Comparison of thrice-daily lispro 50/50 *vs* thrice-daily lispro in combination with sulfonylurea as initial insulin therapy for type 2 diabetes

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ABSTRACT

Aims/Introduction: Basal–bolus intensive insulin therapy has been believed to achieve best the glycemic control, but is also complicated as a result of the number of injections required and the type of insulin. This study compared the effect of thrice-daily lispro 50/50 (prandial premixed therapy [PPT]) with thrice daily lispro given in combination with sulfonylureas (prandial bolus therapy with sulfonylurea [PBTS]) as initial insulin therapy for type 2 diabetes.

Materials and Methods: This 24-week, observational, parallel trial comprised a 12-week screening period and a 24-week intervention period for 31 diabetes patients who were poorly controlled with submaximal sulfonylurea. At the start of the intervention period, we commenced thrice-daily insulin injections and divided the 31 patients into either lispro 50/50 with discontinuation of sulfonylurea (PPT, $n = 15$) or lispro added to sulfonylurea (PBTS, $n = 16$). The same dose-adjustment algorithm was used for analyzing both groups; HbA_{1c}, plasma glucose, insulin daily dose, bodyweight and number of hypoglycemic episodes were evaluated.

Results: At the end of the study, HbA_{1c} was significantly improved in both groups ($P < 0.00001$), but no difference was apparent between the groups. The daily doses of PPT were more than those of PBTS, albeit the difference was statistically insignificant ($P = 0.051$). There were significantly fewer hypoglycemic episodes encountered with PPT than with PBTS.

Conclusions: Thrice-daily injections of lispro 50/50 provide an effective and safe regimen as initial insulin therapy for type 2 diabetes. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00025.x, 2010)

KEY WORDS: Insulin lispro, Mid-mix insulin, Hypoglycemia

INTRODUCTION

The guidelines for treatment of type 2 diabetes recommend initiating insulin therapy when HbA_{1c} reaches 7.0[1]–7.5%[2] and above, regardless of lifestyle modification and use of oral antidiabetic drugs (OAD). Most type 2 diabetes patients eventually require insulin therapy[3], which is the most effective strategy for lowering hyperglycemia, has no maximal dose as for OAD and can improve any value of HbA_{1c} to, or close to, the therapeutic goal when used appropriately[1].

When we initiate insulin therapy in patients previously uncontrolled by maximal or submaximal OAD, we use basal insulin first[4–8]. However, this once-daily basal insulin therapy often does not achieve a high treat-to-target rate. Hence, we have also used premixed insulin twice daily, preprandial or basal–bolus intensive insulin therapy. It has been reported that at least preprandial or basal–bolus intensive insulin therapy can achieve a high treat-to-target rate[9]. However, the effectiveness of premix twice daily, in particular low mix, is controversial, resulting in the non-recommendation of these insulin therapies during dose adjustments, except in cases where the proportion of rapid- and intermediate-acting insulins is similar to the fixed proportions available[10,11]. Unlike the low-mix insulin, insulin replacement therapy at a 50/50 ratio (mid-mix) with each meal would mimic physiological insulin secretion more closely than once-daily basal insulin treatment[12–15]. Furthermore, it has been reported that mid-mix thrice daily treatment achieved the target HbA_{1c} value of <7.0% more than prandial bolus insulin therapy without sulfonylurea[13]. Both of these treatments require the same number of injections (thrice daily) and a single type of insulin. We have reported previously that continuation of sulfonylureas after switching to insulin therapy (low-mix twice daily) provides a better chance of strict glycemic control with a lower daily dose of insulin than the discontinuation of sulfonylureas[16]. These findings led us to expect a possible advantage in the addition of sulfonylurea to thrice-daily lispro. In these backgrounds, we compare the effects and safety of thrice-daily mid-mix insulin (lispro 50/50) with thrice-daily lispro combined with sulfonylureas as the initial insulin therapy for type 2 diabetes.

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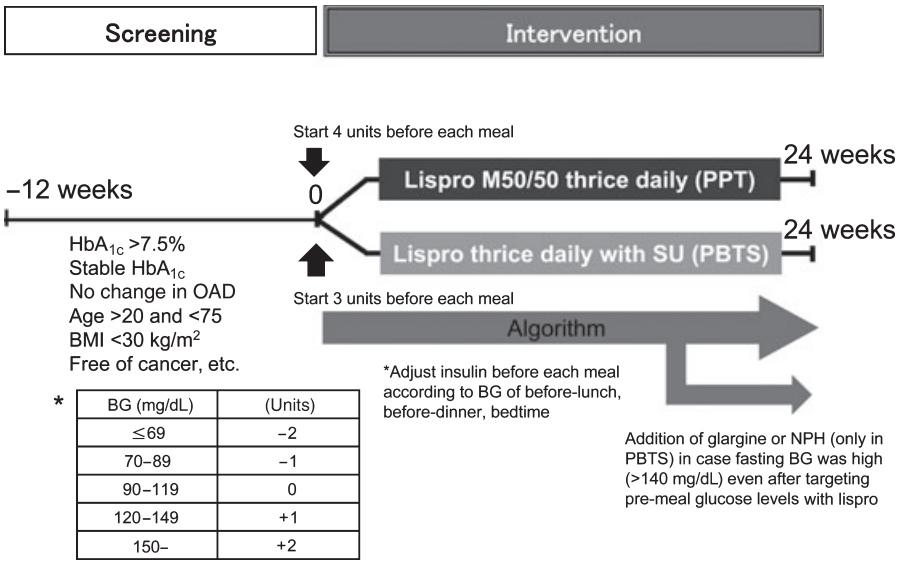

Figure 1 | Study protocol. BG, blood glucose; BMI, body mass index; OAD, oral antidiabetic drugs; NPH, Neutral Protamine Hagedorn insulin; PBTS, prandial bolus therapy with sulfonylurea; PPT, prandial premixed therapy; SU, sulfonylurea.

SUBJECTS AND METHODS

Subjects

We recruited patients who had type 2 diabetes for at least 12 months and who fulfilled the following criteria: (i) had been treated with maximally or submaximally tolerated doses of sulfonylureas along with or without biguanides and/or alpha-glucosidase inhibitors for at least 12 weeks; (ii) were 20–75 years-of-age; (iii) body mass index (weight in kilograms divided by the square of height in metres) ≤30 kg/m^2; and (iv) HbA_{1c} > 7.5% and on a stable diabetes therapy regimen of at least 12-week duration. All patients were insulin-naive and outpatients. Patients were excluded if they had any of the following: (i) concomitant chronic disease including anaemia (hemoglobin ≤ 11.0 g/dL); (ii) kidney disease (plasma creatinine >1.50 mg/dL); (iii) liver pathology (AST > 80 IU/L or ALT > 80 IU/L); (iv) cardiovascular disease; (v) a recent acute illness; (vi) been treated with glitazone within the previous 24 weeks; (vii) proliferative diabetic retinopathy; (viii) been treated with steroids; or (ix) suspected or confirmed to be pregnant. All patients provided informed consent and confirmed their willingness to inject insulin and carry out glucose self-monitoring. The study protocol was approved by the ethics review committee of Juntendo University Hospital, Tokyo, Japan. The study was carried out in accordance with the ethics principles stated in the Declaration of Helsinki.

Study design, insulin initiation and titration

The present study was an open-label, multicentre, observational, parallel study to compare the effect of thrice-daily lispro 50/50 with thrice daily lispro combined with sulfonylurea as the initial insulin therapy for type 2 diabetes. The study consisted of an initial 12-week screening period followed by a 24-week intervention period (Figure 1). Patients visited the clinic every 4 weeks during the study. After the 12-week screening period, we commenced thrice-daily insulin injections and divided the 31 patients by turns into either lispro 50/50 with no sulfonylurea (prandial premixed therapy [PPT], n = 15) or lispro plus sulfonylurea (prandial bolus therapy with sulfonylurea [PBTS], n = 16). Patients were allowed to continue biguanides and/or alpha-glucosidase inhibitors, but were prohibited from changing medications during the study. The initiation dose was 4 units before each meal (12 units per day) for PPT and 3 units before each meal (9 units per day) for PBTS. The sulfonylureas previously prescribed were continued for PBTS, although the dose was decreased to 40 mg for glicrazide, 1 mg for glimepiride, and 2.5 mg for glibenclamide regardless of the dose used in previous therapy, and these doses were not changed during this study. The dose of sulfonylurea at baseline and at 24 weeks, which is shown in Table 1, was indicated as glimepiride. For the conversion of drugs, 40 mg of gliclazide was converted into 1 mg of glimepiride and 2.5 mg of glibenclamide was converted into 2 mg of glimepiride. Baseline uses of sulfonylurea were glimepiride for six patients, glibenclamide for nine patients and gliclazide for one patient in the PPT group. In the PBTS group, baseline uses of sulfonylurea were glimepiride for eight patients, glibenclamide for three patients and gliclazide for four patients.

We adjusted the doses of both types of insulin at breakfast according to blood glucose level of before lunch, those of lunch according to that of before dinner, and those of dinner according to that of bedtime. The same dose-adjustment algorithm was used in both groups (Figure 1). Basal insulin (glargine) could be added in patients on thrice daily PBTS in case fasting

Table 1 | Characteristics of the patients at week 0 (baseline)

	PBTS	PPT	*P* value
n, Sex (male/female)	16 (9/7)	15 (8/7)	NS
Age (years)	64.5 ± 11.4	60.6 ± 1.2	NS
Bodyweight (kg)	60.3 ± 12.2	62.1 ± 10.3	NS
Body mass index (kg/m^2)	22.9 ± 3.0	23.7 ± 2.8	NS
Duration of diabetes (years)	10.0 ± 5.9	12.6 ± 6.4	NS
Systolic blood pressure (mmHg)	127.9 ± 16.3	130.7 ± 19.1	NS
Diastolic blood pressure (mmHg)	73.6 ± 11.5	78.5 ± 15.4	NS
HbA_{1c} (%)	9.2 ± 1.4	10.2 ± 2.1	NS
Dose of sulfonylurea at baseline (glimepiride, mg)	3.5 ± 1.7	3.1 ± 2.4	NS
Dose of sulfonylurea at 24 weeks (glimepiride, mg)	1.6 ± 0.9	0	–
Biguanides	4	2	NS
Thiazolidines	2	2	NS
α-glucosidase inhibitors	5	7	NS

Data are number of patients or mean ± SD. Dose of sulfonylurea at baseline and at 24 weeks was indicated as glimepiride, 40 mg of gliclazide was converted into 1 mg of glimepiride and 2.5 mg of glibenclamide was converted into 2 mg of glimepiride.
NS, not significant; PBTS, prandial bolus therapy with sulfonylurea; PPT, prandial premixed therapy.

plasma glucose was suspended at a high level (>140 mg/dL), even after premeal glucose levels were targeted with lispro. The algorithm for basal insulin was based on fasting blood glucose. The HbA_{1c}, plasma glucose, insulin daily dose, bodyweight and number of hypoglycemic episodes were evaluated.

Clinical measurements

Blood samples for assessment of HbA_{1c} and plasma glucose were obtained every 4 weeks during the study. The patients were provided with blood glucose meters (Glutest Neo or Pro, Sanwa Kagaku Kenkyu-syo, Nagoya, Japan) and diaries, and were instructed to self-monitor blood glucose at least before breakfast, lunch, dinner and bedtime every 3 days. All patients were taught how to recognize the signs and symptoms of hypoglycemia and instructed to obtain and record a blood glucose reading whenever such symptoms occurred. Hypoglycemic episodes were classified as major if blood glucose dropped below 70 mg/dL and was accompanied by neurological symptoms that did not allow patient self-treatment, and as minor if blood glucose was <70 mg/dL, but with symptoms that were managed successfully by the patient or without symptoms. Safety was also assessed by general physical examination, assessment of vital signs, ECG, clinical hematology and chemistry, urinalysis, and reporting of adverse events.

Statistical analysis

All data are expressed as mean ± SD unless otherwise indicated. To compare the parameters in each group, one-way repeated measurement analysis of variance (ANOVA) was carried out using Bonferroni's post-hoc test. To compare the change of HbA_{1c} from baseline, paired *t*-test was carried out. The non-paired *t*-test was used to compare between-group differences. The mean rates of hypoglycemia were compared using the Mann–Whitney *U* test. A *P* value <0.05 was considered statistically significant.

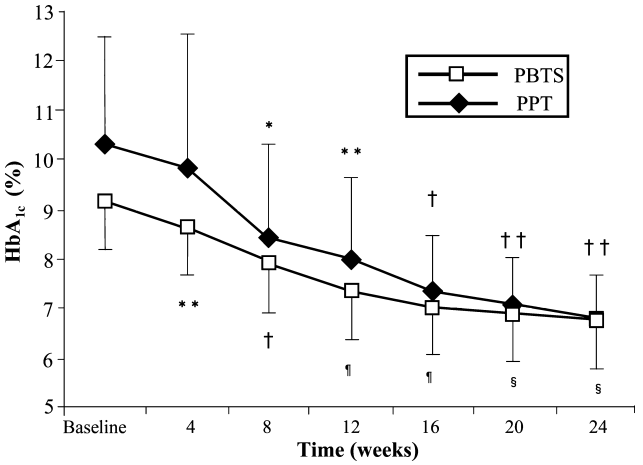

Figure 2 | Changes in mean (±SD) HbA_{1c} of prandial bolus therapy with sulfonylurea (PBTS) and prandial premixed therapy (PPT groups). $^*P < 0.05$, $^{**}P < 0.01$, $^{\dagger}P < 0.001$, $^{\dagger\dagger}P < 0.0001$, $^{\P}P < 0.00001$, $^{\S}P < 0.000001$ *vs* baseline (paired *t*-test).

RESULTS

A total of 37 patients were enrolled in the present study. Six patients (16%) dropped out during the screening phase (two showed improvement of glycemic control by less than 7.5% as measured by HbA_{1c} during the screening period, three changed hospitals, and one was lost to follow-up). A total of 31 patients were finally enrolled and divided by turns into the two treatment groups: the PPT group ($n = 15$) and the PBTS group ($n = 16$). At 0 weeks, the demographic and clinical characteristics were comparable between the two groups (Table 1).

There was no difference in HbA_{1c} between the two groups at 0 weeks. After the 24-week treatment, HbA_{1c} values decreased from 10.3 ± 2.2% to 6.8 ± 0.9% in the PPT group and from 9.2 ± 1.4% to 6.8 ± 1.0% in PBTS patients (Figure 2). HbA_{1c} values significantly improved from week 0 to week 24 in both groups ($P < 0.00001$). At the end of the study, 67% of PPT patients and 69% of PBTS patients achieved the target HbA_{1c} value of <7.0%. Plasma glucose before breakfast improved in both of the groups, with significant differences between the baseline and 24-week results (PPT 207.8 ± 33.4 mg/dL to 142.7 ± 22.1 mg/dL, $P < 0.0005$; PBTS 178.1 ± 39.1 mg/dL to 132.1 ± 43.8 mg/dL, $P < 0.0005$).

The daily insulin doses for PPT patients (0.33 ± 0.11 U/kg per day) were larger than those for PBTS patients (0.25 ± 0.09 U/kg per day), although the difference was statistically insignificant ($P = 0.051$) by the end of the study. Basal insulin was applied to 3 of 16 patients in the PBTS group, because their fasting plasma glucose level was suspended at more

than 140 mg/dL after postprandial injections of insulin lispro. Bodyweight did not change throughout the study in the PBTS patients (58.5–59.1 kg), the PPT group showed statistically significant differences (61.2–63.3 kg, $P < 0.05$) at the end of the study.

No major hypoglycemic episodes or adverse events were observed in either group, although there were significantly more minor hypoglycemic episodes per person per year in PBTS than in PPT patients (PPT 0.60 ± 1.03, PBTS 4.48 ± 7.67, $P = 0.03$).

DISCUSSION

In the present study, we compared the effect of thrice-daily mid-mixed insulin lispro 50/50 (prandial premixed therapy [PPT]) with thrice daily lispro given in combination with sulfonylurea (prandial bolus therapy with sulfonylurea [PBTS]) as initial insulin therapy for type 2 diabetes. This trial showed that both PPT and PBTS significantly reduced HbA_{1c} levels compared with baseline, but that the number of hypoglycemic episodes with PPT was significantly fewer than with PBTS.

The clinical value of PPT with mid-mixed insulin compared with basal insulin therapy has been shown in several studies[12–15]. In contrast, Rosenstock *et al.* reported that PPT had no benefit over basal bolus therapy[17]. However, these investigators also concluded that findings on HbA_{1c} reduction (8.8–6.95%), percentage of patients achieving HbA_{1c} targets (54% with $A_{1c} < 7.0\%$), hypoglycemia and the number of injections required should be considered on a case-by-case basis in the decision-making process of initiating insulin therapy in type 2 diabetes.

After the 24-week treatment, HbA_{1c} values improved remarkably in both groups from week 0 onward. At the end of the study, 67% of PPT patients and 69% of the PBTS patients had achieved the target HbA_{1c} value of <7.0%. The only difference observed between the PPT and PBTS groups was frequency of hypoglycemic episodes. Holman *et al.* also reported a high frequency of hypoglycemia in PBTS patients in the first phase of a 4-T study[9]. These authors compared add-on thrice-daily prandial rapid-acting insulin, twice-daily biphasic insulin, and once-daily (twice-daily if needed) basal insulin to maximally tolerated dose of sulfonylureas (and metformin)[9]. Similar HbA_{1c} values were observed in the groups receiving thrice-daily prandial rapid-acting insulin and twice-daily biphasic insulin, but the group receiving thrice daily prandial rapid-acting insulin had a much higher risk of hypoglycemia with treatment than that given twice-daily biphasic insulin. However, a subsequent study by the same group added a second type of insulin if hyperglycemia became unacceptable during the first year of the study[18]. The addition of basal insulin to the group receiving thrice-daily prandial insulin therapy produced a dramatic decrease in the frequency of hypoglycemia, suggesting that basal insulin could stabilize the effect of bolus insulin. These data were consistent with the differing frequencies of hypoglycemic episodes observed between PPT and PBTS patients in the present study.

The reason why only the PPT patients gained the weight was obscure. While we checked who gained bodyweight one-by-one, the patients whose BMI was originally more than 25 remarkably gained bodyweight in comparison with those who had a BMI less than 25. We might have to pay attention to bodyweight gain while we use PPT for obese patients.

In the present study, three patients in the PBTS group needed the addition of basal insulin to achieve the target for fasting blood glucose. Their clinical backgrounds (including fasting C-peptide, two of which were 1.1 and 2.0 ng/mL, respectively) were not different from those of the rest of the patients in the PBTS group, except for a lower BMI. Mean BMI of the patients in the PBTS group was 22.9, but that of the patients who needed basal insulin was 21.4 (21.2, 22.8 and 20.1, respectively).

The ratio of basal to bolus insulin is generally 1:1 in treatments for type 1 diabetes. This ratio might also be applicable to type 2 diabetes, because increasing this ratio without increasing the total daily insulin dose improved glycemic control in type 2 diabetes patients receiving basal–bolus therapy with glargine[19,20]. In these arguments, endogenous insulin secretion capacity might be important. Unfortunately, we did not examine the complete data of fasting serum C-peptide from which we are able to suspect endogenous insulin secretion. Mean fasting serum C-peptide immune-reactivity levels of the patients who were examined in the present study were 1.7 ± 0.7 ng/mL in the PBTS group (8/16) and 1.7 ± 0.8 ng/mL in the PPT group (7/15), respectively. These data and mean BMI (about 23) might suggest that endogenous insulin secretion capacity, at least in a large part of the patients in the present study, was not so seriously damaged as it was in the patients described by Tamaki *et al.*[20] Lispro 50/50 comprises 50% lispro insulin as bolus insulin and 50% neutral protamine lispro as basal insulin. This prefixed ratio of basal to bolus might enable good glycemic control with a single-insulin therapy without sulfonylureas.

Based on these results, we recommend PPT as a good candidate for initial insulin therapy for type 2 diabetes.

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