The Efficacy of Daily Compared to Twice Weekly Basal Insulin Titration Algorithms Among Patients with Type II Diabetes Mellitus: A 12-Week Randomized Controlled Trial

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Abstract

Introduction: There are a significant number of diabetic patients who remain uncontrolled despite basal insulin therapy due to lack of intensification of treatment. Different insulin titration algorithms are recommended by different treatment guidelines. This study compared two basal insulin titration algorithms in terms of time to achieve target glucose, adherence, hypoglycemia episodes, and HbA1c reduction.

Methods: This is a 12-week randomized clinical trial conducted on insulin-naïve patients with uncontrolled type 2 diabetes mellitus from outpatient clinic of St. Luke's Medical Center Quezon City. Patients on oral hypoglycemic agent/s with HbA1c seven percent and above were included in the study. They were randomized to either daily titration or twice-weekly insulin titration algorithms using basal insulin glargine.

Results: Forty-one patients were included in the study. The daily titration algorithm achieved target capillary blood glucose (CBG) at stable insulin dose earlier (33 vs 41.3 days, *p*-value=0.042) than the twice-weekly titration. Better adherence was also seen among patients on daily titration algorithm as compared to twice weekly (94.94% vs. 91.12%, *p*-value = 0.009). There was no significant difference in incidence of hypoglycemia (*p*-value 0.0.62) for both algorithms. All patients from the two groups had significant HbA1c reduction at the end of the study period.

Conclusion: Daily titration algorithm achieved earlier target fasting plasma glucose and better patient adherence as compared to twice-weekly titration in the adjustment of basal insulin dose. HbA1c reduction and risk of hypoglycemia were similar in both titration algorithms.

Keywords: basal insulin, insulin titration algorithm, type 2 diabetes mellitus

Introduction

Insulin glargine has been shown to be safely used in self-managed dose titration and is effective in achieving glycemic control in patients with longstanding type 2 diabetes mellitus (DM).[1,2] Several basal insulin titration algorithms (TA) are available and numerous clinical trials have been done throughout the years. However, international clinical practice guidelines, such as American Diabetes Association (ADA),[3] Canadian Diabetes Association (CDA)[4], and American Association of Clinical Endocrinologists (AACE)[5] differ in their recommended titration algorithms for insulin dosing.

Insulin therapy has been proven to be potent and most cost effective.[6] However, lack of dose titration could lead to suboptimal glycemic control. For patients on basal insulin who have not reached target glucose control (HbA1c >7%), only 16-24% of primary care physicians intensify their treatment (e.g., addition of OHA or increasing insulin dose) within one year.[8] In a study done by Ahmed et al, 42% had poor glucose control seen in HbA1c and FPG despite medical treatment.[9] These findings prove that lack of treatment intensification remains to be high and contributing factor in failure to achieve glycemic control. In a study done by Dailey et al.,[10] they compared three algorithms for initiation and titration of insulin glargine in patients with type 2 DM. It has shown that there were similar levels of glycemic control and lower rates of hypoglycemia for patients using simpler algorithms (one unit increase once daily or two units every three days, if FPG > target) as compared to treat-to-target algorithm (two to eight IU increase weekly based on two-day mean FPG levels). Patients can manage this algorithm themselves resulting in adequate control of HbA1c and low rates of hypoglycemia.[7] At present, the lack of uniformity in the guidelines and titration algorithms for insulin dosing exist, which can pose a great challenge in the management of diabetes.[7] There has been no direct comparison made between two algorithms in terms of time to achieve target glucose, compliance, hypoglycemia episodes, and HbA1c reduction.

The hypothesis of this study is that there is a significant difference in using the daily and twice weekly basal insulin titration algorithm in terms of efficacy in achieving adequate

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glucose control, safety, and adherence. Thus, it aimed to directly compare these titration algorithms (TAs) using the parameters such as compliance, safety, and time to reach target FBG and stable insulin dose among patients with type 2 DM seen at St. Luke's Medical Center Quezon City (SLMC-QC) outpatient clinics.

Methods

This was a 12-week randomized open-label clinical trial among patients with type 2 DM from SLMC-QC. Included in this study were adult type 2 DM patients 18 years old and above who are insulin naïve and on one or more oral hypoglycemic agents (OHA) with HbA1c 7% and above. Exclusion criteria include pregnancy, estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2, anemia (hemoglobin for male male <13 g/dL and female <12 g/dL), severe hepatic impairment (Childs Pugh B & C), BMI >40 kg/m^2, use of systemic glucocorticoids, patients with active malignancy, and those were on other insulin aside from insulin glargine.

The participants were recruited from SLMC-QC outpatient clinics. The study investigator screened the participants upon referral from attending physicians. Informed consents were obtained. Participants were randomized using web-based generated random numbers to either daily or twice weekly titration algorithms. They were allowed to continue their oral hypoglycemic agent/s and other maintenance medications during the study period. Upon their first visit, they were instructed regarding diet modification using the Pinggang Pinoy method, based on the plate method.

Participants were asked to monitor their capillary blood glucose (CBG) 30 minutes to one hour prior to eating breakfast daily. Insulin glargine was administered immediately after pre-breakfast CBG has been obtained so that patient would be able to adjust insulin dose immediately. If with hypoglycemia episode, they were instructed to consume ½ cup of juice, one tablespoon of sugar/honey or hard candies/jelly beans and check their CBG after 15 minutes. If hypoglycemia persisted, they would repeat the same measures until CBG reaches 100 mg/dl.

Algorithm 1 was the daily insulin dose titration wherein the participants would adjust the dose of glargine everyday by adding one unit to current dose until pre-breakfast CBG is less than 130 mg/dL. If patient would develop hypoglycemia (FBG <80 mg/dL), insulin dose would be decreased by four units.

Algorithm 2 was the twice-weekly insulin dose titration wherein the participants would adjust dose of glargine every three days based on the average CBG for the past three consecutive pre-breakfast CBGs prior to last dose titration. The dose adjustment would be as follows: if average CBG 130-179 mg/dL, they would add two units to current dose; if 180mg/dL and above, they would add four units to current dose. If with hypoglycemia, dose would be decreased by four units.

There was a one-week run-in period where they were asked to monitor their daily fasting CBG with the starting dose of 10 units/day. However, no dose titration was done during this time. On the second week, they were assigned to either of the two titration algorithms as described above. The patient was then be instructed on how to use the titration algorithm and provided with printed copy to which he/she was assigned. They were provided with a glucometer and a logbook of blood glucose level. Study investigator reviewed the CBG level and adherence to the titration algorithm every visit. They were asked to follow-up with their record of daily fasting CBG on the first, second, fourth, eighth, and 12th week of the study for monitoring. Upon completion of the study, HbA1c level was determined.

Sample size of 48 participants was determined at 95% confidence interval, with an alpha of 0.05, 95% power, and 20% attrition rate. This was based on the LANMET study wherein stable dose of insulin was at 68 units/day while in INSIGHT study was 38 units/day. Assuming that the patients were started at 10 units at the beginning of the study, it took a maximum of 40 days (standard deviation 1.03) and 28 days (standard deviation 0.67), respectively, for both studies to achieve the stable dose.

Stable dose is defined as dose of basal insulin at which target pre-breakfast CBG of 80-130 mg/dl is maintained for at least for five consecutive days. Time to reach target FBG with stable insulin dose is defined as the number of days from the time of initiation period until the target pre-breakfast CBG of 80-130 mg/dL for at least five consecutive days is achieved. Target FBG is defined as CBG 80-130 mg/dL during prebreakfast state. Adherence to titration algorithm is defined as the number of days with adherence to the algorithm divided by total number of day of adjustment in a week (for example, subject was able to adjust 81 out of the 84 days is 96.4%). Hypoglycemia is defined as FBG <70 mg/dl with or without symptoms of hypoglycemia. Non-adherence to algorithm defined as either: 1) failure to adjust insulin dose, 2) wrong titration, 3) failure to administer insulin, and/or 4) failure to check pre-breakfast CBG. Average pre-breakfast CBG defined as average CBG level for the three consecutive days taken prior to breakfast.

The data were encoded in Microsoft Excel and data analysis done using SPSS version 20. The study used a two-tailed independent t-test to compare the time to achieve target glucose, number of hypoglycemia events, adherence, and percent reduction of HbA1c from baseline between groups. Chi-square test was used for comparison

Table I. Baseline demographics (n = 24)

	Daily Titration Algorithm n (%)	Twice-weekly Titration Algorithm n (%)	*p*-value
Female	15 (62.5)	19 (79.2)	0.20*
Age (mean +/- SD in years)	58.33 (39-80 y/o) (SD = 11.04)	56.38 (38-86 y/o) (SD = 12.62)	0.57*
BMI (kg/m^2)	27.22 (SD = 3.94)	26.32 (SD = 4.24)	0.45
Waist circumference (cm)	83.48 (60-104 cm) (SD = 13.24)	83.02 (66-108.5 cm) (SD = 10.89)	0.896
HbA1c	9.17 (SD = 1.24)	9.34 (SD = 1.29)	
Hypertension	17 (70.83)	16 (66.67)	0.580**
Sulfonylurea	5 (20.8)	9 (37.5)	0.2
DPP4 inhibitors	18 (75)	13 (54.2)	0.13
SGLT2 inhibitors	2 (8.3)	1 (0.42)	0.55
Metformin	18 (75)	17 (70.8)	0.75
Thiazolidinedione	0 (0)	3 (12.5)	0.07
Duration of diabetes (years)	11.08 (SD = 8.27)	9.21 (SD = 7.48)	0.414*
eGFR (ml/min/1.73 m^2)	69.80 (SD = 24.4)	74.28 (SD = 27.56)	0.55

*Statistical test - *t-test; **chi-square test*

of comorbidities, sex, obese/overweight and medications. Paired t-test was used for difference in the pre and post treatment HbA1c for each of the algorithm. For the posthoc analysis, two-tailed independent t-test was used to compare stable insulin dose and insulin dose at the end of the study between the two groups. Lastly, the level of significance was set at alpha level 0.05.

The subjects proceeded with the study once they have reviewed and gave their written consent. The primary investigator obtained informed consent on the day the patient agreed to participate in the study at the doctor's clinic. The risk of hypoglycemia with the use of insulin was discussed with the subjects at the beginning of the study. The investigator reviewed this on every clinical visit.

The clinical protocol and all relevant documents were reviewed and approved last July 27, 2017 (CT-17064) by the SLMC Institutional Ethics Review Committee, which follows the guidelines of Declaration of Helsinki. Securing their records in a private room ensured anonymity of patient records and patient number was used as identifier. All study data were recorded and investigators were responsible for the integrity of the data i.e. accuracy, completeness, legibility, etc. The data collected will be kept for one year at the section's research library securely locked in a metal cabinet. Afterwards, hard copy of data will be disposed using paper shredder and the study investigator would store the encrypted soft copy of the data.

Results

There were 48 subjects recruited into the study wherein 24 subjects were randomized on each treatment arm. Forty-one subjects were included in the study for the analysis of data. Four patients (8.3%) were lost to follow-up, two withdrew their consent (4.17%), and one patient (2.08%) became pregnant. The baseline demographics of the subjects were similar between the two groups as shown in Table I.

The result of the primary and secondary outcomes was shown on Table II. The mean number of days for CBG to stabilize for the daily and twice-weekly titration groups was 33 days (SD=15.08) and 41.53 (SD=9.9) (*p*-value=0.042) days, respectively. There was better adherence on daily titration algorithm as compared to the twice-weekly titration algorithm (94.94% vs. 91.12%, *p*-value=0.009). The overall incidence of hypoglycemia between the two groups was similar (0.46% vs. 1.2%, *p*-value=0.062). There was also similar HbA1c reduction from pre treatment (*p*-value=<0.001) to post treatment (*p*-value=0.001) of about 2.5% after three months of insulin therapy. Post hoc analysis of insulin dose required to achieve stable target CBG were likewise similar between the two groups. (20.41 vs. 25.05 units, *p*-value=0.052). sFurthermore, there was no significant difference on insulin doses at the end of the study (21.14 vs. 25.32 units, *p*-value=0.14) between the two groups.(Table III)

Discussion

In this study, we compared the daily titration versus twice-weekly titration algorithm using basal insulin glargine in terms of time to achieve target glucose, adherence, hypoglycemia episodes, and HbA1c reduction. Between the two titration algorithms, daily insulin titration has shown superiority in terms of adherence and achieving earlier target FBG. The daily titration algorithm was simpler to follow as compared to twice-weekly titration wherein the patient had to compute for the average FBG. The findings were consistent with Daily et al., which showed similar HbA1c reduction for

Table II. Primary and secondary outcomes

Outcomes	Daily titration algorithm (n = 22)	Twice-weekly titration algorithm (n = 19)	*p*-value*
Primary Outcome, mean (SD)			
Time to reach target FBG at stable dose (days)	33 (SD = 15.08)	41.53 (SD = 9.89)	0.04
Secondary Outcomes, mean (SD)			
Adherence	94.94 (SD = 5.09)	91.92 (SD = 7.01)	0.009
Hypoglycemia episodes	0.46 (SD = 0.87)	1.2 (SD = 1.43)	0.62
HbA1c reduction	2.45 (SD = 1.26)	2.57 (SD = 1.23)	0.76

*Statistical test - *t-test*

Table III. Comparison of stable insulin dose and insulin dose at end of study between daily and twice weekly titration algorithm

Outcome	Daily titration algorithm (n = 22)	Twice-weekly titration algorithm (n = 19)	*p*-value*
Stable insulin dose, mean (SD)	20.41 (SD = 9.2)	25.05 (SD = 9.74)	0.13
Insulin dose at the end of study, mean (SD)	21.14 (SD = 8.3)	25.32 (SD = 9.37)	0.14
Post treatment HbA1c 7% and below (%)	14 (63.6%)	10 (52.6%)	0.48

*Statistical test - *t-test*

both titration algorithms. However, there was no difference in the rates of hypoglycemia between the two groups.

Despite several concerns with the use of insulin, adding it in the treatment has been proven to have better control of HbA1c level as compared to conventional therapy with oral agents alone.[11] There are numerous factors that affect glucose control such as compliance and availability of medications, financial status, lifestyle, and diet of the patient. In addition, failure of healthcare providers to intensify timely treatment contributes to suboptimal glycemic control. The failure of healthcare providers to initiate or intensify treatment when indicated can be defined as `clinical inertia.' It may contribute to the longstanding inadequate glycemic control of patients, which has a significant consequence in terms of quality of life, morbidity and mortality and huge costs associated with complications of diabetes.[12] Clinical inertia may arise at any stage of treatment algorithm and has been most commonly seen in initiating injectable therapies. Among patients with type 2 DM, a large number is still not achieving glucose target despite being on basal insulin leading to higher risk of developing complications that would greatly affect their quality of life. The lack of knowledge as to the appropriate approach in the management could contribute to the untimely intensification of insulin therapy. Different titration algorithms are available based on different clinical studies but no consensus guidelines on one particular algorithm. Effective and easy to follow insulin TAs could bridge the gap between non-adherence and achieving glycemic control through patient-centered model of care.[12]

Thus, this study supports the use of daily titration for patients with type 2 DM uncontrolled on oral hypoglycemic agents to be started on basal insulin. Simple patient-led titration algorithms will allow patients to timely and confidently adjust insulin dose and would require fewer clinic visits. It will allow them to be comfortable with their insulin regimen and have a sense of control in the management of their diabetes. Most importantly, it will lower down the barriers in initiation of insulin and provide better adherence compared with more complex algorithms.

Conclusion

This study has shown that superiority of daily titration algorithm versus twice weekly in terms of adherence and earlier achievement of FBG among patients with type 2 DM. Both algorithms showed significant HbA1c reduction and low risk of hypoglycemia.

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