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ORIGINAL RESEARCH

Effects of switching from prandial premixed insulin therapy to basal plus two times bolus insulin therapy on glycemic control and quality of life in patients with type 2 diabetes mellitus

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Background: The effects of switching from prandial premixed insulin therapy (PPT) injected three times a day to basal plus two times bolus insulin therapy (B2B) on glycemic control and quality of life were investigated in patients with type 2 diabetes mellitus.

Methods: The clinical course was prospectively observed during the first 16 weeks after switching to B2B (insulin glargine plus insulin glulisine before breakfast and dinner) in 27 subjects previously treated with PPT using 50/50 premixed insulin. The Diabetes Treatment Satisfaction Questionnaire (DTSQ) was administered at the start and end of the study.

Results: The glycated hemoglobin (HbA_{1c}) level (8.3%±1.8% to 8.2%±1.1%) and the DTSQ score did not change between the start and end of the study. An improvement in HbA_{1c} level was found in nine (33%) subjects. The change in HbA_{1c} showed a significant negative correlation with baseline HbA_{1c}, and was significantly better in patients with a baseline HbA_{1c} >8.0% than in those with an HbA_{1c} ≤8.0% (–0.9±2.0 versus 0.3±0.6, respectively, P=0.02). The change in DTSQ score representing treatment satisfaction was significantly greater in patients whose HbA_{1c} level was improved than in those in whom it was not (2.7±3.6 versus –0.8±3.5, P=0.04).

Conclusion: B2B was noninferior to PPT with regard to HbA_{1c} levels in patients with type 2 diabetes mellitus. B2B should be considered particularly for subjects whose glycemic control is poor despite PPT.

Keywords: type 2 diabetes mellitus, insulin therapy, basal plus two times bolus insulin therapy, prandial premixed insulin therapy, Diabetes Treatment Satisfaction Questionnaire

Introduction

Basal-bolus insulin therapy is an ideal regimen for improving uncontrolled hyperglycemia in patients with diabetes mellitus.[1] Prandial premixed insulin therapy (PPT), injected three times a day, is also effective for glycemic control in type 2 diabetics.[2–9] Further, PPT is convenient for patients, because it requires only a single insulin preparation. However, some subjects receiving insulin therapy prefer not to inject insulin before lunch, because they are often away from home during the daytime. This problem is solely attributable to convenience, but may also affect adherence to the insulin injection regimen and quality of life for patients.

The position statement published by the American Diabetes Association and the European Association for the Study of Diabetes recommends basal insulin injection once daily as the initial insulin regimen for patients with type 2 diabetes mellitus who have high glycated hemoglobin (HbA_{1c}) levels (≥9.0%) despite treatment with

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oral antihyperglycemic agents.[1] If glycemic control is not achieved by basal insulin therapy, a basal plus mealtime insulin regimen consisting of 1–3 injections of rapid-insulin analogs can be considered.[1] Basal plus two times bolus insulin therapy (B2B) does not require injection before lunch, so patients' quality of life may be preserved even though insulin preparations are injected three times daily, similar to PPT.

As of February 2014, there were no studies assessing the effectiveness of switching from PPT to B2B. Therefore, we tested the hypothesis that B2B (insulin glargine plus insulin glulisine before breakfast and dinner) would show noninferiority in terms of glycemic control and quality of life when compared with PPT in patients with type 2 diabetes mellitus who want to be able to avoid injecting insulin before lunch.

Patients and methods

Twenty-eight outpatients with type 2 diabetes mellitus receiving PPT and who visited the Department of Diabetes, Metabolism and Kidney Disease at Edogawa Hospital between September 2012 and August 2013 were eligible for this 16-week prospective trial. Physicians in this department treat more than 2,000 patients with diabetes mellitus each year.[10–12] The criteria for enrollment were type 2 diabetes treated with PPT using 50/50 premixed insulin (Humalog® Mix 50, Eli Lilly Japan KK, Kobe, Japan: 50% insulin lispro protamine suspension and 50% insulin lispro or NovoRapid® 50 Mix, Novo Nordisk Pharma Ltd, Kanagawa, Japan: 50% protamine cocrystallized insulin aspart and 50% insulin aspart) for at least 2 months and a preference to discontinue insulin injection before lunch, based on an interview conducted at the hospital visit. All patients who met these criteria were included in the study. Diabetes mellitus was diagnosed based on the criteria published by the Japan Diabetes Society.[13] No individuals with positive antiglutamic acid decarboxylase antibodies were identified. The initial doses of insulin glargine (Lantus®, Sanofi KK, Tokyo, Japan) and insulin glulisine (Apidra®, Sanofi KK) for B2B were determined based on the total dose of premixed insulin being used at entry to the study. A half dose of the total premixed insulin was used as insulin glargine once daily before breakfast or dinner. The other half was divided into two equal doses of insulin glulisine for injection twice daily, before breakfast and dinner. Registered diabetologists were allowed to adjust subsequent doses of insulin at each hospital visit. If oral antihyperglycemic agents were being used at the start of the study, the doses of these agents were maintained throughout the trial.

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) was administered at the start of the study and again 16 weeks later in order to assess the influence of treatment with insulin on the patient's quality of life.[14,15] Treatment satisfaction was estimated by scoring on questions 1, 4, 5, 6, 7, and 8 of the DTSQ. Perceived hyperglycemia and hypoglycemia were expressed as the scores on questions 2 and 3, respectively.

All patients received an explanation of the protocols to be performed and then gave their consent to inclusion in this trial. This study was conducted according to the principles expressed in the Declaration of Helsinki. The ethics committee of Edogawa Hospital approved the study protocol.

Twenty-seven patients (mean age 62±16 years; 19 males and eight females; mean duration of diabetes mellitus, 14±8 years; mean duration on insulin treatment, 48±46 months; mean duration of treatment with PPT using 50/50 premixed insulin, 22±24 months) completed the study (Table 1). Data were excluded for one patient who wished to suspend insulin injections during the study period and withdrew. Seventeen and ten patients, respectively, were receiving PPT (Humalog Mix 50 and NovoRapid 50 Mix) before the study. Answers to the DTSQ were obtained from 25 and 21 subjects at the start and end of the study, respectively.

Statistical analysis

All data are shown as the mean ± standard deviation. Analysis of variance was used for between-group comparisons of continuous variables. The paired *t*-test was used to determine whether there were any differences in HbA_{1c}, body weight, body mass index, serum lipid concentrations, or DTSQ scores at the end of the study when compared with baseline values. A least-squares model was used to determine the relationship between HbA_{1c} levels, DTSQ scores, and patient clinical characteristics. Differences with values of $P<0.05$ (two-tailed) were considered to be statistically significant. JMP version 8.0.1 software (SAS Institute, Cary, NC, USA) was used to perform all analyses.

Results

The clinical characteristics of the patients during the study period are shown in Table 2. Insulin dose, body weight, and body mass index were not significantly different between baseline and the end of the study. HbA_{1c} and serum lipid levels also did not change significantly. The change in HbA_{1c} (ΔHbA_{1c}) was −0.1±1.4 points, and improvement was found

Table 1 Clinical characteristics of study subjects

Number	Age (years)	Sex	Duration of diabetes (years)	BMI (kg/m^2)	Dose of insulin (units/day)	HbA_{1c} (%)
1	22	Male	6	23.6	16	10.8
2	30	Male	24	37.5	26	9.8
3	42	Male	8	23.3	20	7.4
4	43	Male	13	24.0	24	7.6
5	44	Male	15	28.9	42	10.4
6	51	Female	0.8	22.0	22	6.9
7	52	Male	17	24.1	22	7.1
8	57	Male	7	29.4	18	12.5
9	58	Male	23	24.9	40	8.2
10	60	Female	14	22.3	24	14.5
11	61	Male	18	23.8	26	6.9
12	61	Female	4	22.8	12	7.0
13	61	Male	11	26.1	50	8.0
14	61	Male	7	24.4	12	7.9
15	62	Male	19	24.8	26	6.8
16	65	Male	14	19.8	14	6.9
17	69	Male	10	33.4	18	7.7
18	70	Female	20	25.6	40	8.0
19	71	Female	12	28.7	42	8.1
20	74	Male	29	22.5	44	8.1
21	76	Female	9	24.0	26	6.9
22	76	Male	19	30.6	40	7.7
23	77	Female	16	20.7	32	7.5
24	78	Male	34	23.6	12	7.7
25	79	Male	15	27.5	30	8.1
26	80	Male	0.3	26.3	18	7.0
27	83	Female	9	24.6	28	9.5

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin.

at the end of the study compared with baseline in nine (33%) subjects. DTSQ scores reflecting treatment satisfaction, perceived hyperglycemia, and perceived hypoglycemia were not significantly different between the start and end of the study. No episodes of severe hypoglycemia, defined as any symptomatic hypoglycemic event that required assistance by another individual, occurred during the study period.

Table 2 Changes in clinical characteristics during the study period

	Baseline	16 weeks	*P*-value
Dose of total insulin (units/day)	26.8±11.0	25.8±9.6	0.33
Dose of basal insulin (units/day)	13.4±5.5	13.6±5.8	0.80
Body weight (kg)	69.3±15.1	69.6±14.8	0.38
Body mass index (kg/m^2)	25.5±3.9	25.6±3.9	0.31
HbA_{1c} (%)	8.3±1.8	8.2±1.1	0.64
LDL cholesterol (mmol/L)	2.6±0.7	2.6±0.7	0.97
HDL cholesterol (mmol/L)	1.4±0.4	1.4±0.4	0.28
Non-HDL cholesterol (mmol/L)	3.3±1.0	3.2±0.8	0.53
DTSQ score			
Treatment satisfaction	23.7±7.1	24.5±6.4	0.41
Perceived hyperglycemia	3.7±1.7	3.6±1.4	0.74
Perceived hypoglycemia	1.7±1.9	1.9±1.7	0.70

Abbreviations: HbA_{1c}, glycated hemoglobin; DTSQ, Diabetes Treatment Satisfaction Questionnaire; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

The ΔHbA_{1c} showed a significant negative correlation with baseline HbA_{1c} (Figure 1A), but was not associated with patient age, gender, duration of diabetes, body weight, body mass index, serum lipid concentrations, or type of premixed insulin used before the study. The correlation between ΔHbA_{1c} and baseline HbA_{1c} did not change, even after adjusting for age, sex, disease duration, body mass index, and dose of total insulin at baseline. The ΔHbA_{1c} was significantly lower in patients with a baseline HbA_{1c} >8.0% than in those with baseline HbA_{1c} ≤8.0% (–0.9±2.0 points versus 0.3±0.6 points, P=0.02), as shown in Figure 1B.

Table 3 shows a comparison of baseline DTSQ scores divided by baseline HbA_{1c} between the two groups. The baseline DTSQ score reflecting treatment satisfaction was not significantly different between the groups for patients with a baseline HbA_{1c} >8.0% and those with a baseline HbA_{1c} ≤8.0%. The DTSQ score reflecting perceived hyperglycemia was significantly higher in the group with a baseline HbA_{1c} >8.0%, whereas the score for perceived

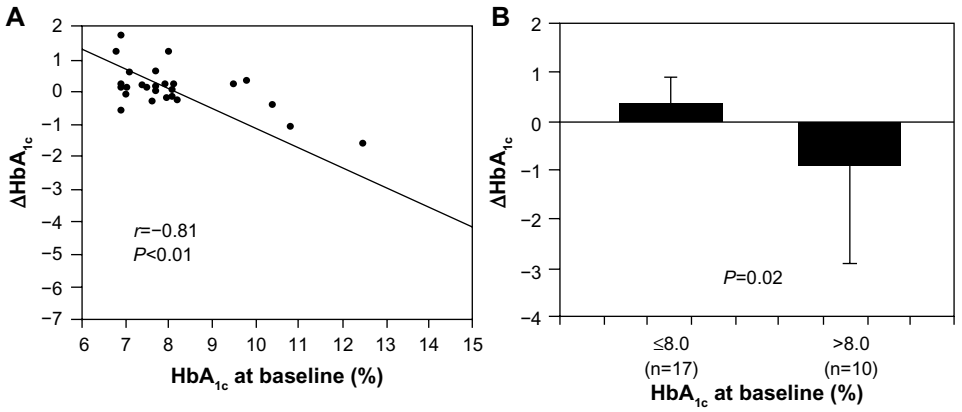

Figure 1 (**A**) Relationship between changes in HbA_{1c} after initiation of B2B (ΔHbA_{1c}) and baseline value of HbA_{1c}. (**B**) Comparison of ΔHbA_{1c} between subjects with baseline HbA_{1c} ≤8.0% and those with baseline HbA_{1c} >8.0%.
Abbreviations: B2B, basal plus two times bolus insulin therapy; HbA_{1c}, glycated hemoglobin.

hypoglycemia did not differ significantly between the two groups. The change in DTSQ score reflecting treatment satisfaction was significantly greater in patients whose HbA_{1c} level was improved at the end of the study than in those who showed no significant improvement (Table 4). The change in DTSQ score reflecting treatment satisfaction also showed a significant negative correlation with ΔHbA_{1c} (r=–0.61, P<0.01).

Discussion

PPT using 50/50 premixed insulin is widely used in the treatment of type 2 diabetes mellitus,[2–8] although this regimen does not demonstrate noninferiority compared with basal-bolus insulin therapy.[2,3] However, PPT using 50/50 premixed insulin[4–6] or biphasic insulin aspart, consisting of 30% rapid-acting insulin aspart and 70% protaminated insulin aspart,[9] has been shown to be more effective in controlling blood glucose levels than twice-daily administration (before breakfast and dinner) of premixed insulin. An advantage of B2B is that it is unnecessary for patients to inject the insulin before lunch, so their quality of life might be improved compared with that in patients on PPT and basal-bolus insulin therapy regimens. Although it is often difficult to control blood glucose levels before breakfast in subjects treated with PPT using 50/50 premixed insulin,[2,6] this problem can be overcome by increasing the dose of basal insulin in patients treated with B2B. However, blood glucose levels after lunch might be higher in patients treated with B2B, given that these patients do not inject insulin before lunch.

No previous studies have investigated the effectiveness of switching from PPT to B2B. In the present study, the B2B regimen using insulin glargine and insulin glulisine demonstrated noninferiority to PPT with regard to HbA_{1c} level, although the quality of life for patients was not significantly improved. Of note, the B2B regimen was more effective for glycemic control in one third of the subjects previously treated with PPT using 50/50 premixed insulin. Improvement in HbA_{1c} was greater in patients with poor glycemic control (HbA_{1c} >8.0%) at the start of the study. It has been previously reported that diabetic patients treated with insulin occasionally omit their insulin injection in the real-world clinical setting.[16,17] The improved glycemic control in patients with higher HbA_{1c} levels is considered to have been due to better adherence with insulin injections. We propose that changing

Table 3 Comparison of baseline DTSQ scores between the groups divided by baseline HbA_{1c} level

	Baseline HbA_{1c} (%)		
	≤8.0 (n=15)	>8.0 (n=10)	*P*-value
Baseline DTSQ score			
Treatment satisfaction	23.1±5.8	25.5±7.8	0.39
Perceived hyperglycemia	2.9±1.3	4.7±1.3	<0.01
Perceived hypoglycemia	1.9±1.8	1.3±1.9	0.41

Abbreviations: HbA_{1c}, glycated hemoglobin; DTSQ, Diabetes Treatment Satisfaction Questionnaire.

Table 4 Comparison of changes in DTSQ scores between groups divided by change of HbA_{1c} after initiation of B2B

	HbA_{1c}		
	Improved (n=9)	Unimproved (n=12)	*P*-value
Change in DTSQ score			
Treatment satisfaction	2.7±3.6	–0.8±3.5	0.04
Perceived hyperglycemia	–0.6±1.4	0.3±1.1	0.17
Perceived hypoglycemia	0.7±1.5	–0.3±1.8	0.23

Abbreviations: B2B, basal plus two times bolus insulin therapy; HbA_{1c}, glycated hemoglobin; DTSQ, Diabetes Treatment Satisfaction Questionnaire.

from PPT to B2B should be considered for subjects with poor glycemic control. If B2B is not effective, then basal-bolus insulin therapy should be initiated.

DTSQ scores reflecting treatment satisfaction at the start of the study were not significantly different between the groups when divided by their initial HbA_{1c} level. However, treatment satisfaction increased in subjects who showed an improvement in HbA_{1c} at the end of the study. Better adherence with the insulin regimen might have caused both increased treatment satisfaction and the reduction in HbA_{1c}.

DTSQ scores were determined by the patients themselves, so scores reflecting perceived hyperglycemia or hypoglycemia did not always match actual blood glucose or HbA_{1c} levels. Even if the level of blood control was poor, the DTSQ score reflecting treatment satisfaction may have been high in some patients who do not worry about their glycemic control. The results of the present study may therefore reflect only a relationship between improved convenience of insulin injection and satisfaction with treatment.

The present study has some limitations that should be kept in mind when interpreting its findings. First, it evaluated preliminary data in a small number of patients. Because the statistical power was insufficient to detect a difference in HbA_{1c} levels between two groups, a further study in a larger group of diabetic patients is necessary. Second, we did not record daily variations in blood glucose by self-monitoring of blood glucose or continuous glucose monitoring. Our study evaluated only the change in HbA_{1c} level. It would be necessary to investigate the daily profile of blood glucose in order to clarify the effects of the B2B regimen in detail. Third, the present study was a one-way protocol, ie, switching from PPT to B2B. A crossover design would be desirable to compare the effectiveness of B2B and PPT.

In conclusion, switching from PPT to B2B was noninferior to PPT alone in terms of HbA_{1c} levels in patients with type 2 diabetes mellitus. B2B should be considered, particularly in subjects whose glycemic control is poor despite PPT.

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References

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2012;55(6): 1577–1596.
2. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. *Diabetes Care*. 2008;31(1):20–25.
3. Jain SM, Mao X, Escalante-Pulido M, Vorokhobina N, Lopez I, Ilag LL. Prandial-basal insulin regimens plus oral antihyperglycaemic agents to improve mealtime glycaemia: initiate and progressively advance insulin therapy in type 2 diabetes. *Diabetes Obes Metab*. 2010;12(11):967–975.
4. Schernthaner G, Kopp HP, Ristic S, Muzyka B, Peter L, Mitteregger G. Metabolic control in patients with type 2 diabetes using Humalog Mix50 injected three times daily: crossover comparison with human insulin 30/70. *Horm Metab Res*. 2004;36(3):188–193.
5. Cucinotta D, Smirnova O, Christiansen JS, et al. Three different premixed combinations of biphasic insulin aspart – comparison of the efficacy and safety in a randomized controlled clinical trial in subjects with type 2 diabetes. *Diabetes Obes Metab*. 2009;11(7):700–708.
6. Nakashima E, Kuribayashi N, Ishida K, Taketsuna M, Takeuchi M, Imaoka T. Efficacy and safety of stepwise introduction of insulin lispro mix 50 in Japanese patients with type 2 diabetes inadequately controlled by oral therapy. *Endocr J*. 2013;60(6):763–772.
7. Jacober SJ, Scism-Bacon JL, Zagar AJ. A comparison of intensive mixture therapy with basal insulin therapy in insulin-naïve patients with type 2 diabetes receiving oral antidiabetes agents. *Diabetes Obes Metab*. 2006;8(4):448–455.
8. Kazda C, Hülstrunk H, Helsberg K, Langer F, Forst T, Hanefeld M. Prandial insulin substitution with insulin lispro or insulin lispro mid mixture versus basal therapy with insulin glargine: a randomized controlled trial in patients with type 2 diabetes beginning insulin therapy. *J Diabetes Complications*. 2006;20(3):145–152.
9. Garber AJ, Wahlen J, Wahl T, et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). *Diabetes Obes Metab*. 2006;8(1):58–66.
10. Ito H, Antoku S, Furusho M, et al. The prevalence of the risk factors for atherosclerosis among type 2 diabetic patients is greater in the progressive stages of chronic kidney disease. *Nephron Extra*. 2013;3(1):66–72.
11. Ito H, Mifune M, Abe M, et al. Hypertension resistant to antihypertensive agents commonly occurs with the progression of diabetic nephropathy in Japanese patients with type 2 diabetes mellitus: a prospective observational study. *BMC Nephrol*. 2012;13:48.

12. Ito H, Oshikiri K, Mifune M, et al. The usefulness of the revised classification for chronic kidney disease by the KDIGO for determining the frequency of diabetic micro- and macroangiopathies in Japanese patients with type 2 diabetes mellitus. *J Diabetes Complications*. 2012;26(4):286–290.
13. Seino Y, Nanjo K, Tajima T, et al. Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus. *J Diabetes Investig*. 2010;1(5):212–228.
14. Bradley C. Diabetes Treatment Satisfaction Questionnaire (DTSQ). In: Bradley C, editor. *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetic Research and Practice*. Chur, Switzerland: Harwood Academic Publishers; 1994.
15. Ishii H, Bradley C, Riazi A, Barendse S, Yamamoto T. [The Japanese version of the Diabetes Treatment Satisfaction Questionnaire (DTSQ): translation and clinical evaluation]. *Journal of Clinical and Experimental Medicine*. 2000;192(7):809–814. Japanese.
16. Davies MJ, Gagliardino JJ, Gray LJ, Khunti K, Mohan V, Hughes R. Real-world factors affecting adherence to insulin therapy in patients with Type 1 or Type 2 diabetes mellitus: a systematic review. *Diabet Med*. 2013;30(5):512–524.
17. Mashitani T, Hayashino Y, Okamura S, et al. Patient-reported adherence to insulin regimen is associated with glycemic control among Japanese patients with type 2 diabetes: Diabetes Distress and Care Registry at Tenri (DDCRT 3). *Diabetes Res Clin Pract*. 2013;100(2):189–194.