Comparing the Glycaemic and Weight Control Effects of Basal-bolus and Premixed Insulin Regimen among Patients with Type 2 Diabetes Mellitus in Johor

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Abstract

Introduction: In Malaysia, conventional or human insulins are more commonly used than insulin analogues but studies comparing basal-bolus insulin regimen and premixed insulin regimen using conventional insulins are very limited.
Objective: To compare the glycaemic and weight control effects of conventional basal-bolus and conventional premixed insulin regimens in patients with type 2 diabetes mellitus (T2DM) in Kluang District, Johor, Malaysia.
Methods: A retrospective observational study was conducted on 122 T2DM adult patients in government primary health clinics in Kluang, Johor who received conventional insulin therapy. Patients were on either basal bolus or premixed insulin regimens. Changes in HbA1c, fasting blood sugar and body weight from baseline to the endpoint of study were recorded.
Results: No significant differences ($p > 0.05$) in HbA1c, pre-breakfast and pre-bed fasting blood sugar and body weight changes were observed between patients with conventional basal-bolus insulin regimen and conventional pre-mixed insulin regimen. Basal-bolus insulin regimen significantly reduced pre-lunch and pre-dinner FBS compared to premixed insulin regimen.
Conclusion: Basal-bolus conventional insulin regimen provides better control of pre-lunch and pre-dinner FBS. However, the decision of insulin regimens shall be based on clinical judgement of the healthcare providers and preference or compliance of the patients.

Keywords: type 2 diabetes mellitus, conventional insulin, premixed insulin, basal-bolus insulin, fasting blood sugar, HbA1c, weight control

NMRR ID: NMRR-16-1307-31592

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Introduction

The main aim of diabetes mellitus treatment is to prevent complications by controlling blood glucose levels[1]. Findings from United Kingdom Prospective Diabetes Study (UKPDS) revealed that the Type 2 Diabetes mellitus (T2DM) patients usually lose half of their β-cell functions at the point of diagnosis, with a further annual decline of 5%[2]. The progressive β-cell destruction along with the course of the disease justifies the possible development of both basal and prandial insulin deficiency in T2DM patients[3]. Thus, insulin treatment, as one of the available options for such insulin deficiencies condition, can help to reduce blood glucose levels effectively and hence, improving glycaemic control[1]. Many patients of type I and type 2 diabetes mellitus would require insulin therapy to manage hyperglycaemia, particularly when insulin deficiency develops[3]. However, there is no consensus regarding the optimal regimen for insulin therapy[3].

Among various insulin regimens, basal-bolus insulin regimen is considered more closely mimicking the human physiological insulin secretions. A basal-bolus regimen generally involves three injections of rapid-acting insulin before each meal and one injection of long-acting insulin a day[1,3]. Attempts have been made to reduce the physical and mental burden associated with diabetes treatment such as fear over frequent insulin injections required by basal-bolus therapy, risk of hypoglycaemia, weight gain and lifestyle restrictions[1,3], with the use of premixed insulin. Several studies using analogue insulins have shown that twice-daily injections of pre-mixed insulin therapy resulted in comparable percentage of HbA1c reduction comparing to basal-bolus therapy, but requiring fewer injections[1].This offers a convenient alternative to the basal-bolus therapy for T2DM patients requiring insulin therapy.

The use of conventional insulin (also known as human insulin) supersedes the use of analogue insulin in the public primary healthcare clinics in Malaysia. This may be due to the lower price of conventional insulin compared to insulin analogues. To date, many studies have evaluated and compared the glycaemic and weight control in patients receiving analogue basal-bolus and analogue premixed insulin regimes. Nevertheless, similar studies comparing conventional basal-bolus and premixed insulin regimens are very limited. Considering the lower cost of conventional insulin and its more common use in the local setting, evaluating the effectiveness of basal-bolus and premixed regimen using conventional insulin is necessary. This information is important to help healthcare providers in choosing the more favourable insulin regimen for the patients. Therefore, this study was carried out to compare the glycaemic and weight control effects of conventional basal-bolus and conventional premixed insulin regimes in patients with T2DM in Kluang District, Johor, Malaysia.

Methods

Study design and sampling

This research was registered on the Malaysian National Medical Research Register (NMRR) (ID NMRR-16-1301-31592) and approved by the Medical Research Ethical Committee (MREC) of Ministry of Health Malaysia. This retrospective study was conducted in all government primary health care clinics in Kluang District, Johor between 1 Jan 2016 to 31 Dec 2016. Data was collected from patients' medical records in the outpatient diabetic clinics. Inclusion criteria were: patients diagnosed with T2DM with a period of more than 12 months, aged 18 years and above, HbA1c value above 7.5%, on a stable conventional insulin therapy for at least 3 months (no change in treatment / regimen and less than 30% change in dosage), and on either basal-bolus or premixed insulin regimens. In this study, patients diagnosed with type 1 diabetes mellitus (T1DM), had switched insulin regimen at any time in between baseline to endpoint, and with incomplete medical record within the one-year study period were excluded. In addition, patients who experienced severe hypoglycaemia episodes within the last 3 months, impaired hepatic functions, and active proliferative diabetic retinopathy 6 months prior to screening were also excluded.

Power and Sample Size Calculation software version 3.0.43 by Dupont & Plummer (2003) was used to calculate the sample size. A minimum sample size of 61 patients were needed in each group to achieve a power of 80% to detect an absolute difference of 0.4% in HbA1c reduction between the groups (standard deviation of 1.1%, two-sided $\alpha = 0.05$ and $\beta = 0.2$) in order to obtain statistical significance in this study. Data extracted from patients' medical records in outpatient diabetic clinics were: demographic information (age, race, gender, ethnicity, weight, duration of years with diabetes), medication regimens (conventional basal-bolus or conventional premixed insulin), laboratory parameters (HbA1c and fasting blood sugar (FBS)), and doctor's interventions. Data were recorded in a data collection form prior to data entry and statistical analysis.

Statistical analysis

Using SPSS version 18.0, data processing and statistical analyses were conducted. Characteristics of the patients were analysed and presented as descriptive statistics (e.g. mean and standard deviation and frequency as well as percentage and proportions). Prior to conducting inferential statistics, the data were examined using Kolmogorov-Smirnov and Shapiro-Wilk tests for ascertaining normality. Independent sample t-test was carried out to compare two groups (Basal-bolus Insulin Regimen and Premixed Insulin Regimen) based on their mean changes of HbA1c and FBS from baseline to endpoint. Level of significance of 0.05 was used for assigning any statistical significance.

Results

A total of 122 patients fulfilled the inclusion criteria and were included in the study, with 61 patients in each group (Basal-bolus Insulin Regimen and Premixed Insulin Regimen). The demographics and baseline characteristics of the patients were comparable ($p>0.05$) (Table 1). Both groups of patients had similar mean age (around 59 years old) and mean duration of T2DM history (around 12 years). In addition, both groups had similar baseline HbA1c, FBS levels, baseline weight and comparable incidence of co-existing diabetes-related disorders. All patients received same brand of human insulins manufactured by Sanofi-Aventis Deutschland GmbH, Germany. In the Basal-bolus Insulin Regimen group, patients received Insuman Basal (long acting human insulin) as pre-bed basal dose, and Insuman Rapid (rapid-acting human insulin) as pre-prandial doses, while all patients in the Premixed Insulin Regimen group received Insuman Comb, which is a biphasic isophane insulin suspension consisting of 25% dissolved insulin and 75% crystalline protamine insulin.

Table 1: Demographics and baseline characteristics of the study population

Characteristics*	Basal-bolus (n=61)	Premixed (n=61)
Gender, n (%)		
Male	24 (39.3)	31 (50.8)
Female	37 (60.7)	30 (49.2)
Age, mean (SD)	57.82 (10.6)	58.95 (8.8)
Duration of diabetes (years), mean (SD)	11.93 (6.1)	12.06 (5.9)
Race, n (%)		
Malay	51 (83.6%)	50 (82%)
Chinese	7 (11.5%)	8 (13.1%)
Indian	3 (4.9%)	3 (4.9%)

*Levene's test for homogeneity-of-variance ($p>0.05$); SD – standard deviation

Changes in HbA1c, FBS and body weight throughout the course of the study at baseline and endpoint were shown in Table 2. The difference in mean HbA1c reduction between Basal-bolus regimen and Premixed regimen in the study population was not statistically significant. Likewise, there

were no significant differences between the two groups in pre-breakfast and pre-bed FBS baseline-to-endpoint changes. Nevertheless, the baseline-to-endpoint changes in pre-lunch and pre-dinner FBS were significantly different. On the other hand, the mean changes in body weight in both groups were not statistically different.

Table 2: HbA1c and FBS concentrations at baseline and endpoint

Variables	Basal-bolus (n=61), mean (SD)	Premixed (n=61), mean (SD)	p-value
HbA1c (%)			
Baseline	11.65 (2.30)	10.98 (2.40)	
Endpoint	10.85 (2.09)	11.05 (2.53)	
Mean HbA1c difference	-0.8048 (2.51)	0.0682 (3.00)	p=0.084
Adjusted mean difference in HbA1c change between groups, % (95% CI)	-0.873 (-1.866, 0.1206)		
Pre-breakfast FBS (mmol/l)			
Baseline	11.82 (5.75)	14.03 (15.60)	
Endpoint	11.39 (5.48)	11.15 (3.76)	
Baseline-to-endpoint change	-0.43 (0.86)	-2.89 (15.68)	p=0.263
Pre-lunch FBS (mmol/l)			
Baseline	16.63(21.78)	12.10 (4.75)	
Endpoint	12.59 (5.29)	13.02 (5.00)	
Baseline-to-endpoint change	-4.04 (2.32)	0.92 (3.92)	p=0.038*
Pre-dinner FBS (mmol/l)			
Baseline	12.61 (5.71)	12.05 (4.72)	
Endpoint	11.56 (4.42)	13.52 (5.82)	
Baseline-to-endpoint change	-1.05 (3.75)	1.48 (4.02)	p=0.001*
Pre-bed FBS (mmol/l)			
Baseline	11.32 (5.39)	12.07 (5.09)	
Endpoint	11.73 (5.44)	13.14 (5.06)	
Baseline-to-endpoint change	0.41 (0.68)	1.06 (3.53)	p=0.429
Weight (kg)			
Baseline	71.06 (17.68)	73.49 (16.27)	
Endpoint	71.68 (14.89)	73.02 (26.13)	
Baseline-to-endpoint change	0.62 (3.37)	-0.47 (5.52)	p=0.190

* the difference between the two groups was statistically significant

Discussion

Type 2 diabetes mellitus (T2DM) is a chronic disease with progressive loss of beta-cell function[3]. This means that most patients with long-standing T2DM may ultimately require insulin therapy alongside oral antidiabetics to achieve optimal glycaemic control (HbA1c ≤ 6.5%). The targeted HbA1c level may not be achieved due to non-compliance with the prescribed insulin regimen, especially with the concurrent issue of polypharmacy. Thus, it is essential to provide an effective, safe and flexible insulin regimen to maximise the effect of insulin therapy.

Clinical trials (e.g. PREFER study[4]), systematic review[5] and economic evaluation[6] had shown that insulin treatment with basal-bolus regimen was superior in the overall glycaemic control compared to premixed insulin. In line with the findings of previous studies, our study showed that the basal-bolus regimen reduced mean HbA1c from baseline to endpoint while premixed showed a slightly increase of HbA1c in the study populations. However, the difference between the mean decrease in HbA1c in the two groups [-0.8048% (SD 2.51) versus 0.0682% (SD 3.00)] was not statistically significat (p>0.05).

The result supported the LanScape study[7], which concluded that basal-bolus regimen was non-inferior to biphasic insulin twice daily in term of HbA1c reduction.

In addition, we observed no significant differences between groups in pre-breakfast and pre-bed FBS concentration. Nevertheless, the pre-lunch and pre-dinner FBS of patients with basal-bolus regimen were reduced compare to premixed regimen in which the FBS of patients were slightly increased. These results were similar to the findings by Yamada *et al*. (2013) which suggested that basal-bolus regimen achieves better glucose profiles than premixed insulin therapy in T2DM patients, particularly after lunch[8]. However, the basal-bolus approach usually requires once daily subcutaneous administration of basal insulin in combination with three pre-prandial or corrective doses of rapid-acting insulin. The complexity of this approach may limit its acceptance among T2DM patients especially when compared to the premixed insulin regimen which usually only requires two subcutaneous injections per day.

Another important consideration when selecting a treatment for diabetes is the effect on body weight. Medications-induce weight gain is undesirable in diabetes given that majority of T2DM patients are already obese or overweight, and obesity is a risk factor for diabetes and cardiovascular diseases. There was, however, a slight weight gain in the basal-bolus group comparing to slight weight lost in the premixed insulin group, although difference in baseline-to-endpoint weight changes between the two groups were not statistically significant. This result was comparable with the randomised pragmatic trial[6] conducted using insulin analogue, which also showed that patients with basal-bolus regimen had higher weight gain than the premixed regimen at its follow-up.

There are several limitations in the study. We acknowledged that our study sample size was small and was a retrospective observational in design which could limit the generalisation of the findings. As all information were extracted from patients' medical records, there may be errors due to the absence of information or incorrect information in the records. Furthermore, this study was not able to capture adverse events reports such as the frequency of hypoglycaemia, allergic reactions and cardiovascular events. Discontinuations or deaths due to insulin treatment during the study period was not detected. Also, patients with acute or chronic kidney failure was not excluded as majority of the patients with renal impairment were on basal-bolus, eliminating them will result in lack of subjects. In addition, there were lack of information on patients' compliance to insulin administration, insulin injection technique and diets, which were important factors affecting diabetic control in the primary care setting. Furthermore, the greatest limitation of study was the 12-month duration from baseline to endpoint for the measurement of HbA1c changes instead of 3 months, due to cost limitations of laboratory tests the non-interventional design of the study. These might affect the quality of the data. It is recommended that future studies should compare the safety and cost-effectiveness of basal-bolus and premixed insulin regimens in T2DM patients in the primary care settings. Also, large-sized prospective clinical trials with more frequent HbA1c and FBS monitoring are needed to confirm the findings of our study.

Conclusion

In summary, there were no significant differences in HbA1c reductions, pre-breakfast and pre-bed FBS changes and weight changes between conventional basal-bolus and conventional premixed insulin regimens, while basal-bolus insulin regimen significantly reduced pre-lunch and pre-dinner FBS compared to premixed insulin regimen. Since basal-bolus conventional insulin regimen provide better control of pre-lunch and pre-dinner FBS, it may be indicated for patients who require better control FBS. Nevertheless, the decision of insulin regimens shall be based on clinical judgement of the healthcare providers and preference or compliance of the patients.

Acknowledgement
The author would like to thank the Director General of Health Malaysia for his permission to publish this article.

Conflict of Interest Statement
No external funding was received and the authors declared no conflict of interest.

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