Effect of Initiation of Basal Insulin Glargine on Glycemic Control in Patients with Diabetes: Real Life Experience from Hong Kong

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Abstract

Introduction: To assess the changes in glycemic control after initiating or switching to a basal insulin analogue in patients with diabetes mellitus. Methods: A retrospective, observational analysis was conducted using electronic data from a Hong Kong regional hospital. Data from adult patients with type 1 and 2 diabetes mellitus (T1DM and T2DM, respectively) who had been prescribed with basal insulin glargine in 2008-2010, with recorded HbA1c levels at the time of initiation, at 6 and 12 months thereafter, were analysed. Results: Data from 106 eligible patients were analysed. Substantial reduction in HbA1c and fasting sugar levels were reported in both T1DM (∆ HbA1c = 1.5%, ∆ FBG = 1.3 mmol/L p < 0.05) and T2DM (∆ HbA1c = 1.2%, ∆ FBG = 2.9 mmol/L p < 0.05) patients after 12 months of therapy. A total of 42% of T1DM and 26% of T2DM patients achieved HbA1c levels < 7.0%. After adjustment, T2DM patients who were insulin naive achieved a statistically greater HbA1c reduction (∆ = 1.7%) than those who previous treated with premixed or basal bolus insulin (∆ = 0.3%) (p < 0.05). Percentage of patients experiencing hypoglycaemia reduced from 69% to 62% in T1DM but increased from 26% to 36% in T2DM patients. All hypoglycaemic episodes recorded were either asymptomatic or mild and self-limiting. Only 4% of the patients discontinued treatment at the end of 12 months. Conclusions: In real life clinical practice, a single daily basal insulin analogue therapy provided effective glycemic control with an acceptable risk of mild hypoglycaemia.

Keywords

Glycemic Control, Insulin Initiation, Insulin Glargine, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Hong Kong
1. Introduction

With an estimation of 60% of the world’s diabetic population living in Asia [1], diabetes has a significant impact not only on mortality [2], but also on morbidity [2], treatment cost [3] and quality of life [4] in this region. Since the first reports on the epidemiology of diabetes were published in Hong Kong in the early 1990s [5], the prevalence of diabetes mellitus has been increasing steadily from 4.5% in 1990 to 10% recently [6]. Currently, it is estimated that 10% - 12% of the adult population in Hong Kong are suffering from type 2 diabetes mellitus (T2DM) [7] and the age of onset in type 1 diabetes mellitus (T1DM) is getting lower [8].

The main focus of antidiabetic therapy is to achieve and maintain glycemic control in order to slow disease progression and prevent diabetic complications together with no or minimal hypoglycaemia [9] [10]. Insulin therapy may be initiated as a supplement or as a replacement in patients with uncontrolled diabetes [11]. For most of the patients, starting with once daily intermediate- or long-acting basal insulin is a readily acceptable and practical method. The goal of basal insulin is to suppress hepatic glucose production and improve fasting hyperglycaemia [12]. Clinical trials have showed that the use of the long acting insulin analogues enables diabetic patients to reach glycemic targets with a low risk of hypoglycaemia [13].

Insulin glargine (Lantus®) is the a long-acting basal insulin that is indicated for the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above. It was shown to be as effective as other commonly used basal insulins—Neutral Protamine Hagedorn (NPH) insulin [14] and Detemir [15]. Despite the plethora of evidence from various randomised clinical trials confirming the benefits of basal insulin analogue therapy in the management of diabetes, the extent to which these results translates in real life clinical practice is unclear [16] [17]. Several observational studies have attempted to address this issue but those studies were conducted in the Caucasian population [18] [19]. In this retrospective analysis, we aim to assess the effects of initiating a basal insulin analogue on glycemic control in type 1 and 2 diabetes patients in a local clinical setting in Hong Kong. Specifically, we intend to determine the effect of such therapy on HbA1c control and other therapeutic and safety parameters—FBG, weight gain, insulin dosage and hypoglycaemia.

2. Materials and Methods

2.1. Study Design

This was a retrospective case series review.

2.2. Eligibility Criteria and Data Evaluation

Patients with T1DM or T2DM, aged ≥21 years, who had been prescribed basal insulin glargine, either as a supplementary insulin or as a part of basal-plus regimen, in Jan 2008-Dec 2010 at Tseung Kwan O Hospital (a regional hospital in Hong Kong) were included. Their baseline HbA1c and other pertinent data
(FBG, weight, insulin dose and incidence of hypoglycaemia) at the time of initiation of insulin glargine and at 6 and 12 months thereafter, were collected through electronic health records system.

The principal analysis was to evaluate the change in HbA1c over a 6 and 12-month period after glargine initiation. Secondary analysis included change in fasting blood glucose (FBG), body weight (kg), incidence of hypoglycaemia, and daily insulin dose (IU) at 6 and 12-month. Information on associated comorbidities including hypertension, coronary artery disease, myocardial infarction, PCI/CABG, heart failure, stroke, peripheral vascular disease, limb amputation, dyslipidaemia, dialysis/transplant, and obesity was also extracted.

The point-of-care testing reading less than 4 mmol/l with compatible symptom(s) was considered to have hypoglycemia. Those episodes requiring third party assistance were defined as severe hypoglycemia. The frequency and severity of hypoglycemic episodes were expeditely reviewed in the electronic health records.

2.3. Patient Disposition

A total of 120 adult patients had been prescribed with insulin glargine in 2008-2010. Of these, 106 patients had complete data at baseline and follow up visits after glargine treatment were included for analysis. Their insulin glargine therapies were initiated in the period of January 2002 to February 2010. Patient’s electronic health records from January 2002 to March 2011 were subsequently reviewed.

2.4. Statistical Analysis

All data recorded were analysed in an explorative manner. Missing HbA1c data was imputed when patients had at least baseline and 6 months measurements during the 12 month period. The mean change during the 12 months following the switch was calculated. Continuous variables were presented as frequency, mean, median and standard deviation while categorical variables were described by the frequencies of each modality. The change in HbA1c and FBG from baseline to 6 months and from baseline to 12 months was estimated and adjusted by repeated measure ANOVA (analysis of variance). Linear mixed effect model was applied to assess whether there is any fixed effects of 1) disease duration, and 2) prior regimen on the change in HbA1c level. The data was adjusted for repeated measure per patient over time with change in HbA1C relative to time of insulin initiation as the dependent variable. The fixed effects for assessment of disease duration are baseline HbA1C value, disease duration, the time since insulin initiation as a categorical variable, and the interaction between disease duration and the time since insulin initiation. The fixed effects for assessment of prior regimen type are baseline HbA1C value, prior regimen type, the time since insulin initiation as a categorical variable, and the interaction between prior regimen type and the time since insulin initiation. All statistical analyses were performed at 5% significance using 2-sided tests or confidence intervals. Statistical analysis
was performed using the SPSS software version 14 (IBM, New York, USA).

3. Results

3.1. Baseline Characteristics

About three-quarters of the patients (75.5%, n = 80) had T2DM, while one-quarter of the patients (24.5%, n = 26) had T1DM. The mean age of the patients with T1DM was 36.5 years and that of T2DM patients was 61.1 years. Mean HbA1c at baseline before switching was similar in each group (9.1% and 9.0% respectively). Mean duration of diabetes in patients at the time of recording was 14.6 years for T1DM and 16.7 years for T2DM. Patients with T2DM had a greater number of comorbidities than those with T1DM patients (2.2 versus 0.9). Nearly 80% of patients have hypertension and dyslipidaemia while 15% of the patients have coronary artery disease. 95% of T2DM patients were already put on oral antidiabetic (OAD) agents with 90.0%, 83.8%, 20.0% and 18.8% on metformin, sulfonylurea, glitazone, DPP4 inhibitors respectively. The proportion of patients reporting prior hypoglycaemia was higher in T1DM (69.2%) than in T2DM patients (26.3%) (Table 1).

In T1DM patients, the primary reason of switching to glargine was to reduce the incidence of hypoglycaemia (reported in 50% of the patients) while, in T2DM patients, the main reason was to improve glycemic level (reported in 81% of the patients) (Table 1).

3.2. Glycaemic Control

After 12 months on insulin glargine, the mean HbA1c levels dropped significantly by 1.5% (from 9.1% ± 2.3% to 7.6% ± 1.3%, p < 0.05) in T1DM patients and by 1.2% (from 9.0% ± 1.5% to 7.8% ± 1.4%, p < 0.05) in T2DM patients (Figure 1). When mean baseline HbA1c level (≥7.0% - 7.9%, ≥8.0% - 8.9%, ≥9.0% - 9.9% and ≥10.0%) was listed against the improvement in HbA1c after switching, patients with HbA1c ≥10.0% had a greater numerical reduction in mean HbA1c (Δ for T1DM = 3.8%; Δ for T2DM = 2.3%) while patients with HbA1c < 8.0% had a smaller improvement (Δ for T1DM = 0.3%; Δ for T2DM = 0.3%) [Not shown].

In addition, T2DM who had a short disease duration (< 5 years of diabetes) had a greater reduction in HbA1c numerically ((Δ = 1.8%, p < 0.05) than those with long disease duration (6 - 10 years: Δ = 1.2%, p < 0.05 and > 10 years: Δ = 1.0%, p < 0.05) (Figure 2). The change in HbA1c between the subgroups of different disease duration, however, did not reach statistical significance (p > 0.05).

On the other hand, T2DM patients who were insulin naïve achieved a statistically greater HbA1c reduction (Δ = 1.7%) than those who previously used basal bolus or premixed basal insulin (Δ = 0.3%) at 12 months after the switch (Figure 3). The proportion of patients achieving HbA1c < 7.0% after 12 months of initiating glargine was 42% (n = 11) in T1DM and 26% (n = 21) in T2DM [Not shown].
Table 1. Baseline characteristics of enrolled diabetic patients.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>T1DM¹</th>
<th>T2DM²</th>
</tr>
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<tbody>
<tr>
<td>N = 26</td>
<td>N = 80</td>
<td></td>
</tr>
<tr>
<td>Males, N (%)</td>
<td>11 (42.3)</td>
<td>37 (46.3)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>36.5 (13.3)</td>
<td>61.1 (10.9)</td>
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<tr>
<td>Weight (kg), mean (SD)</td>
<td>61.8 (15.9)</td>
<td>63.3 (16.7)</td>
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<tr>
<td>Hb1Ac (%), mean (SD)</td>
<td>9.1 (2.3)</td>
<td>9.0 (1.5)</td>
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<tr>
<td>Duration of diabetes (years), mean (SD)</td>
<td>14.6 (9.3)</td>
<td>16.7 (7.8)</td>
</tr>
<tr>
<td>Number of comorbidities, mean (SD)</td>
<td>0.9 (1.0)</td>
<td>2.2 (1.3)</td>
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<table>
<thead>
<tr>
<th>N(%)</th>
<th></th>
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<tbody>
<tr>
<td>Hypertension</td>
<td>8 (30.8)</td>
<td>63 (78.8)</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>2 (7.7)</td>
<td>12 (15.0)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1 (3.8)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>0 (0.0)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (3.8)</td>
<td>6 (7.5)</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>0 (0.0)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>12 (46.2)</td>
<td>65 (81.3)</td>
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<tr>
<td>Renal Impairment</td>
<td>0 (0.0)</td>
<td>11 (13.8)</td>
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<tr>
<td>PCI/CABG</td>
<td>0 (0.0)</td>
<td>9 (11.3)</td>
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<tr>
<td>Limp amputation</td>
<td>0 (0.0)</td>
<td>1 (1.3)</td>
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<tr>
<td>Dialysis/transplant,</td>
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<td>1 (1.3)</td>
</tr>
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<table>
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<tr>
<th>OAD's prescribed prior to commencing insulin, mean (SD)</th>
<th>0.1 (0.4)</th>
<th>2.2 (0.9)</th>
</tr>
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<tbody>
<tr>
<td>Patients reporting prior hypoglycaemia, N (%)</td>
<td>18 (69.2)</td>
<td>21 (26.3)</td>
</tr>
<tr>
<td>N = 26</td>
<td>N = 80</td>
<td></td>
</tr>
<tr>
<td>Insulin naïve</td>
<td>5 (19.2)</td>
<td>48 (60.0)</td>
</tr>
<tr>
<td>OAD</td>
<td>2 (7.7)</td>
<td>76 (95.0)</td>
</tr>
<tr>
<td>NPH¹</td>
<td>3 (11.5)</td>
<td>17 (21.3)</td>
</tr>
<tr>
<td>Basal bolus</td>
<td>16 (61.5)</td>
<td>7 (8.8)</td>
</tr>
<tr>
<td>Premixed</td>
<td>3 (11.5)</td>
<td>8 (10.0)</td>
</tr>
<tr>
<td>Reasons to switch to glargine, N(%)</td>
<td>N = 26</td>
<td>N = 80</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>13 (50.0)</td>
<td>14 (17.5)</td>
</tr>
<tr>
<td>Uncontrolled HbA1c²</td>
<td>12 (46.2)</td>
<td>65 (81.3)</td>
</tr>
<tr>
<td>Convenience</td>
<td>1 (3.8)</td>
<td>0 (-)</td>
</tr>
<tr>
<td>Others</td>
<td>0 (-)</td>
<td>1 (0.0)</td>
</tr>
</tbody>
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¹Type 1 diabetes mellitus. ²Type 2 diabetes mellitus. ³Oral antidiabetic. ⁴Neutral Protamine Hagedorn. ⁵Glycosylated haemoglobin.

3.3. Overall Change in FBG

Within 12 months of initiation with insulin glargine, the mean FBG dropped from 11.1 ± 4.2 mmol/L at baseline to 9.7 ± 4.9 mmol/L in T1DM patients [Not shown]. In T2DM patients, the mean FBG reduced from 10.1 ± 3.3 mmol/L to 7.2 ± 3.3 mmol/L. The reduction in FBG was statistically significant in T2DM patients (p < 0.05) but not in T1DM patients.
3.4. Insulin Dose and Body Weight Change

The total daily dose of insulin glargine remained the same at 18.8 IU in T1DM patients (0.33 IU/kg at 6 months and 12 months) but increased slightly from 19.2 IU at 6 months to 20.3 IU at 12 months in T2DM (0.30 IU/kg and 0.32 IU/kg at 6 months and 12 months respectively).

There was no significant change in weight in T1DM (mean body weight of 61.8 ± 15.9 kg at baseline and 61.8 ± 10.8 kg after 12 months of treatment with insulin glargine). In T2DM patients, mean body weight increased slightly from
**Figure 3.** Reduction in HbA1c in insulin naive T2DM patients and previous T2DM Insulin users. Abbreviations: BB-Basal Bolus Regimen.

64.9 ± 13.4 kg to 66.7 ± 10.8 kg but this increase was not statistically significant.

### 3.5. Hypoglycaemia and Discontinuation

At baseline, 69% of T1DM and 26% of T2DM experienced hypoglycaemia. After 12 months of using insulin glargine, the percentage of T1DM patients who experienced hypoglycaemia deceased to 62% while the percentage of T2DM patients who experienced hypoglycaemia increased to 36% ([Figure 4](#)). The increase in rate of hypoglycaemia in T2DM was observed mainly in insulin naive patients. In fact, there was a decrease in hypoglycaemia in patients who had used once daily NPH or premixed/basal-bolus insulin at baseline. The percentage of T2DM patients who had used once daily NPH previously and experienced hypoglycaemia dropped from 47% at baseline to 0% over the 12 months following the switch while the percentage of patients who used premixed/basal bolus regimen previously and experienced hypoglycaemia dropped from 60% to 0% during the same time interval ([Figure 5](#)). All recorded episodes of hypoglycaemia were either asymptomatic or mild and self-limiting.

There were only four percent of patients (n = 3) having discontinued the insulin therapy within 12 months following its commencement.

### 4. Discussion

Insulin therapy is the mainstay of T1DM treatment and may be the ultimate therapy for a group of T2DM patients [11]. This retrospective, observational study showed that T1DM and T2DM patients who have been switched to glargine experienced a HbA1c reduction of 1.5% and 1.2% respectively within 12 months after the switch. The improvement was achieved without a significant increase in body weight or severe hypoglycaemia. These findings are in agreement with data from other observational studies in which patients were switched
Figure 4. Percentage of patients experiencing hypoglycemic episodes on insulin glargine at baseline, 6 months and one year.

Figure 4. Percentage of patients experiencing hypoglycemic episodes on insulin glargine at baseline, 6 months and one year.

to a glargine based regimen [16]-[21]. Our analysis demonstrated a relationship between baseline HbA1c values and the improvement in HbA1c levels. Patients with baseline HbA1c > 8% showed a reduction of 1.5%, while those with HbA1c > 10% experienced a greater reduction of 2.8%, suggesting even a single daily insulin injection could be effective when glycaemic control was exceptionally poor.

The optimal time for initiating insulin in T2DM patients, whether early or late till OAD failure, is still controversial but there are studies linking delayed insulin treatment with disease progression [22]. In real life clinical practice, however,
Figure 5. Percentage of patients experiencing hypoglycemic episodes on insulin glargine at baseline, 6 months and one year (by Type of Prior Therapy). Abbreviations: T1DM-type 1 diabetes mellitus, T2DM-type 2 diabetes mellitus, NPH-neutral protamine Hagedorn.

timely initiation of insulin was often hampered by concerns about weight gain, hypoglycaemia, and patient’s fear of injections [23] [24]. In our study, 60% of T2DM patients (mean HbA1c: 9.0%; mean duration of diabetes: 16.7 years) were insulin-naïve at baseline despite a prolonged disease duration. Our results demonstrated that T2DM patients with early disease (<5 years of diabetes) at the time of initiation of glargine had a numerically greater improvement in HbA1c levels when compared to those with late stage disease (>10 years of diabetes). Also, T2DM patients who were insulin naïve achieved a statistically greater HbA1c reduction (Δ = 1.7%) than those who previously used basal bolus or premixed basal insulin (Δ = 0.3%) at 12 months after the switch. Latest international consensus and clinical guidelines are shifting towards prompt insulinisation in order to achieve glycaemic control as early as possible [25] and our findings confirmed the benefits of this shift in a routine clinical practice.

Despite the improvement in HbA1c in our study, our analysis revealed less than half of T1DM and one-third of T2DM reached the HbA1c goal of less than 7% within 12 months of glargine initiation. In comparison, the findings from the large-scale, multination International Diabetes Management Practice Survey showed a HbA1c target achievement of 25% in T1DM patients and 35% in T2DM patients [26] [27]. However, other studies assessing glycaemic control following basal insulin glargine in T2DM have reported higher rates of HbA1c target achievement [14] [28] [29]. One explanation for this subpar target achievement in our patients could be suboptimal insulin dosing. The FBG for T1DM patients after 12 months of glargine initiation was still at 9.7 mmol/L and the average glargine dose was only 0.34 IU/kg, which means further up-titration could be done to optimise the FBG level. We, however, could not ascertain the reason behind the suboptimal dosing and can only speculate that care delivery limitation and fear of hypoglycaemia are contributing factors. Another possibility was the financial burden, as all the patients in this study paid for this insulin
out of pocket as it was then not provided in the public health care setting where the study was conducted.

A major concern with regards to the use of insulin is the fear of hypoglycaemia. One of the advantages of insulin glargine over NPH is the reduced risk of hypoglycaemia in insulin-naïve patients as well as in patients who have previously treated with other insulins [20]. In our study, the primary reason for glargine initiation in T2DM patients was to improve glycaemic control while in T1DM patients; it was used to reduce the incidence of hypoglycaemia associated with previously used insulins. In the 12 months after initiation of or switch to insulin glargine, there was a notable decrease in the proportion of T1DM patients experiencing hypoglycaemia (from 69% to 62%). On the other hand, the proportion of patients with type 2 diabetes who experienced hypoglycaemia increased to 36%. Nonetheless, all the T2DM patients who experienced an increase in hypoglycaemia were patients who have not used insulin before (i.e. insulin naïve patients) and basal insulin was known to increase the risk of hypoglycaemia [11]. For the other T2DM patients who were switched from other insulin formulations, there was a reduction in the proportion of patients who experienced hypoglycaemia after switching to glargine. This improvement in hypoglycaemia among patients who switched to a long acting basal insulin analogue from other insulin regimens (such as NPH or premixed/basal-bolus) has also been reported in other studies [14] [15] [30]. Most importantly, all hypoglycaemic episodes reported in our study were either asymptomatic or mild and self-limiting.

The success of insulinization in attaining glycaemic control depends on adherence to the prescribed regimen [25]. Adherence to insulin therapy was reported to be inadequate [30] [31] and numerous factors related to patient and physician perceptions were thought to be responsible for treatment compliance [28]. In our study, a discontinuation rate was of only four percent at the end of 12 months following the initiation of insulin glargine. It indicated that once daily insulin injection is acceptable for most of all diabetic patients [32].

This is the first retrospective analysis on the real-life data of long acting insulin analogue in patients with diabetes in Hong Kong. However the analysis was associated with certain shortcomings. First, this retrospective observational study did not provide the same robust level of evidence as randomised controlled trials. Second, it was not designed to allow collection of all hypoglycaemic episodes. As a result, our hypoglycaemia rate might have been under-reported. Also, there were 3 cases where the 12 month HbA1c levels were missing. Extrapolation on that last data points were required. Since it involved only a minority of patients (<2.8%), it would not affect the overall results of this study. Third, the decision to switch insulin treatment was not based on a standard treatment algorithm but instead on the clinical judgement of individual clinicians, thereby introducing bias in the selection of patients. Fourth, the analysis depended on the electronic medical records from a hospital, which did not record patient healthcare utilization outside the data capturing system.
Despite these shortcomings, observational studies such as the current one are generally regarded as a better approach to assess the actual health outcomes of patients in routine care, more than randomised controlled trials [19] [20]. In our study, the decision to initiate long acting basal insulin analogue was based on the clinical judgment of the managing physicians and the results shed light on the effects of this kind of insulin preparations in the real life situation.

5. Conclusion

In conclusion, this observational study showed that, in T1DM and T2DM patients who have been treated with OADs or with other insulins with suboptimal efficacy or poor tolerability, long acting basal insulin analogue was effective in improving glycemic control with a reduced risk of hypoglycaemia in T1DM patients and T2DM patients switched from other insulins.

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