A Study on the Control of Fasting and Postprandial Hyperglycemia by Glargine Insulin Combined with Oral Hypoglycemic Agent

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Abstract

Objective: To investigate the effect and safety on the control of fasting and postprandial hyperglycemia by glargine insulin combined with oral hypoglycemic agents (OHA).
Methods: 136 T2DM cases with not well controlled hyperglycemia were divided randomly into groups A and B. Groups A and B patients received national glargine and imported glargine respectively in addition to OHA of Metformin and Repaglinide. Blood glucose target rate and the safety, as well as hyperglycemia rate were observed.
Results: Levels of FPG, 2hPG and HbAl c were decreased in post-versus pre-treatment at 2 weeks of treatment. The levels of FPG and 2hPG reached targets at 4 weeks in both groups and HbA1C reached target at 2 months in the schedule of insulin plus OHA. At the end of the study, parameters were improved significantly (all $P<0.01$) in two groups and the differences between 2 groups showed no statistical significance ($P>0.05$). Incidence rates of hyperglycemia were 4.2% and 4.6% in groups A and B respectively ($P>0.05$).
Conclusions: (1) Therapeutic effect is similar between imported and national glargine. (2) Combined glargine and Metformin or Repaglinide schedule is effective and safe.
Keywords: Glargine insulin, Metformin, Repaglinide, Blood glucose.

A strict control over blood glucose may prevent and delay the occurrence of chronic diabetic complication. In the past, neutral protamine hagedorn was needed before bedtime when OHA couldn't produce good effect, but this was easy to cause nocturnal hypoglycemia. Glargine insulin can maintain the insulin concentration close to the physiological basal status for 24 hours. Glargine insulin injected before bedtime can not only reduce the level of morning FPG but control the level of all-day blood glucose. Therefore, T2DM cases with not well controlled blood glucose by oral sulfonylureas were given national and imported glargine insulin in addition to OHA of Metformin and Repaglinide. The levels of FPG and 2h PG hyperglycemia rate were observed in both groups after the treatment in order to provide a safe and effective schedule on the control of blood glucose.

Object and Methods

1. Research Object

Total 136 T2DM cases are hospitalized in our special clinical and endocrinology department and all meet the WHO criteria 1999 for diabetes diagnosis. The level of blood glucose was not well controlled by OHA among these patients before the hospitalization (FPG>7.0retoo/L, 2hPG>10mmol/L, HbAl c>7.5%). In addition, the objects also include hypertension cases, obesity cases, dyslipidemia cases and the cases with obvious impaired hepatic and renal functions as well as T2DM cases in pregnancy and lactation period.

2. Research Methods

All cases were randomized into Basalin (NG) group and Lantus (IG) group. NG group had 71 cases, including 42 male and 29 female; IG group had 65 cases, including 38 male and 27 female. All objects were treated with new schedule after stopping original OHA. NG group patients were given national

glargine insulin-Basalin (manufactured by Gann & Lee Pharmaceutical) via subcutaneous injection once before bedtime; IG group patients were given imported glargine insulin- Lantus (manufactured by Sanofi-Aventis) via subcutaneous injection once before bedtime. The original insulin dosage in both groups was 10U/d, combined with Metformin orally taken. The insulin's and Metformin's dosages were adjusted every 3-4 days according to the levels of FPG and 2hPG after the treatment. Metformin started from 0.25g, orally taken three times each day, maximal <1.5g/d. This trial target was that FPG was controlled at 4.5~6.5mmol/L, 2hPG 4.5~8.0 mmol/L, HbA1c 6.0%~6.5%. If 2hPG still couldn't reach the target 2 weeks in the schedule of treatment, Repaglinide would be given three times each day in the original dosage of 0.5mg per time, maximal <6mg/d. Adjust the dosage of glargine insulin when FGP couldn't reach the target. Both groups were observed for 2 months. Record the frequency of incidence of hypoglycemia which diagnostic criterion was < 4.0mmol/L.

3. Statistical Treatment

The significance analysis of the parameters was completed with t in two groups before and after the treatment.

Results

1. General clinical and biochemical parameters in two groups of diabetic patients (Table 1).

Table-1: General Clinical and Biochemical Parameters in Two Groups of Diabetic Patients ($\bar{X} \pm S$).

Group	n	Age (Year)	Course (Year)	HbA1c (mmol/L)	FPG	2PG (mmol/L)	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
NG	71	53±7	7.6±4.4	8.46±1.83	9.57±2.32	15.76±3.31	26.12	121±9	81±7	4.91±0.86	1.25±0.98	1.31±0.27	3.14±0.89
IG	65	53±8	8.4±5.3	8.41±1.74	9.16±2.17	15.09±2.87	25.97	120±9	80±7	4.83±0.95	1.31±0.83	1.34±0.32	2.98±0.76

NG: national glargine; IG: imported glargine.

The parameters of age, disease course, blood pressure and blood glucose were close between two groups and the differences between them showed no statistical significance (P>0.05).

2. Comparison of the average dosage of medicines in two groups of patients (Table 2).

Table-2: Comparison of the average dosage of medicines per day in two groups of patients.

Group	n	National glargine	Imported glargine	Metformin	Repaglinide
NG	71	16.2	-	1.12	3.5
IG	65	-	15.4	1.06	3.9

The dosages of Basalin, Lantus, Metformin and Repaglinide per person per day were close between groups and the differences between them showed no statistical significance (P>0.05).

3. Changes of biochemical indexes in two groups of patients (Table 3).

Table-3: Changes of FPG.2hPG and HbA1c levels before and after treatments in group A and group B patients ($\bar{\chi} \pm S$).

Group		n	FPG	2hPG	HbA1c
NG	Pre-Tx	71	9.57±2.32	15.76±3.31	8.46±1.83
	2W Post-Tx	68	7.15±1.89	10.12±2.16	7.39±1.08
	4W Post-Tx	63	5.62±0.83	7.58±0.95	6.24±0.76
	8W Post-Tx	61	5.42±0.46	7.14±0.62	5.42±0.35
IG	Pre-Tx	65	9.16±2.17	15.09±2.87	8.41±1.74
	2W Post-Tx	65	7.29±1.52	10.36±1.97	7.42±1.26
	4W Post-Tx	61	5.71±0.78	7.56±0.88	6.35±0.68
	8W Post-Tx	59	5.79±0.35	7.25±0.64	5.66±0.65

VS Pre-Tx, #P<0.05, ##P<0.01.

Levels of FPG, 2hPG and HbA1C were significantly decreased at 2 weeks of treatment in two groups (P<0.05, and P<0.01). Levels of FPG, 2hPG and HbA1C reached the targets respectively at 2 weeks and 4 weeks of treatment in two groups, and the difference between 2 groups showed no statistical significance (P>0.05). After the treatment, the frequency of hypoglycemia in NG group was 3/71 at the incidence rate of 4.2%; the frequency of hypoglycemia in IG group was 3/65 at the incidence rate of 4.6%. The difference of incidence rate between 2 groups showed no statistical significance (P>0.05).

Discussion

The key to prevent and delay the incidence of diabetic complication is to control the level of blood glucose up to the target. The level of blood glucose cannot be well controlled amongst the patients who have long course of disease or are given OHA only. Therefore, T2DM patients should receive insulin as early as possible to reduce the toxicity of hyperglycemia level and protect islet cell b function. According to the trial result, among T2DM patients whose blood glucose level could not be well controlled by OHA only, the levels of FPG, 2hPG and HbA1c were significantly decreased and reached the target when glargine insulin was given in combination with Metformin and repaglinide. The therapeutic effect was similar between these two groups having low incidence rate of hyperglycemia in both. This shows that both national and imported glargine insulin have a pharmacokinetics in conformity with the secretion characteristics of physiological basal insulin and can produce better effect in controlling the level of blood glucose and reducing the incidence rate of hyperglycemia, similar to results as reported. This is possibly because glargine insulin, as a long-action insulin analog, can simulate the secretion of physiological basal insulin of islet cell b and can steadily act for 24 hours without peak value.

In this trial, the levels of FPG and 2hPG in two groups were well controlled via medication in combination with Metformin and Repaglinide, respectively. Metformin can inhibit and delay the gastrointestinal absorption of glucose and strengthen the sensitivity of insulin. Repaglinide can greatly reduce the level of 2hPG and may produce better effect if in combination with Metformin and insulin. If the level of fasting hyperglycemia can't be well controlled by glargine insulin combined with Metformin, Repaglinide may be given to reduce the levels of FPG and 2hPG. It was also found in the trial that two kinds of glargine insulin (Basalin and Lantus) had similar effect on the control of blood glucose. Therefore, glargine insulin combined with Metformin and Repaglinide is a safe and effective schedule on the control of blood glucose.

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