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ORIGINAL ARTICLE **OPEN ACCESS**

Efficacy and Safety of Degludec versus Glargine in Type2 Diabetic Patients with Oral Hypoglycemic Agent

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ABSTRACT

Insulin Degludec and Insulin Glargine have both proven effective in managing diabetes. This study aimed to evaluate the effectiveness and safety of degludec in comparison to glargine among type 2 diabetic patients using oral hypoglycemic agents. Conducted at the Department of Diabetology, NRI General Hospital, Guntur, this prospective observational study spanned 8 months from August 2022 to March 2023, involving 54 subjects diagnosed with type 2 diabetes mellitus. Of these, 27 were treated with insulin glargine, and the remaining received insulin degludec, alongside oral hypoglycemic agents. Both degludec and glargine groups demonstrated a significant change in HbA1c levels, with no statistical difference between treatments (estimated treatment difference of 0.11%, CI 95%, P=0.410). Degludec provided improved glycemic control comparable to glargine, resulting in similar reductions in HbA1c. There was no notable change in BMI from baseline to three months after treatment in either group. The combined administration of insulin glargine and degludec with oral hypoglycemic agents consistently achieved glycemic control in type 2 diabetes patients, with lower rates of nocturnal confirmed hypoglycemia observed with degludec. Nasopharyngitis emerged as the most common adverse drug reaction in both groups, with a higher incidence in the degludec group.

Keywords: *Type 2 Diabetes Mellitus,; Insulin Glargine; Insulin Degludec; oral hypoglycemic agents.*

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is marked by insulin resistance and dysfunction of beta cells. Initially, there is an increase in insulin production to regulate blood glucose levels effectively. However, as the condition progresses, changes in beta cells occur, resulting in insufficient insulin output to maintain stable glucose homeostasis, ultimately leading to hyperglycemia. [1]

For individuals with type 2 diabetes who do not respond adequately to optimal doses of oral anti-hyperglycemic agents, the initiation of insulin therapy becomes necessary. Insulin glargine (IGlar), administered once daily as a long-acting insulin, ensures a sustained basal insulin level throughout the day. The primary adverse effect associated with insulin glargine is hypoglycemia. [2]

In recent years, there has been a notable transformation in diabetes management following the approval of insulin degludec (IDeg) U-100. As an advanced basal insulin, insulin degludec U-100 sets itself apart with its exceptional ultra-long duration of action. IDeg is distinctive as the only insulin analogue capable of self-associating into multi-hexamers upon subcutaneous (SC) injection, forming a soluble depot. Numerous head-to-head studies comparing IDeg with IGlar U-100 consistently emphasize that IDeg not only exhibits longer durations of action but also demonstrates lower rates of hypoglycemia. [3]

Previous comparative studies between degludec and glargine did not comprehensively measure all the following parameters: reduction in glycosylated haemoglobin (HbA1C), occurrences of nocturnal confirmed hypoglycemia (NCH), changes in Body Mass Index (BMI), and identification of adverse effects, all within a single study. Our research aimed to encompass all these parameters.

MATERIAL AND METHODS

This is a prospective observational study conducted to assess the efficacy and safety of Insulin Degludec vs Insulin Glargine in Type 2 diabetic patients with Oral hypoglycemic agents (OHAs) in the Department of Diabetology, NRI General Hospital, Guntur.

Study duration

The study encompassed a duration of 8 months, starting in August 2022 and concluding in March 2023.

Study population

The study systematically examined all individuals who visited the Department of Diabetology, and the study population was determined based on the specified inclusion and exclusion criteria.

Inclusion criteria

- Individuals aged ≥18 and ≤75, of any gender, diagnosed with type 2 diabetes mellitus and receiving either IGlar (100IU/ml) or IDeg.
- Patients may be included with or without elevated liver enzymes, lipid profile abnormalities, and renal function test variations.
- All patients must be currently undergoing treatment with DPP4 inhibitors, Sodium- SGLT2 inhibitors, with or without Metformin, Glimepiride, sulfonylureas, or alpha-glucosidase inhibitors as oral hypoglycemic therapy.

Exclusion criteria

- Subjects with type I diabetes mellitus or gestational diabetes.
- Subjects with Glomerular Filtration Rate (GFR) <30ml/min.

Study Procedure

All subjects presenting with symptoms of diabetes had their diagnosis of T2 DM confirmed through blood glucose level assessments in the Diabetology department, where they were closely monitored on a monthly basis. Information required for clinical outcomes and adverse drug reactions in T2 DM including subjects' details, medication information and the assessment of efficacy and safety of both the groups were collected and meticulously documented in appropriately designed data collection forms. The 3 month follow-up process involved interviews with the subjects and a review of their charts.

STUDY OUTCOMES

- The primary endpoints included assessment of efficacy by alterations in HbA1c and BMI from the baseline to the three-month mark.
- The secondary outcome involved assessing the rate of nocturnal confirmed hypoglycemia (NCH) over the course of three months in both study groups.

RESULTS AND DISCUSSION

The study included a total of 54 participants diagnosed with type 2 diabetes mellitus (T2DM) who met the inclusion criteria. Among the study population, 17 (31%) fell within the 40-49 age range, followed by 14 (26%) in both the 50-59 and 60-69 age groups. The mean age of the study subjects was 55.01 ± 10.87 years, aligning with *Meneghini et al.*'s findings reporting a mean age of 56.4±9.6 years in their study. In our research, females showed a slight preponderance, accounting for 28 (52%) of the participants, compared to males at 26 (48%). The female-to-male ratio was determined to be 1.07:1, consistent with *Asoy et al.*'s observations where females constituted 55% of individuals affected by T2 DM, while males accounted for approximately 45%. [4]

The majority of patients in both the IGlar and IDeg groups exhibited hypertension as a co-morbidity, with proportions of 12 (44%) and 9 (33%), respectively. Following this, hypothyroidism was observed in 7 (26%) and 3 (11%) individuals in the IGlar and IDeg groups, while skin and soft tissue infections were reported in 1 (4%) and 4 (15%) patients in the IGlar and IDeg groups, respectively. Other co-morbidities included diabetic neuropathy, with 3 (11%) and 1 (4%) cases in the IGlar and IDeg groups, respectively. These findings closely resemble those reported by *Zinman et al.,* where 70.8% of the IGlar group and 72.6% of the IDeg group had hypertension, and diabetic neuropathy was observed in 12 (4.7%) and 67 (8.7%) individuals in the IGlar and IDeg groups, respectively. [6]

Duration of Diabetes Mellitus

The majority of patients had a duration of 9–13 years, with 8 (30%) and 9 (33%) in the IGlar and IDeg groups, respectively. The mean diabetes duration in the IGlar group was 13.03 years, while in the IDeg group, it was 10.92 years. These findings align with the study by *Aso Y et al.,* where the mean diabetes duration in the IGlar group was 13 years and 10 years in the IDeg group. [5]

Oral hypoglycemic agents prescribed in the study subjects

Figure.1 depicts the prescribed oral hypoglycemic agents for the study participants. with the majority receiving Dapagliflozin (37, 69%), followed by Vildagliptin (15, 28%). A combination of Metformin +

Sitagliptin was prescribed to 10 participants (19%), while a smaller number of subjects were prescribed Metformin (7, 13%), Teneligliptin (6, 11%), Glimepiride + Voglibose + Metformin (2, 4%), Glimepiride + Metformin (2, 4%), Glimepiride (4, 7%), and Metformin + Voglibose (1, 2%). These findings were compared with the study by *Zinman B et al.,* where metformin was prescribed to 300 subjects (61.6%), sitagliptin to 164 subjects (21.1%), and vildagliptin to 16 subjects (3.3%). [6]

Change in HbA1c levels

Figure.2 displays the alteration in HbA1c levels from the initial level to 3 months after treatment in both groups. A significant decrease in HbA1c levels was noticeable in both groups. Following 3 months of treatment, the mean ± SD HbA1c showed a decrease from 10.1 ± 1.4% at baseline to 8.6 ± 1.4% with IDeg and from 10.1 ± 1.6% at baseline to 8.5 ± 1.4% with IGlar. There was no statistically significant change amongst the treatments, with an estimated treatment difference of 0.11% (CI 95%, P = 0.410). These results align with those reported by *Rodbard HW et al.,* where the treatment difference was 0.07% (95% CI, P = 0.339). Thus, IDeg demonstrates enhanced glycemic control, comparable to IGlar, with similar reductions in HbA1c levels. [7]

Body Mass Index

The data in Figure.3 depicts the change in BMI from baseline to after 3 months of treatment in both study groups. Following 3 months of treatment, the observed mean ± SD BMI increased from 27.37 ± 2.6 Kg/m2 at baseline to 27.92 ± 2.4 Kg/m2 with IDeg, and from 26.71 ± 4.2 Kg/m2 at baseline to 26.31 ± 4.2 Kg/m2 with IGlar. In both groups, there was no clinically significant change in BMI between baseline and three months after the treatment.

Nocturnal confirmed Hypoglycemia

The data in Table.1 illustrates the mean rate and estimated rate ratio (ERR) of NCH in both study groups. After three months of treatment, the occurrence of NCH was lower with IDeg, registering 0.01 episodes per patient-month compared to 0.03 episodes per patient-month with IGlar. The ERR was 0.31 (CI 95%, P = 0.005), indicating a 31% reduction in the incidence of NCH with IDeg. These results align with the findings of *Rodbard HW et al.,* where NCH was notably 43% lower with IDeg at the conclusion of the trial, with rates of 0.27 vs. 0.46 episodes per patient-year and an ERR of 0.57 (CI 95%, P = 0.002). [7]

Safety

The data in Figure.4 reveals ADRs reported in the IDeg and IGlar groups. The most frequently reported ADR was nasopharyngitis following this, upper respiratory tract infections. The least reported ADR was injection site disorder Nasopharyngitis was the predominant ADR in both groups, with a higher incidence in the IDeg group. Upper respiratory tract infections (URTIs) were prevalent in both groups, while injection site disorder was the least common ADR, more prevalent in the IGlar group.

Upon administration of the WHO-UMC Causality Assessment Scale and the ADR severity Assessment Scale with Modified Hartwig and Siegel all the ADRs were found to be mild, and are considered to be probably related to the use of these basal insulins. Similar observations were noted in *Zinman B et al.,* where 96% of adverse events were mild or moderate and were deemed by the investigator as possible or probable associated with basal insulin. The most commonly reported adverse events in both groups were nasopharyngitis and headache. Injection site reaction rates were uncommon, and none were severe. [6]

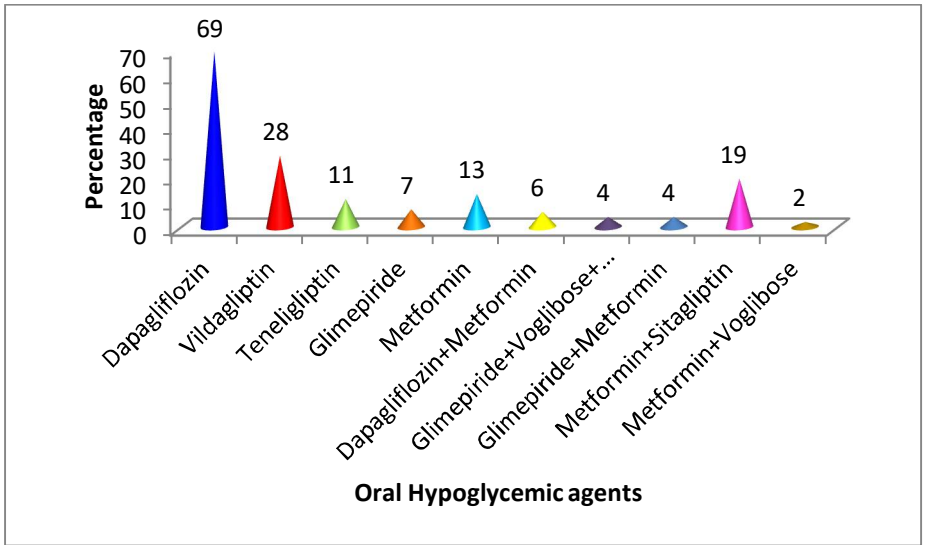

Figure 1.Oral hypoglycemic agents prescribed in study subjects

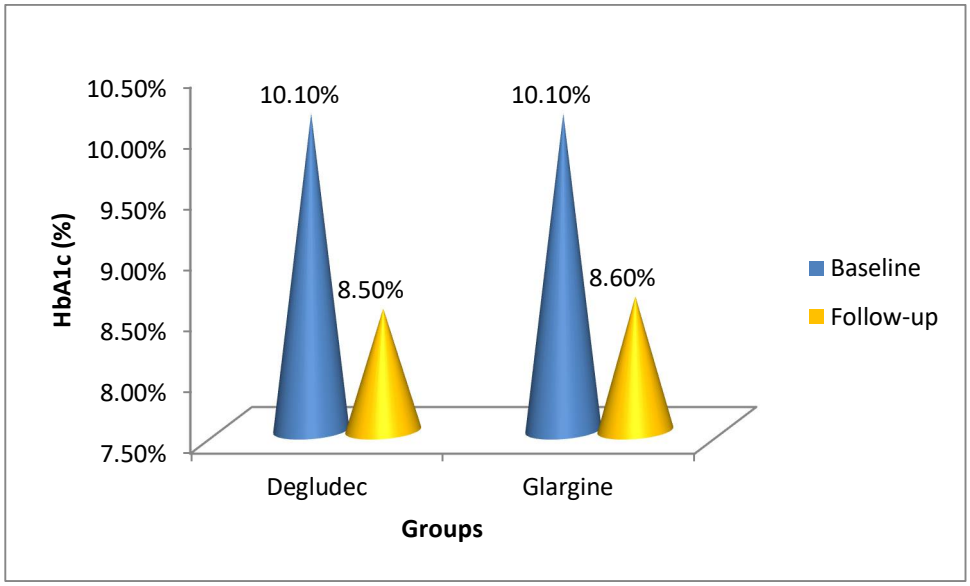

Figure 2. Change in HbA1c levels from baseline to after 3 months

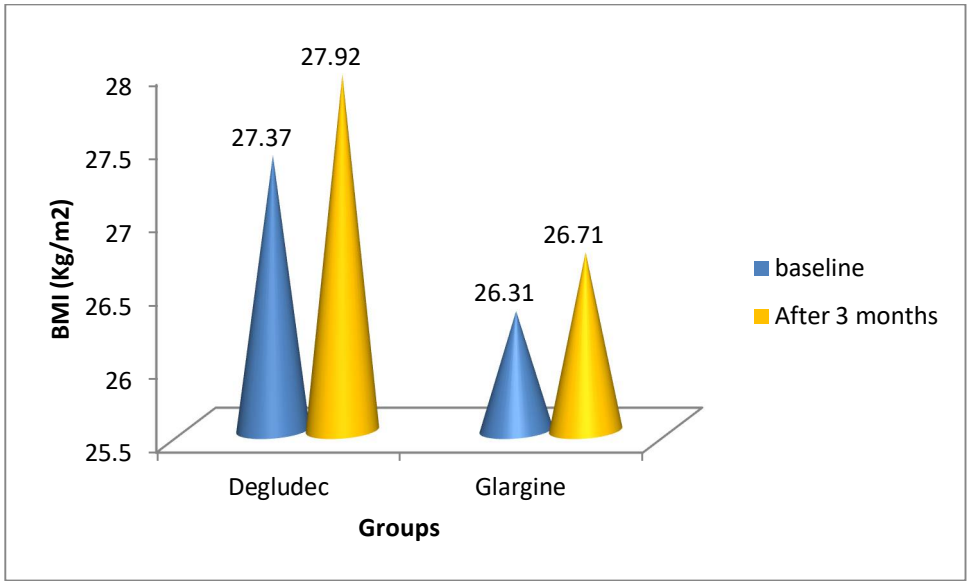

Figure 3. Change in BMI from Baseline to Follow-up

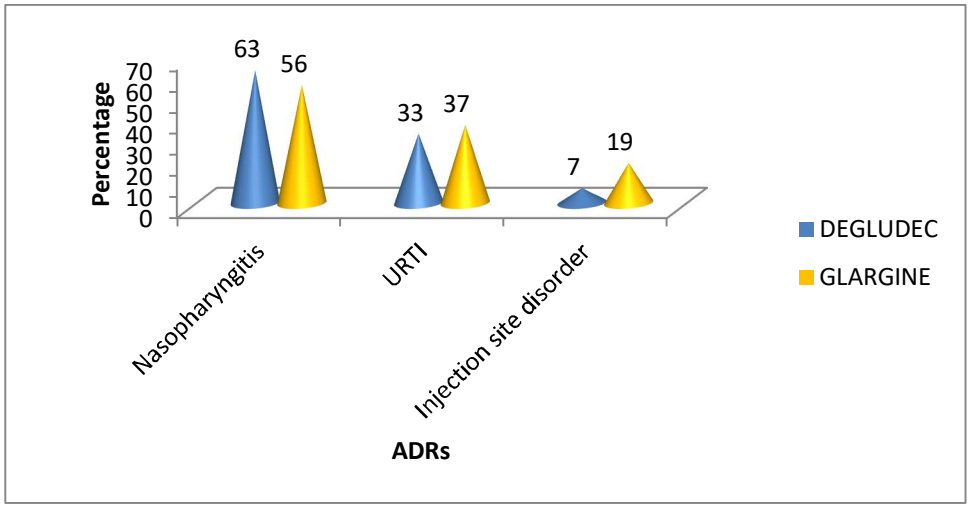

Figure 4. Adverse drug reactions reported in both groups

Table.1. Rate of Nocturnal Confirmed Hypoglycemia

S.NO	Time (in months)	IDeg (N=27)			Igla (N=27)			ERR(IDeg/IGla). CI95%
		Subjects (n)	Episodes	Rate	Subjects (n)	Episodes	Rate	Ideg/Igla
1	0-1	0	0	0	1	2	0.025	-
2	1-2	1	1	0.012	2	3	0.038	-
3	2-3	2	2	0.023	3	4	0.046	-
				=0.011			**=0.036**	**=0.30**

CONCLUSION

In individuals with T2 DM, the co-administration of IGlar or IDeg with oral hypoglycemic agents consistently achieved effective glycemic control, displaying lower rates of confirmed hypoglycemia during the night with IDeg. There was no noticeable difference in BMI between baseline and three months after treatment in both groups. Nasopharyngitis emerged as the most frequent ADR in both groups, particularly in the IDeg group. URTIs were prevalent in both groups. Injection site disorder was the least common ADR, with a higher prevalence in the IGlar group.

ABBREVIATIONS

ADRs	Adverse Drug Reactions
AE	Adverse Events
BMI	Body Mass Index
DPP4	Dipeptidyl peptidase 4 inhibitors
ERR	Estimated Rate Ratio
GFR	Glomerular Filtration Rate
HbA1c	Glycosylated Haemoglobin
IDeg	Insulin Degludec
IGlar	Insulin Glargine
NCH	Nocturnal Confirmed Hypoglycemia
OHA	Oral Hypoglycemic Agents
SC	Subcutaneous
SGLT2	Sodium Glucose Co Transporter 2 Inhibitors
URTI	Upper Respiratory Tract Infections
WHO	UMC – World Health Organization

AUTHOR CONTRIBUTIONS

Each author made substantial contributions to the study's design, data collection, and interpretation. They actively participated in composing or revising the article and collectively agreed to submit it to the present journal.

CONFLICTS OF INTEREST

In this study, the authors assert that they have no conflicts of interest to disclose.

ETHICALAPPROVAL

The study protocol received thorough review and approval from the Institutional Human Ethical Committee of Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur, under Ref. No. IEC/01/2022.

INFROMED CONSENT

Informed consent was acquired from all the study subjects.

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