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Comparison of efficacy, compliance and incidence of hypoglycemia between conventional basal bolus and Oral hypoglycemic (OHA) regimen with a basal plus oral hypoglycemic regimen

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ABSTRACT:

OBJECTIVE: *Compare efficacy, compliance and incidence of combined day time and nocturnal hypoglycemia of a conventional basal bolus regimen and Oral hypoglycemic only regimen with a basal plus oral hypoglycemic agents (OHA) regimen in patients with type 2 diabetes (T2D) who have been previously insulin naïve.* ***RESEARCH DESIGN AND METHODS:*** *This multicenter trial randomized 150 patients with T2D treated with a basal-bolus regimen with insulin degludec given once daily and aspart before meals, a basal plus regimen with a daily dose of degludec and OHA (either Metformin, sufonylurea plus voglibose or a Metformin, DPP4 Inhibitor with voglibose for BG >140 mg/dL, or combination of OHA. All patients were prescribed a 1600 kcal diabetic diet and were advised lifestyle modifications in addition to their medications. All patients were Insulin naïve at the start of the study and were matched for the baseline characteristics. They all had a starting HBA1c between 10-12.* ***RESULTS:*** *Improvement in mean daily blood glucose (BG) after the first day of therapy was similar between basal-bolus and basal plus OHA groups (P = 0.1), and both regimens resulted in a lower mean daily BG than did OHA alone (P<0.05). In addition, treatment with basal-bolus and basal plus OHA regimens resulted in less treatment failure (defined as >2 consecutive BG >240 mg/dL or a mean daily BG >240 mg/dL) than did treatment with OHA alone (P < 0.05) and thus higher compliance. A BG <70 mg/dL occurred in 15% of patients in the basal-bolus group, 8% in the basal plus OHA group, and 2% in the OHA only group (P<0.05). There was no difference among the groups in the frequency of severe hypoglycemia (<40 mg/dL; P = 0.5).* ***CONCLUSIONS:*** *The use of a basal plus regimen with degludec once daily plus OHA resulted in glycemic control similar to a standard basal-bolus regimen. The basal plus OHA approach is an effective alternative to the use of a basal-bolus regimen in general medical and surgical patients with T2D. Despite the benefits of a basal-bolus regimen in improving glycemic control in non-critically ill patients (1, 2), many health care providers and hospitalists are reluctant to integrate this approach into their clinical practice, probably because of its complexity and a fear of hypoglycemia (3-8).*

KEYWORDS:

Diabetes, OHA, DPP4 Inhibitor, sulfonylurea, degludec, metformin, hypoglycemia, insulin

RESEARCH DESIGN AND METHODS

In this multicenter, prospective, open-label, randomized study, we enrolled 150 adult patients who were on regular follow up at diabetes clinics. We recruited patients with a known history of T2D and with a BG before randomization between 140 and 400 mg/dL, a known history of T2D for >3 months, insulin naive patients with HBA1c between 10-12 and age between 18 and 80 years, and treatment with any combination of oral anti-diabetic agents with lifestyle modification advices.

BG was measured before meals and at bedtime with ACCU CHEK®. Patients were recruited when BG was >140 mg/dL.

We excluded patients with an admission, patients with any BG >400 mg/dL before randomization or with a

history of hyperglycemic crises, patients with hyperglycemia without a known history of diabetes, patients admitted to or expected to require ICU admission, patients undergoing cardiac surgery, patients receiving corticosteroid therapy, patients with clinically relevant hepatic disease or impaired renal function (serum creatinine ≥1.6 mg/dL), patients with a history of diabetic ketoacidosis (9), pregnant patients, and patients with any mental condition rendering them unable to give informed consent.

Patients were randomized according a 1:1:1 ratio to one of three regimens: a basal-bolus regimen with insulin degludec given once daily and aspart before meals, a basal plus regimen with a daily dose of degludec and OHA (Metformin, sufonylurea plus voglibose or a Metformin, DPP4 Inhibitor with voglibose for BG >140 mg/dL, or combination of OHA. (10-13)

Patients in the basal-bolus group were started at a total daily dose (TDD) of 0.5 units/kg divided with half as insulin degludec once daily and half as insulin aspart before meals. Patients in the basal plus OHA group received 0.25 units/kg of degludec plus either Metformin plus sulfonylurea plus voglibose or Metformin plus a DPP4 inhibitor plus voglibose. Dose of Insulin was titrated up or down every 4 days by based on Fasting and pre-meal glucose levels (10-13)

The goal of insulin therapy was to maintain fasting and premeal glucose concentrations between 100 and 140 mg/dL.

During treatment, treatment failure was arbitrarily defined as a mean daily BG level >240 mg/dL or two consecutive values >240 mg/dL (3,4).

This study was conducted at 3 centres in Kolkata. The study protocol and consent form were approved by the institutional review board at each participating institution. A computer-generated randomization table was followed to coordinate the randomization and treatment assignment.

Outcome measures

The primary outcome of the study was difference in glycemic control, as measured by mean daily BG concentration, among patients treated with basal-bolus, basal plus OHA, and OHA only regimens.

Secondary outcomes included differences between treatment groups in any of the following measures: number of hypoglycemic events (BG <70 and <40 mg/dL) after the first day of treatment and subsequently during the entire duration of study, number of episodes of hyperglycemia (BG >200 mg/dL)and compliance to a particular regimen.

Statistical analysis

The non-inferiority study design is based on the hypothesis that the difference in mean daily BG between basal plus OHA and basal-bolus and OHA only regimen should be no greater than 18 mg/dL (1 mmol/L) (3,4).

A BG difference of such a magnitude has been reported as clinically insignificant and is typically smaller than the significant treatment effects detected in other superiority trials (3,4).

Two-sample *t* tests or Wilcoxon tests (one-sided, $\alpha = 0.05$), was applied to a 80% power was ensured to reject the non-inferiority hypothesis, with Bonferroni correction applied to adjust for multiple comparisons.

A *P* value <0.05 was considered significant. Statistical analyses were performed with SAS statistical software, version 9.2. The data are generally presented as mean ± SD for continuous variables and *n* (%) for discrete variables.

RESULTS

A total of 150 patients with T2D consented and were included in the study. A total of 50 patients in the basal-bolus group, 50 patients in the basal plus OHA group, and 50 in the OHA only group were included in the final analysis.

There were no significant differences among groups in mean age, racial distribution, BMI, duration of

diabetes, type of treatment before admission, or mean hospital stay.

Clinical characteristics of study patients:

The mean admission glucose for the entire cohort was 190 ± 92 mg/dL, and the mean HbA_{1c} was 11.2 ± 1.4%.

All treatment regimens resulted in prompt and sustained improvement in mean daily BG concentration. Treatment with basal-bolus and basal plus OHA regimens resulted in similar improvements in daily BG after the first day of therapy and both regimens resulted in better glycemic control than did treatment with OHA ($P<0.05$).

The percentages of glucose readings within the target range between 70 and 140 mg/dL were higher in the basal plus OHA (45%) and basal-bolus (42%) regimens than in the OHA only treatment group (13%; $P = 0.04$), and the percentages of glucose readings >180 mg/dL were lower in the basal-bolus and basal plus OHA groups than in the OHA only group (21, 25, and 54%, respectively); which was statistically significant ($P < 0.05$). In addition, OHA resulted in higher number of treatment failures than did the basal plus OHA and basal-bolus regimens (7, 0, and 1%, respectively; $P < 0.05$).

In all cases, hypoglycemia was corrected with oral dextrose, and no episodes were associated with adverse outcomes.

CONCLUSIONS

This prospective, multicenter, randomized clinical trial compared the efficacy and safety of a daily dose of degludec plus OHA against a standard basal-bolus regimen and OHA only regimen in patients with T2D. We observed that treatment with basal plus OHA and basal-bolus regimens resulted in similar improvements in glycemic control, and both regimens resulted in better glycemic control and in a lower number of treatment failures than did OHA only treatment.

In this study, we report that the basal plus OHA approach resulted in a similar improvement in mean daily BG to the basal-bolus regimen, with no difference in the number of treatment failures and similar numbers of hypoglycemic events, and both regimens had better glycemic control and fewer treatment failures than did treatment with OHA only regimen.

In agreement with previous studies (3, 4, 14), we show that the use of basal insulin alone or as part of a basal-bolus regimen is well tolerated with a low rate of hypoglycemia.

In the RABBIT 2 medical trial, 3% of patients in the basal-bolus group had a BG <60 mg/dL and no patients had a value <40 mg/dL (3).

In the current study, a BG <60 mg/dL was seen in 9 and 4% of patients treated with basal-bolus or basal plus OHA regimens, and only 1% had a BG <40 mg/dL. As previously reported, treatment with OHA resulted in a significantly lower rate of hypoglycemia (3,4).

We acknowledge the following limitations in this study. We excluded patients with clinically relevant hepatic disease or with serum creatinine ≥1.6 mg/dL, patients with severe hyperglycemia, and those receiving insulin before admission.

For such patients, higher insulin doses or a standard basal-bolus approach may be the preferred approach in achieving glycemic control. (4).

Finally, in this study we observed a lower rate of BG within target range compared with previous randomized trials, in which we observed 45% of BG within goal in patients treated with a basal-bolus regimen (3, 4). In this trial, we followed a similar starting insulin dose and escalation protocol, increasing insulin dose by 10% if BG was between 140 and 180 mg/dL and by 20% if BG was >200 mg/dL. It is possible that increasing the starting insulin dose and increasing insulin titration will result in better glycemic control; however, it may also increase the risk of hypoglycemic events.

In summary, patients with T2D treated with diet, oral antidiabetic agents can be managed with a single daily dose of basal insulin with supplemental OHA. This basal plus OHA regimen resulted in improvements in glycemic control and frequency of hypoglycemic events similar to those seen with a standard basal-bolus insulin regimen, and both regimens resulted in better glycemic control and in fewer treatment failures than did the use of OHA alone. These results indicate that basal insulin is necessary for stable glucose control and that the basal plus OHA approach is an effective alternative to the basal-bolus regimen for the initial management of hyperglycemia in patients with T2D.

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