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Using continuous glucose monitoring to measure glucose variation of patients with type 2 diabetes: switching from premixed human insulin 70/30 to insulin lispro mix 75/25 or lispro mix 50/50 for 8 weeks

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Abstract

Aim: To compare the impact of premixed human insulin 70/30 and two different premixed insulin analogues (insulin lispro mix 75/25 and 50/50) on glucose variation of the patients with type 2 diabetes (T2D).

Methods: A total of 19 T2D patients who were treated with premixed human insulin 70/30 (PHI70/30) more than 90 days. All patients were divided into two groups receiving either insulin lispro mix 75/25 (LM25) or 50/50 (LM50) for 8 weeks. They were then crossed over to the other arm and continued to receive either LM50 or LM25 for 8 weeks. Continuous glucose monitoring (CGM) was performed on all patients for 72 hours in every stage to examine the differences in variability of interstitial glucose. All patients received questionnaire survey regarding subjective feeling of insulin therapy.

Results: No significant difference was found in HbA1c, mean interstitial glucose (MIG) and mean amplitude of glycemic excursion (MAGE) in whole day among three regimens. However, in the subgroup with baseline MIG≥10.0mmol/L (n=6), MIG in whole day in LM25 regimen was significantly lower than that in PHI70/30 regimen (9.4±1.5 vs. 12.2±2.0mmol/L, P=0.024). The largest amplitude of glycemic excursion (LAGE) and MAGE in LM50 regimen were lower than those in LM25 regimen in the period of 22pm-6am (6.9±3.1 vs. 9.8±2.8mmol/L, P=0.034; 2.2±1.9 vs. 4.0±3.0mmol/L, P=0.043; respectively).

Conclusions: Premixed Insulin analogue may provide better glycemic control compared to human premixed insulin in the patients with higher glucose level. The T2D patients with adequate glycemic control or greater risk of hypoglycemia at night were suitable to LM50.

Keywords: Premixed human insulin, premixed insulin lispro 75/25, premixed insulin lispro 50/50, glucose excursion, continuous glucose monitoring

Background

Glycemic control is one of the independent risk factors for macrovascular complications in patients with diabetes [1-3]. Further study demonstrated the significant relationship between glucose fluctuations and macrovascular complications [4]. Furthermore, hypoglycemic episodes increased incidence and mortality of cardiovascular events of patients with advanced type 2 diabetes mellitus (T2DM) [5,6]. Progressive failure of cells despite gradual intensification of glucose-lowering therapy leads to hyperglycemia in most patients with T2DM. To offset inadequate insulin secretion, insulin treatment is initiated in patients who do not achieve desired glucose control. Clinical physicians face a big challenge that is how to make a choice of efficacy and safety agents.

Insulin replacement therapy includes basal-bolus insulin therapy and premixed human insulin/insulin analogue therapy in China. The latter one was accepted by many patients for receiving fewer times of injection [7]. According data of IMS Health Inc, premixed human insulin (PHI) holds 66% of total insulin market in 2011. Several studies demonstrate post-prandial glycemic control was improved and overall control was similar when T2DM patients were treated with premixed insulin analogue compared to premixed human insulin [8-10].

In recent years, insulin analogues combined at different blend ratios (insulin lispro mix25: 75% insulin lispro protamine suspension and 25% insulin lispro, and insulin lispro mix50: 50% insulin lispro protamine suspension and 50% insulin lispro) have become commercially available. Both insulin lispro mix25 (LM25) and insulin lispro mix50 (LM50) remain rapid-acting characteristic of insulin lispro, which may provide good post-prandial glycemic control, while neutral protamine hagedorn (NPH) insulin component in these preparations may meet basal insulin requirement between meals and during the overnight period. However, there are few reports comparing the effect of these premixed insulin analogue formulation on glycemic variability using in a twice-daily regimen. Therefore, we conducted an open-label, randomized cross-over study in T2DM patients to investigate glucose variation of switching

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from PHI 70/30 to LM25 or LM50 with continuous glucose monitoring (CGM).

Patients and methods

Patients

Male and female patients with T2DM, above 18 years old, who had received premixed human insulin twice daily and/or oral anti-hyperglycemic medications at least 90 days, were enrolled from October 2010 to June 2011 visiting outpatient of endocrinology department in Peking Union Medical College Hospital. Further, HbA1c levels should be 6 to 9%. Patients were excluded if they had liver dysfunction (2.5 times higher than the upper limit of normal reference range), renal insufficiency (serum creatinine: male ≥133μmol/L, female≥110μmol/L), and these conditions causing elevation of blood glucose such as infection, hyperthyroidism, receiving corticosteroids and estrogen therapy, and so on. The study was approved beforehand by the Ethics Committee of Peking Union Medical College Hospital. The trial was performed in accordance with the Declaration of Helsinki and good clinical practice. Patients gave written informed consent before any trial-related activities began.

Methods

The data of medical history (age, sex, duration of diabetes, insulin dose) and the parameters of anthropometry (blood pressure, weight, height and waist circumference) were obtained from 19 recruited patients. All patients filled the questionnaire which included four questions: general degree of satisfaction, frequency of symptomatic hypoglycemia, incidence of missed injection, convenience of injection to investigating the subjective feeling of patients. The 19 patients receiving PHI70/30 twice daily were performed CGM for 72 hours and HbA1c.

Then, they were randomly divided into two groups (group A and B) according to random number table. Group A (10 patients) received LM25 twice daily for 8 weeks and group B (9 patients) also received LM50 twice daily for 8 weeks. The insulin dose was switched according to prior dose of PHI70/30. All patients received self-monitoring of blood glucose (SMBG). They tested a glucose profile covering whole day (included fasting, post-prandial three times daily after meals and at bedtime) in one day every week, and were adjusted insulin dose based on results of SMBG when followed up in every two weeks. At the end of 8th week, all patients were performed CGM for 72 hours. Then, they crossed over to the other study arm for 8 weeks. The insulin dose was switched according to the dose prior to crossing-over. All patients received SMBG and were adjusted insulin dose according to the above-mentioned method again. At the end of 16th week, all patients were performed CGM for 72 hours again. All patients maintained the sort and dose of formal oral anti-hyperglycemic medications and lifestyle during the whole trial period. In every end of stage, all patients performed blood pressure, body weight, waist circumference and HbA1C, recorded daily dosage of insulin, and filled the questionnaire (**Figure 1**).

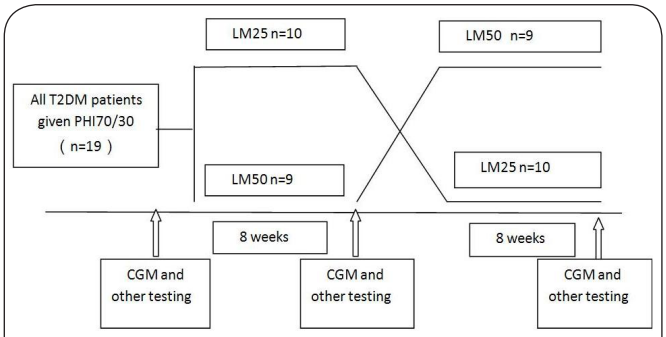

Figure 1. Study protocol.

CGM was performed on all subjects using CGMS system GOLD (Medtronic Inc., USA) which measured interstitial glucose (IG). All data were divided to four periods: 6am-11am, 11am-16pm, 16pm-22pm and 22pm-6am. All parameters including the mean interstitial glucose (MIG), the largest amplitude of glycemic excursion (LAGE), and mean amplitude of glycemic excursion (MAGE) were calculated respectively in every period. 24-hour MIG, ratio of duration of hypoglycemia (IG ≤3.9mmol/L) and 24-hour MAGE were calculated using data from 0-24 hours during three days. MAGE was calculated by taking the arithmetic mean of glucose increase and descending segments exceeded the value of 1SD [**11**].

CGM provided more valuable information on glycemic excursions to assess stability of glucose compared to traditional glucose monitoring [**12**]. Some studies showed that parameters of glycemic excursion evaluated by CGM were significant related to plasma markers (glycoalbumin, and 1, 5-anhydroglucitol) [**13**,**14**]. MAGE was a good marker for intraday fluctuation of glucose, because it did not depend on whole glucose level. In other word, MAGEs could be different even if the values of HbA1c are similar.

Statistical analysis

Measurement data were presented as the mean ±standard deviation (SD). Enumeration data were presented as frequency. Measurement data were compared using paired t-test or one-way ANOVA where appropriate. Enumeration data were compared using McNemar test. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 11.5 software (SPSS, USA).

Results

Baseline characteristics

Subjects comprised 19 T2DM patients (male: female=6:13; mean age 60.6±8.9 years, duration of diabetes 14.1±8.3 years; BMI 25.8±3.8 kg/m^2; HbA1c 7.4±0.7%; systolic blood pressure 128±22 mmHg; diastolic blood pressure 75±11 mmHg; weight 66.9±12.1Kg; waist circumference 90.3±12.9

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Table 1. Baseline characteristics of subjects.

Subject (n)	19
Male/Female	6/13
Age (y)	60.6±8.9
Duration of diabetes (y)	14.1±8.3
BMI (kg/m^2)	25.8±3.8
HbA1c (%)	7.4±0.7
SBP (mmHg)	128±22
DBP (mmHg)	75±11
Weight (kg)	66.9±12.1
Waist circumference (cm)	90.3±12.9
Total insulin dose (U/day)	36.6±10.7
Mean insulin dose (U/kg/day)	0.55±0.14

cm; total insulin dose 36.6±10.7 U/day; mean insulin dose 0.55±0.14 U/kg/day) (**Table 1**).

Comparison of parameters of CGM and clinical markers in every stage of study

MIG in three different regimens

No significant difference was found in MIG in every period of whole day among PHI70/30, LM25 and LM50 (**Table 2**). All patients were divided into two subgroups according to baseline value of MIG: MIG≥10.0mmol/L (n=6), MIG<10.0mmol/L (n=13). In the subgroup with baseline MIG≥10.0mmol/L (n=6), MIG in whole day in LM25 regimen was significantly lower than that in PHI70/30 regimen (9.4±1.5 vs. 12.2±2.0mmol/L, P=0.024), and LM50 was similar to LM25 (9.4±3.4 vs. 9.4±1.5mmol/L, P=0.845). LM50 seemed superior to PHI70/30, but the difference was not significant (9.4±3.4 vs 12.2±2.0mmol/L, P=0.092). In the subgroup with baseline MIG<10.0mmol/L (n=13), there was no significant difference in MIG among PHI70/30, LM25 and LM50 (8.8±0.9 vs. 9.0±1.0 vs. 9.0±2.6mmol/L, P=0.620) (**Table 3**).

LAGE and MAGE in three regimens

LAGE in LM50 regimen was lower than that in LM25 regimen in the period of 22pm-6am (6.9±3.1 vs. 9.8±2.8mmol/L, P=0.034). No significant difference was found in LAGE in the other periods of whole day among three regimens (**Table 2**). MAGE in LM50 regimen was lower than that in LM25 regimen in the period of 22pm-6am (2.2±1.9 vs. 4.0±3.0mmol/L, P=0.043). No significant difference was found in MAGE in the other periods of whole day among three regimens (**Table 2**).

Hypoglycemia in three regimens

No significant difference was found in frequency at the different ratio of duration of hypoglycemia among PHI70/30, LM25 and LM50 (**Table 2**).

Clinical characteristics in three regimens

There was no significant difference in HbA1c among PHI70/30, LM25 and LM50 (7.4±0.7%, 7.5±0.9% and 7.4±0.9%, respectively, P>0.05). Similarly, no significant difference was found in SBP, DBP, weight, waist circumference, total insulin dose, mean insulin dose among three regimens (**Table 2**).

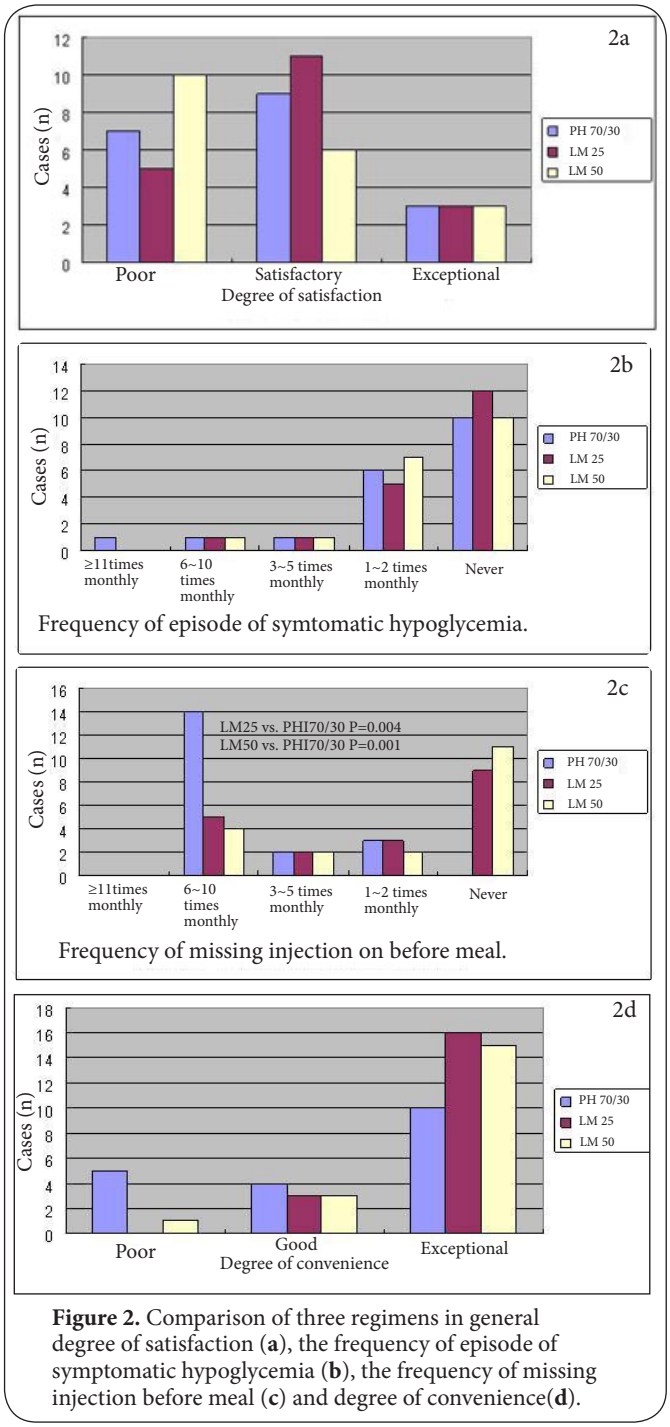

Figure 2. Comparison of three regimens in general degree of satisfaction (**a**), the frequency of episode of symptomatic hypoglycemia (**b**), the frequency of missing injection before meal (**c**) and degree of convenience(**d**).

Results of questionnaire in every stage of using insulin

No significant difference was found in general degree of satisfaction and frequency of episode of symptomatic hypoglycemia among PHI70/30, LM25 and LM50 (**Figures 2a**,**2b**).

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Table 2. Comparison of parameters of CGM and clinical characteristics among three regimens.

	PHI70/30	LM25	LM50
6am-11am			
MIG (mmol/L)	9.5±2.4	8.9±1.6	9.1±2.5
LAGE (mmol/L)	8.7±3.0	9.8±2.7	8.2±4.0
MAGE (mmol/L)	5.3±3.2	4.8±3.0	4.5±2.8
11am-16pm			
MIG (mmol/L)	10.2±2.7	10.1±1.6	9.8±2.8
LAGE (mmol/L)	9.3±3.7	11.6±4.0	8.9±3.5
MAGE (mmol/L)	3.8±1.9	4.8±1.9	3.5±2.4
16pm-22pm			
MIG (mmol/L)	9.9±2.4	10.0±1.3	10.0±3.0
LAGE (mmol/L)	10.2±3.6	11.2±4.2	8.9±3.5
MAGE (mmol/L)	4.8±3.1	4.3±2.5	3.4±1.8
22pm-6am			
MIG (mmol/L)	8.4±2.1	8.3±1.7	8.1±2.7
LAGE (mmol/L)	8.3±3.4	9.8±2.8	6.9±3.1□
MAGE (mmol/L)	2.6±1.6	4.0±3.0	2.2±1.9□
MIG in whole day (mmol/L)	9.4±2.2	9.2±1.1	9.1±2.6
MAGE in whole day (mmol/L)	5.75±3.46	6.55±2.76	5.06±2.61
HbA1c (%)	7.4±0.7	7.5±0.9	7.4±0.9
SBP (mmHg)	128±22	127±15	125±18
DBP (mmHg)	75±11	77±9	77±9
Weight change (kg)	-	-0.25±1.79	0.62±1.97
Waist circumference change (cm)	-	0.84±2.46	1.00±2.40
Total insulin dose (U/day)	36.6±10.7	37.2±12.2	38.3±10.6
Mean insulin dose (U/kg/day)	0.55±0.14	0.55±0.16	0.57±0.15

*: vs. PHI70/30, P<0.05; □: vs. LM25, P<0.05.

Table 3. Comparison of MIG in whole day among three regimens in subgroup with baseline MIG≥10.0mmol/L and <10.0mmol/L.

	PHI70/30	LM25	LM50
Subgroup with baseline MIG≥10.0mmol/L (n=6)	12.2±2.0□	9.4±1.5*	9.4±3.4
Subgroup with baseline MIG<10.0mmol/L (n=13)	8.8±0.9	9.0±1.0	9.0±2.6

*:vs. PHI70/30, P<0.05; □:vs. LM25, P<0.05.
Baseline MIG of 12.2 nmol/l is translated to HBA1C of 9.3%.

The frequency of missing injection before meal was decreased with LM25 and LM50 compared to PHI70/30 (P=0.004, and P=0.001, respectively). There were 14 patients who missed injection before meal 6-10 times monthly in PHI70/30, but there were 5 and 4 patients in LM25 and LM50 (**Figure 2c**).

LM25 was superior to PHI70/30 in convenience (P=0.024). LM50 seemed superior to PHI70/30, but there was no significant difference (P=0.053) (**Figure 2d**).

Discussion

Many studies have suggested that overall glucose control and risk of hypoglycemia are similar with premixed human insulin compared to premixed insulin analogue [**9**,**15**,**16**]. There is only one study reported in the literature comparing premixed human insulin and insulin analogue using CGM. That study suggested biphasic insulin aspart 30 was associated with fewer nocturnal episodes of hypoglycemia [**17**]. But there is no study in comparing the impact of LM25 and LM50 on glucose excursion using CGM. In present study, the finding suggested there were no difference in general glycemia control (HbA1c, MIG) and duration of hypoglycemia between premixed human insulin 70/30 and premixed insulin analogue (LM25 and LM50). Furthermore, analysis of subgroup revealed that in high baseline of MIG (≥10.0mmol/L), although just including six patients, LM25 was superior to PHI70/30, LM50 seemed superior to PHI70/30. However, it should be confirmed in more patients by further study.

In this study, baseline HbA1c levels (baseline HbA1c

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7.4±0.7%) of patients were not so high comparing with most of other studies in which baseline level usually is round or even higher than 8%.

Then the patients were adjusted insulin dose by follow-up. It was most closed to real clinical practice. In this condition, overall glucose control and ratio of duration of hypoglycemia of these patients were similar among PHI70/30, LM25 and LM50. Monnier reported the relative contribution of postprandial glucose excursions was predominant in fairly controlled patients, whereas the contribution of fasting hyperglycemia increased gradually with diabetes worsening [**18**]. Therefore, it will be good general glycemic control if postprandial glucose is well-controlled in fairly controlled patients. Some studies have confirmed premeal injection of premixed insulin analogue significantly reduced overall postprandial glucose excursion compared to premixed human insulin [**8**-**10**]. In this study, we confirmed that even in the patients whose HbA1c was close to target, premixed insulin analogue may provide better general glycemic control if baseline mean interstitial glucose was higher (more than 10.0mmol/L).

There were a few clinical studies of comparing LM25 and LM50. Tanaka *et al.,* assessed the clinical effects of switching from twice daily PHI70/30 or LM25 to twice daily LM50 by measuring blood glucose seven times daily. They found LM50 may control post-prandial blood glucose level and stabilize diurnal blood glucose variations in T2DM patients [**19**]. Nishimura *et al.,* reported on a cross-over study comparing LM25 and LM50 using CGM. Their study demonstrated that twice-daily LM25 provided better overnight glycemic control compared to twice-daily LM50, but both LM25 and LM50 provided inadequately post-lunch glycemic control [**20**]. In above two studies, the baseline values of HbA1c in enrolled patients were high (9.0±1.2% and 8.4±2.1%, respectively), study periods were short (2 days and 6 days, respectively), and monitoring glucose immediately after switching insulin without washout period and adjusting insulin dose. Nishimura *et al.,* only observed mean glucose concentration overnight, did not analyze glucose fluctuation overnight (for example: MAGE overnight).

In this study, we found that LM50 was superior to LM25 in LAGE and MAGE in the period of 22pm -6am. It may be related to the different baseline of HbA1c of enrolled patients. In our study, the baseline HbA1c levels (HbA1c 7.4±0.7%) of patients were relatively lower than that of the other similar trials mentioned above. Therefore the blood glucose levels of our patients should be relatively lower than that of patients in the similar trials. And it is generally believed that the more A1c level close to normal, the more contribution to A1c is given from postprandial glucose. Therefore whenfasting hyperglycemia is predominant, insulin regimen which could provide more basal insulin (such as LM25) may be more appropriate than mid mixtures for long time fasting period like overnight. But the risk of hypoglycemia at night is also increased along with it when comparing with mid mixtures. Vice versa, mid mixtures like LM50 may be more suitable for patients mainly with postprandial hyperglycemia. These kind of patients need higher percentage of rapid-acting insulin (such as LM50) to decrease post-prandial glucose level, meanwhile, overnight glucose fluctuation could be significantly improved.

LM25 and/or LM50 were superior to premixed human insulin in frequency of missing injection before meal and degree of convenience which could be easily explained by the privilege of lispro insulin as fast insulin analog. The survey results of subjective feeling of insulin injection were in accordance with former studies. Premixed insulin analogues were more flexible in time of injection and had better compliance and quality of life [**10**,**21**,**22**].

Conclusion

Our study demonstrated that twice-daily PHI70/30, LM25 and LM50 provided similarly glycemic control and frequency of hypoglycemic episodes after adjusted insulin dose by follow-up. Premixed Insulin analogue may provide better glycemic control compared to human premixed insulin in the patients with higher glucose level. The T2DM patients with adequate glycemic control or greater risk of hypoglycemia at night were suitable to LM50. Premix insulin analogues were preferred in the patients requiring more flexible lifestyle.

Competing interests

The authors declare that they have no competing interests.

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