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Efficacy and Safety of Insulin Degludec for Hyperglycemia Management in Noncritical Hospitalized Patients with Diabetes: An Observational Study

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ABSTRACT

Introduction: To assess the efficacy and safety of insulin degludec administered in a basal-bolus regimen according to the GesTIO protocol in noncritical hospitalized patients with T1DM and T2DM.

Methods: Mean blood glucose levels (BG) and their standard deviations (SD) at admission vs. discharge were compared in 52 subjects (48.1% ≥75 years) managed through a basal-bolus scheme including degludec. The percentages of patients with BG at target (140–180 mg/dl) or below at discharge and the incidence rate (and the 95% confidence interval for it) of hypoglycemia were assessed.

Results: From admission to discharge, fasting BG decreased from 237 to 153 mg/dl ($p < 0.0001$) and SD dropped from 125 to 38 mg/dl ($p < 0.0001$); average BG decreased from 189 to 145 mg/dl (SD dropped from 57 to 32 mg/dl). At discharge, 28.9% had BG at target, while 50.0% had lower levels (average 119.0 ± 14.4 mg/dl). The incidence rate of hypoglycemia was 0.07 (0.05; 0.11) episodes per person-day; 1 out of 27 episodes occurred during the night.

Conclusions: Degludec in hospitalized, mainly elderly patients is effective and minimizes glucose variability and nocturnal hypoglycemia.

Keywords: Diabetes mellitus; Insulin degludec; Noncritical hospitalized patients

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INTRODUCTION

Hyperglycemia management is a common, serious, and costly health care problem in hospitalized patients [1]. Hyperglycemia is associated with a prolonged hospital stay, infection, disability after discharge, and death [2–4]. Hypoglycemia and glycemic variability due to suboptimal management of insulin therapy in the inpatient setting have been associated with increased morbidity, mortality, and overall costs of care [5, 6]. The incidence of hypoglycemia peaks between midnight and 6 a.m. and is very often due to a lack of basal insulin dose adjustment [7]. To improve outcomes, sliding scale insulin (SSI) should be abandoned

in favor of inpatient diabetes management programs involving effective and well-tolerated basal-bolus insulin regimens [1, 8, 9].

Insulin degludec (IDeg) is a new basal insulin that is ultralong-acting; it improves glycemic control to a similar degree to insulin glargine but confers lower risks of overall and nocturnal hypoglycemia [10–14]. In fact, the day-to-day variability in the glucose-lowering effect of IDeg is less than that for glargine, so the effect of IDeg is more predictable [13, 15, 16]. Furthermore, IDeg allows flexibility in the timing of dose administration provided there is a minimum of 8 h between injections. The safe, predictable, and flexible profile of IDeg may be an advantage in the management of diabetic inpatients and for increasing the therapy compliance of insulin-treated patients after discharge.

The GesTIO protocol [17]—a subcutaneous insulin order set for the management of a basal-bolus-correction insulin regimen in inpatients—was developed by a multidisciplinary team of diabetologists, internal medicine, and geriatrics specialist physicians from DIMED at Padua University. It is based on the ADA guidelines and Trence's insulin order form [18, 19]. The safety, efficacy, and benefit of clinical management with the GesTIO protocol have previously been documented with basal insulins other than IDeg [17]. This is the first report of the impact of the GestTIO protocol when IDeg is used as basal insulin.

METHODS

Protocol Characteristics

Based on existing guidelines [1], the main components of our protocol are: adoption of scheduled basal-bolus insulin administration instead of SSI; regular monitoring of blood glucose; algorithm for basal and short-acting insulin dose adjustment based on blood glucose values; achievement of a premeal glucose target of less than 140 mg/dl (7.8 mmol/l) and an average BG during the day of less than 180 mg/dl (10.0 mmol/l), with the possibility of establishing a lower target range for patients who are able to achieve and maintain glycemic control

without hypoglycemia; attention to therapy management in the transition from hospital to home.

In the GesTIO protocol, a set of specific treatment recommendations that can be listed on a single (double-sided) A4 paper are adhered to, including (1) a method for estimating the total daily insulin dose requirement, (2) a section on prescribing the type and scheduling the doses of basal and pre-meal insulin, (3) glycemic goals and alarm levels for risk of hypoglycemia or hyperglycemia, (4) algorithms for supplemental correction-dose insulin to be administered by nurses at pre-meal time, (5) instructions for physicians regarding how to calculate and use the insulin correctional factor in particular situations, and (6) a table relating to the standardized management of hypoglycemia [17] (see Fig. S1 in the Electronic supplementary material, ESM).

Unlike the other basal insulins, which need to be titrated every day, IDeg was titrated every 3 days. Furthermore, due to its time flexibility, IDeg could be taken in the morning or evening according to the needs of the patient.

Data Collection

This is a before and after proof-of-concept study. Data on all consecutive patients with type 1 (T1DM) and type 2 diabetes (T2DM) admitted for any cause to our ward from September 2015 to February 2016 and managed through our protocol were retrospectively collected from electronic medical records. Data included age, sex, type and duration of diabetes, presence of comorbidities, and glucose-lowering therapy applied before admission. HbA1c, glomerular filtration rate (GFR), weight, and body mass index (BMI) were measured at admission. During the hospitalization, information collected in the ward on fasting plasma glucose levels (FPG), average blood glucose levels (BG), units of basal and short-acting insulin, and hypoglycemic episodes (BG <70 mg/dl) was collected. Length of hospital stay and number of self-monitoring blood glucose tests (SMBG) were adopted as measures of the use of healthcare resources.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. The study protocol was approved by the local ethics committee. Informed consent for inclusion in the study was obtained from all patients.

Statistical Analysis

All consecutive patients treated with IDeg were included, and no sample size calculation was performed. Patients' characteristics are expressed as mean and standard deviation (SD) or median and range for continuous variables and frequency (%) for categorical variables, respectively. Mean FPG and mean BG at discharge vs. admission were compared through the Wilcoxon signed-rank test. Mean levels of FPG at day 4 were evaluated since this is when IDeg reaches its steady state [14–16]. The distribution of patients among three ranges of BG at discharge (<140, 140–180, and >180 mg/dl) was assessed. Hypoglycemic episodes and SMBG tests during hospitalization were evaluated with Poisson regression; results are expressed as incidence rates and 95% confidence intervals (IR and 95% CIs). Analyses were performed on the overall population and stratified by insulin therapy (insulin-naïve or switched from another basal insulin at admission) and median of length of stay.

Statistical analyses were performed with SAS software (release 9.4; SAS Institute, Cary, NC, USA).

RESULTS

Overall, 52 noncritical patients (5 T1DM and 47 T2DM) were admitted to the ward for any cause during the selected period.

Patient baseline characteristics are reported in Table S1 of the ESM. Subjects were 57.7% men, they were mainly elderly (mean age of 69.4 ± 16.3 years; 48.1% $\geq$75 years), and had a mean diabetes duration of 9.9 ± 9.8 years. The most prevalent comorbidities were chronic kidney disease (35%) and peripheral vascular disease (23.1%). The mean HbA1c level at admission was $10.0 \pm 2.8\%$; 34.6% had GFR <60 ml/min $\times$ 1.73 m^2 and 44.8% had a BMI $\geq$30 kg/m^2.

Before admission, 31.3% of subjects were treated with glucose-lowering agents, 59.6% with basal insulin (83.9% glargine, 6.5% detemir, 9.7% neutral protamine hagedorn), and 59.6% with short-acting insulin (41.9% lispro, 16.1% aspart, 38.7% glulisine, 3.2% human regular insulin) (see Table S1 of the ESM).

During admission, 11.5% of the patients with T2DM were still treated with oral glucose-lowering agents, and they were prescribed to 28.8% of the patients at discharge.

Mean FPG levels changed from 237 mg/dl at admission to 142 mg/dl after 4 days and to 153 mg/dl at discharge ($p < 0.0001$). SD decreased from 125 mg/dl at admission to 37.9 mg/dl after 4 days and to 37.7 mg/dl at discharge ($p < 0.0001$). Average BG was significantly reduced by -43.7 mg/dl and SD by 24.4 mg/dl (Fig. 1). Statistically significant reductions in mean FPG and BG were obtained in both insulin-naïve ($N = 21$) and previously treated ($N = 31$) subjects and in patients with both short (<5 days) and long ($\geq$5 days) durations of stay (Fig. 1).

At discharge, 78.9% of the sample had BG within the recommended target (i.e., <180 mg/dl). Of these, 28.9% had BG between 140 and 180 mg/dl, and 50% had BG <140 mg/dl (Fig. S2 in the ESM).

IDeg was administered in 44.2% of subjects in the morning and in 55.8% in the evening, and in both groups FPG was reduced by about 80 mg/dl and BG by about 40 mg/dl.

Average starting dose of IDeg was 18.0 ± 9.8 UI at admission and 17.8 ± 9.5 UI at discharge, with no significant differences among the subgroups except for the "switch" subgroup, where lower doses were required (Fig. S3 in the ESM).

The IR (95% CI) of hypoglycemia was 0.07 (0.05; 0.11) episodes per person-day; 34.6% of the patients had at least one episode of hypoglycemia, up to a maximum of four episodes. Among a total of 27 recorded episodes, one occurred at night (Table S2 in the ESM). No episode of severe hypoglycemia occurred.
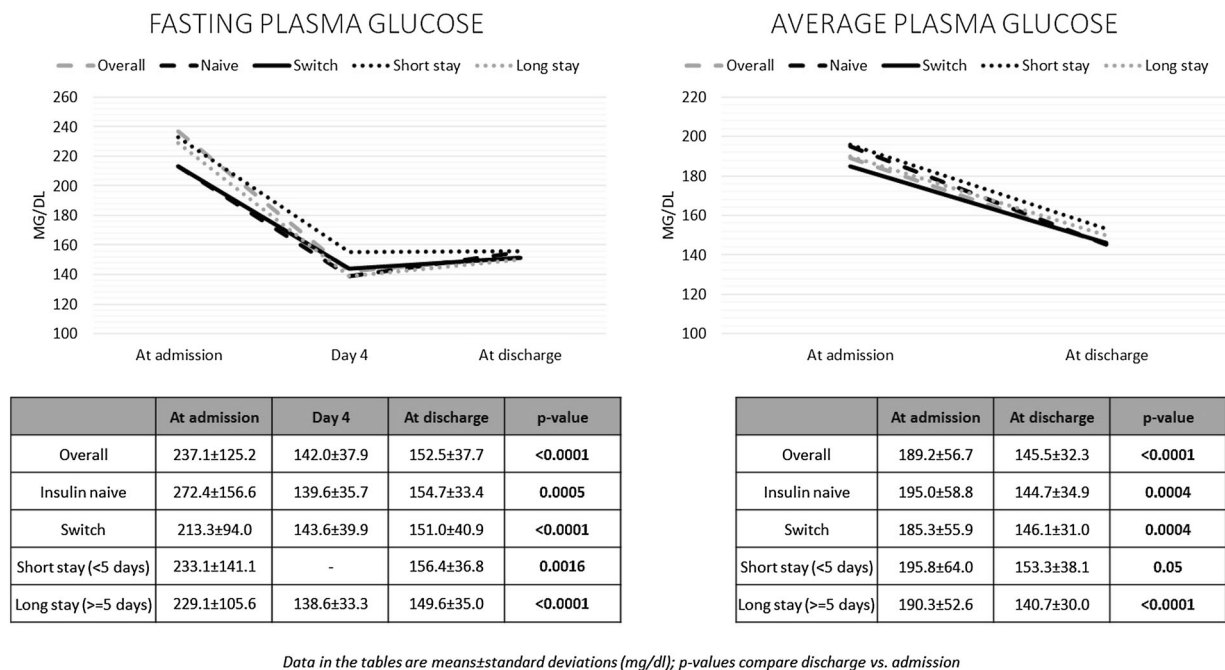
FASTING PLASMA GLUCOSE

--- Overall --- Naive ——Switch ••••• Short stay ····· Long stay

	At admission	Day 4	At discharge	p-value
Overall	237.1±125.2	142.0±37.9	152.5±37.7	**<0.0001**
Insulin naive	272.4±156.6	139.6±35.7	154.7±33.4	**0.0005**
Switch	213.3±94.0	143.6±39.9	151.0±40.9	**<0.0001**
Short stay (<5 days)	233.1±141.1	-	156.4±36.8	**0.0016**
Long stay (>=5 days)	229.1±105.6	138.6±33.3	149.6±35.0	**<0.0001**

AVERAGE PLASMA GLUCOSE

--- Overall --- Naive ——Switch ••••• Short stay ····· Long stay

	At admission	At discharge	p-value
Overall	189.2±56.7	145.5±32.3	**<0.0001**
Insulin naive	195.0±58.8	144.7±34.9	**0.0004**
Switch	185.3±55.9	146.1±31.0	**0.0004**
Short stay (<5 days)	195.8±64.0	153.3±38.1	**0.05**
Long stay (>=5 days)	190.3±52.6	140.7±30.0	**<0.0001**

Data in the tables are means±standard deviations (mg/dl); p-values compare discharge vs. admission

Fig. 1 Changes in blood glucose levels from admission to discharge overall and by subgroup

In terms of healthcare resources, 4.8 (4.6–5.1) SMBG tests per person-day were performed during admission; the median (range) length of stay was 5 (1–24) days (Table S3 in the ESM).

CONCLUSIONS

The efficacy and safety of IDeg within basal-bolus regimens in nonhospitalized patients with type 1 and type 2 diabetes have been documented [10, 11], whereas, to our knowledge, this is the first study on hospitalized patients with T1DM and T2DM who were treated with IDeg. Data show that the use of IDeg within a protocol for scheduled insulin administration is effective and safe in noncritical hospitalized elderly patients. FPG and BG were significantly improved and nocturnal hypoglycemia occurred in only one instance. With the GesTIO protocol, a SD of less than 1/3 of the mean BG (defined as acceptable glycemic variability) was reached in a median of 5 days [20]. The impact was positive in insulin-naïve and previously treated patients, irrespective of length of stay. At discharge, about 80% were at the BG target or below it.

Different trials have been conducted to identify the best therapies for the hospital setting, and different basal-bolus regimens or basal-oral therapies have been compared to SSI [8–13]. A recent meta-analysis [21] showed that a significantly lower mean daily BG was achieved with basal-bolus schemes than with SSI, with no difference in the risk of severe hypoglycemia or in mean length of stay, but an increased risk of mild hypoglycemia. The increased risk of mild hypoglycemia can be explained by a pool of factors, such as fasting conditions before laboratory tests, lack of appetite due to disease, and short-acting and basal insulin therapy. In our study, only one episode of nocturnal hypoglycemia occurred, suggesting that basal insulin played only a marginal role in the incidence of overall hypoglycemia, which was more likely to be related to short-acting insulin and fasting conditions.

The main strength of our study is the novelty of using this protocol, which adheres to the most recent guidelines [1], in conjunction with basal IDeg in inpatients. Since the role of IDeg in this context is totally unknown, our investigation represents a proof of concept that IDeg can be used in hospital with potential clinical

implications. The main limitations of the study are the small sample size and the lack of a control group; furthermore, information was not collected after discharge.

In conclusion, the use of IDeg when used in a basal-bolus regimen has the potential to improve metabolic control, glycemic variability, and nocturnal hypoglycemia in inpatients.

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