Original Article

Correlation between Basal Insulin Glargine Dose Required in Achieving Target Fasting Blood Glucose and Various Clinical and Laboratory Parameters in Hospitalized Noncritical Patients

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Abstract

Aims: The primary objective was to study the interrelationship between the basal insulin glargine dose and baseline clinical and laboratory parameters in noncritically ill hospitalized patients who have achieved the stable fasting blood glucose in the target range of 100–140 mg/dl. **Patients and Methods:** This was retrospective, cross-sectional, observational study. Consenting, nonpregnant, adult patients on basal-bolus insulin who had fasting capillary blood glucose in the range of 100–140 mg/dl as measured by glucometer for 3 consecutive days were included in this study. Patient receiving any basal insulin other than insulin glargine were excluded from this study. The data collected for these patients included age, sex, glycated hemoglobin (HBA1c) at the time of admission, timing of basal insulin, basal insulin dose (BID), BID/kg, weight, and serum creatinine. BID/kg was correlated with other parameters using regression analysis (Pearson's). Comparison of BID/kg in various subgroups was analyzed using Student's *t*-test. Parametric data of more than three groups were compared using ANOVA. The $P < 0.05$ was considered as statistically significant. **Results:** A total of 180 patients were included in the study. On correlating the BID/kg with various parameters, we found statistically significant correlation between BID/kg and glycated hemoglobin (HbA1c) at the time of admission ($P = 0.044$). Patients with HbA1c ≥8.0% had higher BID/kg compared to those with HbA1c <8.0% ($P = 0.004$). The mean BID in patients with renal failure was significantly higher compared to those without renal failure. **Conclusion:** HbA1c at the time of admission is the most important parameter for determining the appropriate BID in hospitalized patients. Patients with renal failure may require a higher dose of basal insulin than those not having renal failure.

Keywords: Basal insulin, glargine, hospital hyperglycemia, in-hospital hyperglycemia

Introduction

Management of hyperglycemia in hospitalized patients needs to be done effectively and quickly to achieve euglycemia. The Endocrine Society Guidelines recommend the use of basal-bolus insulin in the management of hyperglycemia in hospitalized patients.[1] The guidelines recommend that starting dose insulin as 0.2–0.5 units/kg, of which 50% is basal insulin which makes the starting dose of basal insulin as 0.1–0.25 units/kg. This recommendation comes from the RABBIT-2 trial. The trial used insulin glargine as the choice of basal insulin. If the fasting blood glucose was >140 mg/dl, then the basal insulin glargine dose was increased by 20% everyday to achieve a target range of 70–140 mg/dl in the aforementioned trial.[2]

It is often noticed in clinical practice that the starting dose of basal insulin as recommended by the guidelines is often inadequate. In various trials done for the use of basal insulin in outpatient department (OPD), the basal insulin dose (BID) requirement has been anywhere from 23 units/day to as much as 80 units/day to reach a target fasting blood glucose <130 mg/dl from a baseline value of an average of 200 mg/dl.[3] It is, hence, obvious that a starting dose of 0.2 units/kg of basal insulin would surely be inadequate to achieve a desired glycemic control in patients who typically present in the hospital with high fasting plasma glucose values. In addition, while in OPD patients, the clinician has the luxury of gradual titration of the

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insulin dose, and in hospitalized patients, there is often a sense of urgency to achieve a good glycemic control as early as possible. In such a scenario, the prescribed BID by Endocrine Society may prove inadequate.

The primary objective was to study the interrelationship between the basal insulin glargine dose (in units/kg) and baseline clinical and laboratory parameters in noncritically ill hospitalized patients who have achieved the stable fasting blood glucose in the target range of 100–140 mg/dl.

Patients and Methods

Study design

This was a retrospective, cross-sectional, observational study. This study was conducted at a single tertiary care institution in New Delhi. Permission for the study was granted by the institutional ethics committee. This study was conducted from January 2015 to August 2015.

Study group

Nonpregnant, adult, and diabetic patients admitted to noncritical beds in the hospital and treated with basal-bolus insulin regime were screened for eligibility for inclusion in the study. The BID was titrated in all patients as described in the protocol of the RABBIT-2 trial, and the Endocrine Society Guidelines to achieve a fasting capillary blood glucose in the target range of 100–140 mg/dl.[1,2]

Patients who achieved stable fasting capillary blood glucose in the target range of 100–140 mg/dl as measured by glucometer for 3 consecutive days were included in the study. Written consent was taken from the patients who were eligible for inclusion in the study.

Patient receiving any basal insulin other than insulin glargine were excluded from the study. Patients who refused to give consent, those taking oral antidiabetics during the hospital stay or those who were on glucocorticoids were excluded from the study.

Data collection

The data collected for these patients included age, gender, glycated hemoglobin (HBA1c) at the time of admission, timing of basal insulin, BID, BID/kg, weight, and serum creatinine. The data for the BID and BID/kg were taken during the period of stable fasting plasma blood glucose in the range of 100–140 mg/dl.

Clinical and laboratory methods

Body mass index (BMI) was calculated from weight (in kg) and height (in m) of the patients as weight/height.[2] Estimated glomerular filtration rate (eGFR) was calculated from the MDRD study equation.[4]

Contour® Next glucometer was used for capillary blood glucose measurements (manufactured by Bayer HealthCare LLC). Fingertips were used for capillary blood glucose sample using standard lancing device provided by the manufacturer. The test strips used flavin adenine dinucleotide-glucose dehydrogenase method for blood glucose testing.[5] The results of the glucometer are referenced to plasma/serum blood glucose values. The measuring range of the glucometer is 10–600 mg/dl.

Plasma glucose concentration was measured with glucose oxidase method on Beckman Coulter Unicel DXC-800 analyzer. HbA1c was measured using ion-exchange high-performance liquid chromatography (Bio-Rad D-10 analyzer). The reference range of the test was from 3.8% to 18.5%.

Statistical analysis

BID/kg was correlated with other parameters using regression analysis (Pearson's). Comparison of BID/kg in various subgroups was analyzed using Student's *t*-test. Multivariate regression analysis was performed with BID/kg as the dependent variable to analyze the individual contributions of age, gender, BMI, HbA1c, and eGFR.

Parametric data of more than three groups was compared using ANOVA. The $P > 0.05$ was considered as statistically significant.

Parametric data were reported as mean ± standard deviation, and nonparametric data were reported as median (with interquartile range). SPSS version 20 (IBM, Chicago, IL, USA) was used for carrying out statistical analysis.

Results

A total of 180 patients were included in this study. The baseline data of the patients are shown in Table 1. The mean BID was 25 ± 12 units, and the mean BID/kg was 0.33 ± 0.14 units/kg.

On correlating the BID/kg with various parameters, we found statistically significant correlation between BID/kg and HbA1c at the time of admission ($P = 0.044$). No significant correlation was found with age, BMI, and eGFR.

Patients with HbA1c ≥8.0% had higher BID/kg (0.44 ± 0.08 units/kg) compared to those with HbA1c <8.0% (0.28 ± 0.11 units/kg) ($P = 0.004$) [Figure 1]. There was no statistically significant difference in BID/kg in patients with HbA1c <6.5% when compared to those with HbA1c between 6.5% and 8.0% ($P = 0.65$).

We compared the mean BID/kg in patients with renal failure (defined as eGFR <60 ml/min/1.73 m^2) with those not having renal failure. The mean BID in patients with renal failure was higher (0.42 ± 0.15 units/kg) than those without renal failure (0.3 ± 0.12 units/kg). The difference between the two groups was statistically significant ($P = 0.013$) [Figure 2].

There was no significant difference in the BID among elderly patients (defined as those having age ≥70 kg) versus nonelderly ($P = 0.84$). The time of the basal insulin administration (morning vs. afternoon vs. evening) did not influence the BID ($P = 0.47$). There was no significant difference in the BID/kg in men versus women ($P = 0.42$).

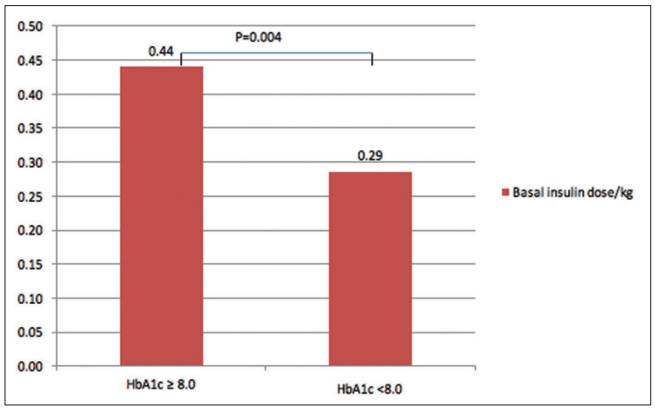

Figure 1: Basal insulin dose/kg in two groups based on glycated hemoglobin

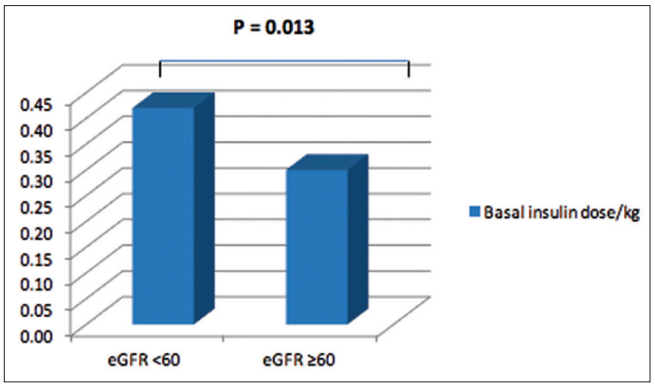

Figure 2: Basal insulin dose/kg and glomerular filtration rate

Multivariate analysis

Multivariate analysis revealed significant and independent correlation between BID/kg and HbA1c (P = 0.04) and eGFR (P = 0.014). The correlation coefficient between eGFR and the BID/kg was negative; meaning the patients with lower eGFR required a higher BID.

Discussion

The recommendation of Endocrine Society for starting BID is shown in Table 2.[1] Some of the results from our study show that the starting BID as recommended by these guidelines may be much lower than what we have seen in our study. The mean BID in the RABBIT-2 trial was 22 ± 2 units, whereas the mean BID in this study was 25 ± 12 units.[2]

Papa *et al*. performed a study to find correlation between various anthropometric, clinical and laboratory parameters, and the BID. Patients on oral antidiabetic agents were also included in the abovementioned study. Papa *et al*. found a difference in the BID between male and female, whereas we found no difference with regards to gender. They also found a correlation between HbA1c and the BID. There was no correlation between age and BID in their study.[6]

The higher basal insulin requirement in patients with high HbA1c in this study can be ascribed to glucotoxicity and lipotoxicity caused by long-standing uncontrolled diabetes. Glucotoxicity and oxidative stress, which are associated with long-standing uncontrolled diabetes, are well known to worsen insulin resistance.[7]

Clinicians often tend to start a lower dose of basal insulin in patients with renal failure. Indeed, the Endocrine Society Guidelines recommend lower starting dose of insulin in patients with renal failure.[1] However, we found in our study that patients with renal failure actually required a higher insulin dose compared to those not having renal failure. Insulin resistance is known to be high in patients with renal failure which can explain the phenomenon that we observed.[8] A study performed in Australia observed patients with higher grades of chronic kidney disease (CKD) have reduced physical activity which can lead to increased insulin resistance. Vitamin D is known to reduce insulin resistance.[9] Patients with advanced CKD have reduced 1,25 dihydroxyvitamin D, especially when the glomerular filtration rate (GFR) is <30 mL/min/1.73 m^2.[10] Hence, reduced 1,25 dihydroxyvitamin D possibly explains the increased insulin resistance seen in advanced CKD. Another explanation is the secondary hyperparathyroidism due to deficiency of vitamin

Table 1: Baseline data of the patients

Parameter	Value
Number of patients	180
Gender	Males - 52%, Females - 48%
Mean age (in years)	56.7 (11.6)
Diabetes type	Type 1-5.5%, Type 2 - 94.5%
Mean admission HbA1c (in %)	7.6 (1.8)
Mean Weight (In kg)	77.7 (20.1)
Mean BMI (kg/m^2)	28.9 (7.9)
Mean Basal insulin dose (Units)	25 (12)
Mean Basal insulin dose/ weight - U/kg	0.33 (0.14)
Timing of basal insulin	Morning (8 am to 12 noon)- 43.2% Evening (6 pm - 9 pm)- 32.4% Bedtime (10 pm-12 am)- 21.6%
Mean eGFR (ml/min/1.73 m^2)	81.8 (34.6)

*Values in mean with standard deviation in brackets

Table 2: Recommended starting dose of basal insulin dose (Adapted from Endocrine society guidelines for In-hospital hyperglycemia

	Endocrine society guidelines	Results from our study
Age >70 years	0.1-0.15 units/kg	No relation between age and Basal insulin dose/weight
GFR <60 ml/ min/1.73 m^2	0.1-0.15 units/kg	Patients with renal failure (GFR <60 ml/min/1.73 m^2) required a higher basal insulin dose/weight than those without renal failure.
Patients no meeting above criteria	0.2-0.25 units/kg	We found HbA1c influencing the basal insulin dose.

D and phosphate retention in CKD may be the etiology for the increased insulin resistance.[8] It has also been proposed that metabolic acidosis seen in patients with advanced CKD, may be responsible for the enhanced insulin resistance. Inflammation and oxidative stress are higher in CKD and may have link with insulin resistance.[8]

The results from our study can prove to be extremely useful to a practicing endocrinologist. HbA1c should be an important determinant while analyzing the BID in hospitalized diabetic patients. We recommend additional research to understand the insulin dosing requirement in patients with renal failure.

Our study is limited by a small patient number. In addition, the study is retrospective in nature, and a prospective study on similar lines may prove very useful in understanding the appropriate BID requirement. The study of other potential parameters such as waist circumference and the presence/absence of diabetic microvascular and macrovascular complications would have given us further insights into the factors affecting the BID requirement.

Conclusion

HbA1c at the time of admission is the most important parameter for determining the appropriate BID in hospitalized patients. Patients with HbA1c >8.0% have a higher mean basal insulin requirement than those with HBA1c <8.0. Patients with renal failure (GFR <60 ml/min/1.73 m^2) may require a higher dose of basal insulin than those not having renal failure. Age, gender, BMI, and timing of basal insulin have little impact on the BID.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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