyzed for both groups.

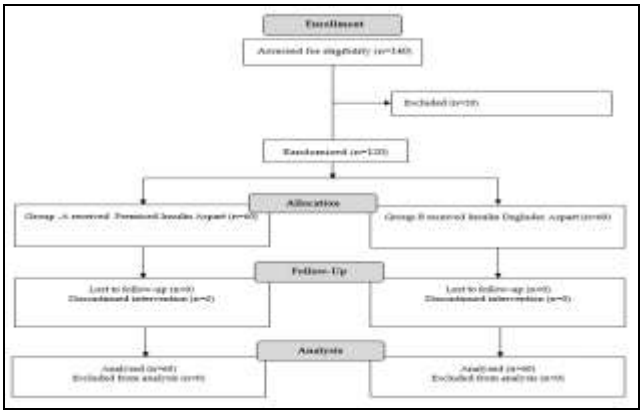

Figure: Patient Flow Diagram (n=120

Statistical Package for Social Sciences (SPSS) version 26.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test and Independent sample t-test were applied to explore the inferential statistics. The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

Out of the 120 participants enrolled in the study, 72 were males and 48 were females. One hundred sixty episodes of confirmed total hypoglycemic episodes were recorded by 49(81.6%) participants in the Premixed Insulin Aspart-Group. 26(43.3%) participants of the Insulin Degludec Aspart-Group recorded 40 episodes of confirmed total hypoglycemia (*p*-value <0.001). Confirmed nocturnal hypoglycemic episodes

were 73 in the Premixed Insulin Aspart-Group, recorded by 43(71.6%) participants and 12 episodes, recorded by 11(18.3%) participants in the Insulin Degludec Aspart-Group (*p*-value<0.001). No participants in the group reported severe hypoglycemic episodes after 12 weeks. The Insulin Degludec Aspart-Group participants reported a statistically significant decline in total and nocturnal hypoglycemic episodes compared to the Biphasic Insulin Aspart-Group (Table).

Table: Demographic attributes and summary of Hypoglycemic Episodes (E) among participants of Study Groups (n= 120)

Characteristics	Premixed Insulin Aspart-Group n(%)	Insulin Degludec Aspart-Group n(%)	*p*-value
Age (years)			
Mean±SD	57.23±9.38	57.63±9.40	0.81
Gender			
Males Females	34(56) 26(44)	38(63) 22(34)	0.5
Confirmed hypoglycemic events	49(81.6)	26(43.3)	<0.001
Confirmed Hypoglycemic Episodes	160(80%)	40(20)	<0.001
Severe Hypoglycemic Events	0(0)	0(0)	0
Confirmed Nocturnal Hypoglycemic Events	43(71.6)	11(18.3)	<0.001
Confirmed Nocturnal Hypoglycemic Episodes	73(85)	12(15)	<0.001
Confirmed Severe Nocturnal Hypoglycemic Events	0(0)	0(0)	0

DISCUSSION

The present study observed the outcomes of switching to Insulin Degludec Aspart therapy from Premixed Insulin Aspart on the hypoglycemic episodes. Initiating treatment with Insulin Degludec as part produced statistically significant results in our study compared with the premixed Insulin Aspart. A substantial reduction in the occurrence of confirmed total and confirmed nocturnal hypoglycemic episodes per week in the Insulin Degludec Aspart Group was noted.

Many studies worldwide have proven the exceeding efficacy of Insulin degludec aspart in reducing daytime and nocturnal hypoglycemia.[12,13] A study by Haahr and his colleagues 2017 evaluated the effect of the pharmacokinetic properties of Insulin Degludec Aspart on glycemic control. They administered Insulin Degludec Aspart to the study participants at a steady state, with the help of a euglycemic clamp. According to Haahr *et al.* the Insulin = Aspart component of Insulin Degludec Aspart is the rapid-acting component, which provides a prompt glucose-lowering effect, as required for post-meal glycemic control. The longer-acting Insulin Degludec component of Insulin Degludec Aspart provided a basal and long-lasting glucose-lowering effect for more than 30 hours in all patients, confirming the role of Insulin Degludec Aspart in lowering the incidence of hypoglycemia in type 2 diabetics, as shown by the outcomes in our study.[14]

A 26-week, multicenter, open-labelled trial was conducted by Fulcher and his colleagues in 2022 in six countries. They compared Insulin Degludec Aspart with other antidiabetic drug therapies, including premixed Insulin = Aspart. Among the 1100 individuals exposed to Insulin Degludec Aspart therapy, 128 experienced hypoglycemic episodes and 59 experienced nocturnal hypoglycemia. Significant reductions in the rates of non-severe hypoglycemia ($P = 0.0004$), non-severe nocturnal hypoglycemia ($P < 0.0001$), and severe hypoglycemia ($P < 0.0001$) were noted after switching to or initiating treatment with Insulin Degludec Aspart.[15] The remarkable reduction in the incidence of total confirmed and nocturnal hypoglycemia episodes supports the findings of our study.

Yang and his colleagues carried out a 26-week, treat-to-target, open-label trial in China in 2019.[16] The efficacy of switching treatment from premixed Insulin Aspart to biphasic Insulin Aspart was studied. The superiority of Insulin Degludec Aspart in reducing the total and nocturnal hypoglycemic episodes was confirmed. Insulin Degludec Aspart reduced the total confirmed hypoglycemic episodes by 43% and nocturnal confirmed hypoglycemic episodes by 47%, validating the findings of the present study.[17]

Another multicenter, prospective, observational study conducted by Kesavadev and his colleagues in India in 2021 evaluated the safety of Insulin Degludec/Insulin Aspart in adult type 2 diabetic

patients in a real-world setting during routine clinical care.[18] The study participants were administered Insulin Degludec Aspart for at least 12 months during the routine diabetes management. Among the 1029 participants included in the study, 67 participants (6.7%) reported 176 hypoglycemic events with other antidiabetic treatment modalities. Eleven participants reported 11 hypoglycemic events (1.1%) during the 12-month treatment period with Insulin Degludec Aspart. No participants taking Insulin Degludec as part reported the severe hypoglycemia.[18] The results of this study support the findings of the present study.

In light of the documented literature, the present study has provided insights on the long-term safety and efficacy of Insulin Degludec Aspart and the reduced incidence of hypoglycemic events observed among the Pakistani population. Practical use of Insulin Degludec Aspart can be implied among the clinical setups of Pakistan in people with type 2 diabetes dreading inadequate glycemic control secondary to the frequent onset of hypoglycemia to improve patient compliance and clinical outcomes in the Pakistani population.

LIMITATION OF STUDY

The study was conducted at a single centre with a small sample size. To determine the outcomes of Insulin Degludec Aspart on a vast scale, a multi-centred study and a long-term follow-up with a larger sample size can be carried out.

CONCLUSION

The present study concludes that a reduced number of hypoglycemic episodes occurred in participants prescribed Insulin Degludec Aspart compared to the conventional Premixed Insulin Aspart Group.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

KMM & SZ: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

SA & MN: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

NI: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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