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ORIGINAL RESEARCH

Efficacy and Safety of Premixed Human Insulin Combined with Sulfonylureas in Type 2 Diabetic Patients Previously Poorly Controlled with Insulin

Ying-Hua Chen · Hui-Zhi Li · Zhao-Sheng Tang · Lei Xu · Hua Wang · Bo Feng

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ABSTRACT

Introduction: Some type 2 diabetes (T2DM) patients treated with premixed insulin alone or in combination with oral glucose-lowering agents (without sulfonylureas) cannot reach the required glucose targets. Clinical studies have demonstrated that diabetes patients treated with sulfonylureas achieve stable glycemic control, with a low hypoglycemic rate. The aim of our study was to evaluate the efficacy and safety of therapy with the combination of premixed insulin and sulfonylureas.

Methods: A total of 120 patients with T2DM who were unable to achieve glycemic control on premixed human insulin were randomized into four groups, namely, a control group (premixed human insulin only) and three groups receiving combination therapy with premixed human insulin and one of the following sulfonylureas: gliclazide sustained release tablets [Diamicron], glipizide extended release tablets [Glucotrol XL], and glimepiride medium-to-long-acting tablets [Amaryl], with 30 patients in each group. Hemoglobin A1c, blood glucose, and adverse events were assessed at baseline and at the end of the 12-week treatment period.

Results: After treatment for 12 weeks, HbA1c, fasting glucose, and 2-h postprandial glucose levels in the four groups were significantly decreased when compared with baseline ($P < 0.05$). However, there was no difference between the four groups at the end of the study. In the control group, the daily insulin dose had been significantly increased at the end of the follow-up when compared with baseline ($P < 0.05$), while there were no significant changes in premixed insulin dose in the three combination therapy groups. There were no significant differences in adverse events among the four groups.

Conclusion: Insulin combined with sulfonylureas could improve glycemic control without increasing daily insulin dose and adverse events. Based on our results, we consider the combination of premixed insulin and sulfonylureas to be effective and safe for the treatment of T2DM.

Trial Registration: This trial was registered as ChiCTR-TRC-14004751. Trial Registration Date: 5 June 2014.

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Y.-H. Chen · H.-Z. Li · Z.-S. Tang · L. Xu · H. Wang (✉) · B. Feng (✉)
Department of Endocrinology, East Hospital, Tongji University, Shanghai 200120, People's Republic of China
e-mail: wh1762@easthospital.cn

B. Feng
e-mail: fengbo2010@sohu.com

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INTRODUCTION

Premixed insulin is the most commonly used form of insulin in China, and it plays an important role in controlling the blood glucose level of diabetic patients in China. However, some diabetic patients are unable to achieve the target glucose levels with premixed insulin alone or in combination with oral glucose-lowering agents (without sulfonylurea). For these patients, increasing the dose of exogenous insulin could assist in controlling the glucose levels, but it would significantly increase the risk of hypoglycemia and weight gain. Several large clinical studies have demonstrated that at least half of the patients with type 2 diabetes mellitus (T2DM) using sulfonylureas have stable glycemic control, as well as a low rate of hypoglycemia [1, 2]. There are, however, some differences among the sulfonylureas used to treat diabetes with respect to their effects; for example, when compared to other hypoglycemic agents, glimepiride showed improved peripheral insulin sensitivity and better promotion of insulin secretion [3, 4]. To date, no head-to-head clinical studies have been conducted which compare the efficacy and safety of treating patients with T2DM with insulin in combination with different sulfonylureas. The aim of the present study was to evaluate the efficacy and safety of premixed human insulin combined with glipizide extended release tablets (Glucotrol XL), gliclazide sustained release tablets (Diamacron), and glimepiride medium-to-long-acting tablets (Amaryl) in patients with T2DM who had achieved poor glycemic control when on premixed human insulin alone or in combination with oral glucose-lowering agents (without sulfonylurea).

METHODS

Ethics

The study was approved by our local ethics committee (Ethics Committee of East Hospital, Tongji University), and all procedures followed were in accordance with the principles of the Declaration of Helsinki of 1964 and its later amendments or comparable ethical standards. In accordance with Chinese drug laws, the study was registered in the Chinese clinical trial registry (ChiCTR-TRC-14004751), on 5 June 2014. Informed consent for being included in the study was obtained from all subjects. Prior to providing informed consent, all subjects were informed of the study objectives and the risks and benefits of the examinations they would undergo. All subjects are given sufficient time to decide whether they wished to participate in the trial.

Sample Size

The study was designed to be an exploratory study with the aim to evaluate the efficacy and safety of premixed insulin combined with different sulfonylureas. Currently there is insufficient data available which would allow calculation of the sample size needed. However, previous pilot trials [5] investigating the glycemic control in T2DM patients who were poorly controlled on premixed insulin therapy and then switched from premixed insulin to a combination therapeutic regimen of insulin glargine + glimepiride and/or metformin used 17–18 subjects in each group. Therefore, our aim was to include 30 subjects in each group.

Study Subjects

The study was a 12-week prospective, randomized study with an open-label design. A total of 120 patients with T2DM with poor glycemic control (hemoglobin A1c [HbA1c] > 7%) attending the outpatient clinic of the Department for Endocrinology, East Hospital, Tongji University, Shanghai, PR China were recruited to the study. To be included in the study, the patient had to meet the 1999 World Health Organization diagnostic criteria for diabetes; aged > 18 and < 75 years; had previous treatment with premixed insulin alone (or combined with oral glucose-lowering agents without sulfonylurea) for at least 3 months with unsatisfactory glycemic

control (HbA1c > 7%); and had a fasting C-peptide level of > 1.2 ng/ml. All participants were capable of understanding the whole process of study and freely volunteered to participate by signing the informed consent forms. The exclusion criteria were: abnormal liver function, defined as alanine aminotransferase (ALT) and/or glutamic-oxaloacetic transaminase (AST) > 1.5 × upper limits of normal and/or total bilirubin > 2.0 × upper limits of normal; abnormal kidney function, defined as estimated glomerular filtration rate of < 60 ml/min; cardiac failure (New York Heart Association functional class III or IV); currently breastfeeding or pregnant; T2DM concomitant with severe infection, diabetic ketoacidosis, disorders or medications affecting glucose metabolism. The exit criteria were: participants could leave the study at any point of time; participants with poor drug safety or poor compliance were recommended to leave the study; pregnancy or preparing for pregnancy; and intolerance to side effects or other reasons.

Study Design

Eligible patients were randomized to groups using a standard randomization table method. The table of random numbers was generated using the Excel® random number macro (Microsoft Corp., Redmond, WA, USA). A total of 120 patients were sequentially enrolled into four groups, with 30 participants in each group, based on the order of the random number tables: control group (original treatment with premixed insulin); Diamacron group (combination of premixed insulin and Diamacron 60 mg/day), Glucotrol XL group (combination of premixed insulin with Glucotrol XL 10 mg/day) and Amaryl group (combination of premixed insulin and Amaryl 3 mg/day) (Fig. 1). During the follow-up, all participants underwent a venous blood glucose test at the clinic every 2 weeks and a capillary blood glucose test at least 4 times each week at home. The researchers adjusted the dosage of insulin every 2 weeks based on their clinical experience with the aim to reach the glucose targets, namely, (1) fasting glucose level of ≤ 7 mmol/L; (2) 2-h postprandial glucose level of ≤ 10 mmol/L; (3) avoidance of hypoglycemia. The dosage and formulation of oral glucose-lowering agents were maintained during clinical observation. Patients were provided with glucose-monitoring devices and educated on their use. They were instructed to measure the blood glucose levels if there were any signs and/or symptoms of low blood glucose. Hypoglycemia was defined as serum glucose levels of ≤ 3.9 mmol/L. Severe hypoglycemia was defined as hypoglycemic symptoms that are not be relieved by food and by blood glucose levels of ≤ 2.8 mmol/L.

Primary and Secondary Outcomes

The levels of glucose, C-peptide, and body weight were measured at baseline and after 3 months of treatment. The primary outcomes of the study were glycemic control and hypoglycemic events. Secondary outcomes included the dose of premixed human insulin.

Statistical Analysis

SPSS 13.0 software (IBM Corp., Armonk, NY, USA) was used for the data analysis. Data were expressed as percentage and mean ± standard deviation. Enumeration data were compared by the chi-square (χ^2) test. Continuous variables were analyzed for distribution status. Continuous variables with a normal distribution were compared using Student's t test; non-normal distribution data were tested with the two-tailed Mann–Whitney U test. Comparisons between multiple groups were performed using one-way analysis of variance followed by a post hoc Tukey's multiple comparisons test for data with normal distribution or Kruskal–Wallis non-parametric test for non-normal distribution data. Statistical significance was set at $\alpha = 0.05$ (two-sided test).

RESULTS

General Information

A total of 120 participants, with a mean age of 59.3 ± 10.2 years and duration of diabetes of

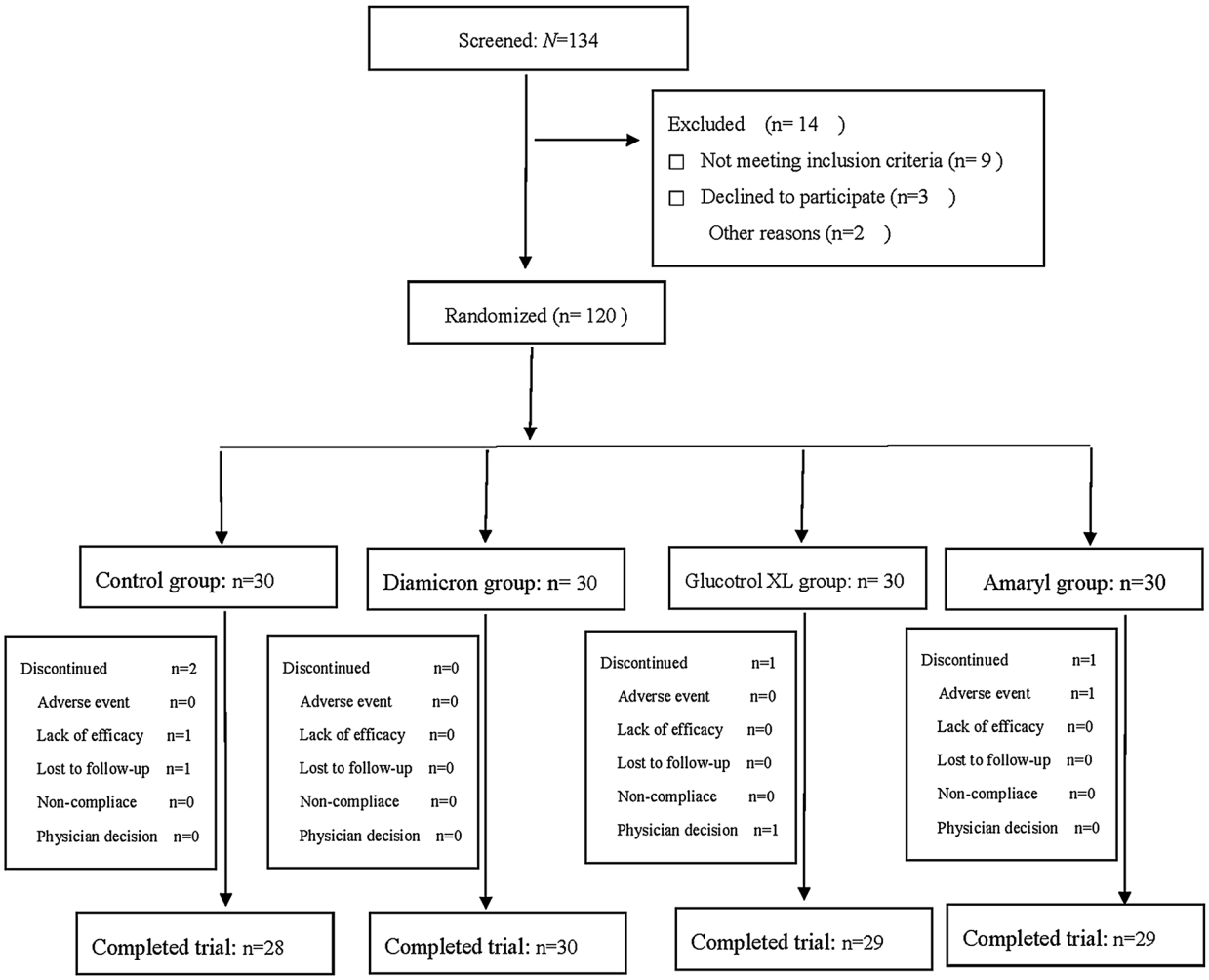

Fig. 1 Flow chart of patient disposition

9.6 ± 6.7 years, were enrolled in the study. At baseline, all patients were being treated with premixed human insulin without sulfonylurea; of these, 51.7% (n = 62) were being treated with premixed insulin alone, 29.2% (n = 35) were receiving combined therapy of premixed insulin and one kind of oral glucose-lowering agents, 15% (n = 18) were receiving combined treatment of premixed insulin with two kinds of oral glucose-lowering agents, and 4.1% (n = 5) were receiving combined treatment with premixed insuin and three kinds of oral glucose-lowering agents concomitantly. Metformin and glucosidase inhibitors were the most commonly used glucose-lowering agents. A total of 116 patients completed the study (Fig. 1). The baseline characteristics of the patients are provided in Table 1; no significant differences were observed between groups.

Glycemic Control and Adverse Events

After treatment for 12 weeks, HbA1c, fasting glucose levels, and 2-h postprandial glucose levels in the four groups were significantly decreased when compared with baseline. However, there was no difference between the four groups at the end of the study (3 months post treatment initiation) (Table 2).

During the follow-up period, a total of 37 hypoglycemic events occurred in 26 cases, including 12 events in seven cases in the

Table 1 Baseline clinical characteristics of patients according to treatment group

	Control group[a]		Diamicron group[a]		Glucotrol XL group[a]		Amaryl group[a]	
	Baseline (n = 30)	Follow-up (n = 28)	Baseline (n = 30)	Follow-up (n = 30)	Baseline (n = 30)	Follow-up (n = 29)	Baseline (n = 30)	Follow-up (n = 29)
Age (years)	58.0 ± 10.1		58.6 ± 12.7		61.7 ± 10.9		59.1 ± 0.2	
Duration of diabetes (years)	9.2 ± 5.8		9.0 ± 2.9		10.3 ± 5.3		9.9 ± 6.4	
Fasting C-peptide (ng/ml)	2.16 ± 0.78	2.44 ± 0.77	2.33 ± 0.94	2.84 ± 1.95	2.08 ± 0.76	2.42 ± 0.90	2.41 ± 0.82	2.42 ± 0.83
Systolic blood pressure (mmHg)	130.1 ± 19.4	124.3 ± 11.8	127.3 ± 23.5	128.6 ± 12.6	131.0 ± 16.3	128.8 ± 13.6	134.3 ± 24.2	129.2 ± 14.5
Diastolic blood pressure (mmHg)	79.3 ± 12.2	76.0 ± 6.8	75.0 ± 10.6	78.9 ± 7.4	78.0 ± 10.1	78.9 ± 8.5	79.0 ± 13.7	77.6 ± 9.8

Values in table are given as the mean ± standard deviation (SD)

[a] Control group: original treatment with premixed insulin; Diamacron group: combination of premixed insulin and Diamacron 60 mg/day; Glucotrol XL group: combination of premixed insulin with Glucotrol XL 10 mg/day; Amaryl group: combination of premixed insulin and Amaryl 3 mg/day

Table 2 Primary and secondary outcomes

Outcomes	Control group		Diamicron group		Glucotrol XL group		Amaryl group	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
FBG (mmol/L)	10.2 ± 2.7	6.7 ± 0.9**	9.7 ± 2.6	5.9 ± 1.0$^{\Delta\Delta}$	10.46 ± 4.1	6.2 ± 1.0$^{\&\&}$	8.8 ± 1.5	6.1 ± 1.1††
2 h BG (mmol/L)	16.7 ± 3.9	11.9 ± 1.7**	16.7 ± 3.7	11.3 ± 2.0$^{\Delta\Delta}$	15.9 ± 5.4	11.1 ± 2.6$^{\&\&}$	15.7 ± 3.1	11.0 ± 2.4††
HbA1c (%)	8.72 ± 1.12	6.60 ± 0.41**	8.25 ± 0.87	6.43 ± 0.73$^{\Delta\Delta}$	8.42 ± 1.20	6.59 ± 0.49$^{\&\&}$	8.37 ± 0.98	6.51 ± 0.56††
Insulin dose (U/day)	36.1 ± 5.5	42.5 ± 9.3**	36.3 ± 5.7	39.4 ± 7.9	38.5 ± 10.0	38.1 ± 6.8	39.4 ± 9.3	39.7 ± 9.1
Body weight (kg)	66.9 ± 10.4	67.0 ± 10.4	68.0 ± 9.7	68.0 ± 9.8	68.6 ± 11.0	68.5 ± 10.9	69.9 ± 13.6	69.8 ± 13.4
Hypoglycemia								
Number of cases		7		7		7		5
Number of events		12		8		9		8

Values in table are given as the mean ± SD

FBG Fasting blood glucose, *2 h BG* 2-h postprandial glucose, *HbA1c* hemoglobin A1c

Significance: Control group 3 months vs. 0 month (baseline): $^{*}P < 0.05$, $^{**}P < 0.01$; diamicron group 3 months vs. 0 month, $^{\Delta}P < 0.05$, $^{\Delta\Delta}P < 0.01$; glucotrol XL group 3 months vs. 0 month, $^{\&}P < 0.05$, $^{\&\&}P < 0.01$; amaryl group 3 months vs. 0 month, $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$

control group, eight events in seven cases in the Diamicron group, nine events in nine cases in the Glucotrol XL group, and eight events in five cases in the Amaryl group (Table 2). There were no statistical differences in the occurrence of hypoglycemia between the groups. There were no significant changes in the body weight of the patients during the treatment course (Table 2). No severe hypoglycemia or other adverse events were reported.

Dose of Premixed Human Insulin

In the control group, insulin dose was 36.1 ± 5.5 units per day at baseline and had been significantly increased to 42.5 ± 9.3 units per day at the end of the follow-up period ($P < 0.01$). There were no significant differences in the daily insulin dose between baseline and the end of the follow-up period in the Diamicron group, Glucotrol XL group, and Amaryl group (Table 2).

DISCUSSION

Premixed human insulin is a mixed formulation of short-acting insulin and intermediate-acting insulin. It is the most commonly used insulin therapy, and there is good compliance to this therapy in Chinese patients as only two injections per day are needed. In patients with T2DM whose blood glucose levels are poorly controlled with premixed insulin, oral glucose-lowering agents, such as metformin, glucosidase inhibitors, dipeptidyl peptidase 4, and thiazolidinedione, are commonly added to the therapeutic regimen. However, to date, but sulfonylureas have not been recommended in the current Chinese guidelines for the prevention and treatment of T2DM (2013 edition) due to hypoglycemic risk and weight gain [6–9]. However, advancements in technology have led to some improvement in the pharmaceutical dosage form and structure of sulfonylureas, and several clinical studies have reported stable glycemic control, with low rate of hypoglycemia and weight gain in patients with T2DM using sulfonylureas [1, 2]. Consequently, concomitant combination therapy with sulfonylureas and insulin may be a safe and effective treatment.

Diamicron, Glucotrol XL, and Amaryl are intermediate-to-long-acting sulfonylureas and are commonly used in China. In the present study, Glucotrol XL, Diamicron, and Amaryl at fixed daily doses were each combined with premixed human insulin and used for the treatment of T2DM patients who had poor glycemic control on premixed human insulin either alone or in combination with glucose-lowering agents. The changes in HbA1c levels, daily insulin dose, and number of hypoglycemic events were evaluated at baseline and at follow-up. Our study demonstrated that after 3 months of treatment, the HbA1c levels in the four groups were significantly decreased compared with baseline values, with no statistical differences between groups. The daily insulin dose in the control group had increased significantly at the end of the follow-up period when compared with baseline values, while no significant changes were observed in the combination treatment groups. These results suggest that the combination therapy of premixed insulin and each of these sulfonylureas could improve glycemic control without the need to increase the daily insulin dose.

There remains an ongoing debate on the clinical use of combination therapy with sulfonylureas and premixed insulin due to the efficacy and the risk of hypoglycemia of such therapeutic regimens [10]. In our study, patients receiving each of the sulfonylureas in combination with premixed insulin reached their targeted glycemic control, similar to the control group, but there were no significant differences in hypoglycemic events and weight gain between the groups. Therefore, for diabetes patients who cannot not reach their target glucose levels with premixed insulin alone or in combination with oral glucose-lowering agents (without sulfonylurea), we suggest that the combination of premixed human insulin and sulfonylureas is a safe and effective treatment.

Due to relatively small sample size and short observation period, clinical studies with a larger sample size and longer course duration are warranted to further confirm our study results.

CONCLUSION

In summary, insulin combined with sulfonylureas were able to control the glycemic levels of our patients with T2DM without any increase in the daily insulin dose and the number of adverse events. We therefore consider the combination of premixed insulin and sulfonylureas to be an effective and safe treatment for patients with T2DM.

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Disclosures. Ying-Hua Chen, Hui-Zhi Li, Zhao-Sheng Tang, Lei Xu, Hua Wang and Bo Feng have nothing to disclose.

Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of our local ethics committee (Ethics Committee of East Hospital, Tongji University) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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