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Original Article

The efficacy of treating newly diagnosed type 2 diabetes with insulin glargine combined with Saxagliptin and their effects on function of β-pancreatic cells

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Abstract: The clinical application of insulin glargine combined with other drugs in treating type 2 diabetes (T2D) is increasingly popular worldwide. But there are few studies about the effects of glargine on function of β-pancreatic cells. Thus we aimed to investigate the efficacy of glargine combined with Saxagliptin on treating newly diagnosed type 2 diabetes and their effects on β-cell function. 120 patients with newly diagnosed T2D, were randomly divided into monotherapy group with glargine and combination therapy group with glargine combined Saxagliptin. With 60 patients in each group, fasting plasma glucose (FPG), 2 hours postprandial blood glucose (PBG2 h) and concentration of glycosylated hemoglobin (HbA1-C) were detected respectively before and after treatment. Meanwhile, insulin and secretion index (FINS/HOMA-IS), the change of insulin resistant index (HOMA-IR), triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) were also detected to evaluate the efficacy of treatment and the effect of drugs on function of β-cells. Some patients experienced adverse events in different degree and were recovered automatically. After treatment, PG, PBG2 h, HbA1-C, HOMA-IR, TG and TC were reduced from baseline ($P<0.05$). The efficacy of combination group was better than monotherapy group ($P<0.05$). After treatment, FINS/HOMA-IS was significantly increased with statistical significant difference in each group and between-group comparison ($P<0.05$). Monotherapy with glargine and combination therapy with glargine combined Saxagliptin could both significantly improve the glycemic and lipid toxicity of newly diagnosed type 2 diabetes and function of β-cells.

Keywords: Insulin glargine, saxagliptin, β-pancreatic cells, newly diagnosed diabetes

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease with the main etiology of dysfunction of insulin secretion in vivo and longtime metabolism disorder and is characterized by elevated blood glucose and could cause dysfunction and failure of general organs such as eyes, kidney, cardiac and nerve system, and dehydration, electrolyte disturbance and acid-base imbalance for some severe patients [1, 2]. With the change of dietary and life habit, the incidence of this disease is on the rise year by year and in tread of young age. Therefore, it is extremely important to investigate clinical drugs for effectively controlling diabetes.

Type 2 diabetes (T2D) is a slowly progressive consuming disease of which main pathology is the whole insulin resistance and hyposecretion of insulin and often combined with the reduction of β-pancreatic cells function, such as impaired of insulin secretion and insulin resistance. And the progress of DM is determined by the level of reduction of β-cell function [1, 2]. To date, the purpose of treating T2D is to protect or improve β-cell function, release insulin resistance and increase or promote insulin secretion [3]. Previous studies indicate that there is 50% β-cell with normal function at the time of newly diagnosed T2D. Thus how to improve the function of β-cell effectively at the early period of the disease is the key to treat newly diagnosed T2D and is an effective measure to control the deterioration of DM [4]. To date intervention of patients' lifestyle is the main clinical treatment of newly diagnosed T2DM and dietary control combined with physical activity are recom-

Table 1. Comparison of age and sex between the two groups

Group	Male/Female (N)	Age (Year)
Monotherapy	29/31	48.22±7.6
Combined therapy	31/29	47.82±8.6
P	1.233	0.95

P>0.05 indicates that there is no statistical significant between the two groups.

Table 2. Summary of adverse events of the two groups

Adverse event	Combination therapy (n)	Monotherapy (n)
Hypoglycemia	2	2
Red	1	0
Swell	1	2
Heat	2	1
Urticaria	0	0
Refraction	1	1
Insulin edema	0	0
Renal function impaired	0	0
Liver function impaired	0	0

mended. Meantime, intensive treatments with insulin or antihyperglycemia drugs with assistant treatment are used to control the progress of DM and some effects are achieved [5].

As a new insulin drug, insulin glargine is compounded by gene and biological technology. This drug is found to have similar titer to human insulin with long time of drug action, stability of plasma concentration and low price and is also a common insulin drug currently available in clinic. Several studies found that treatment with insulin glargine and combined with other drugs could improve the condition of patients with newly diagnosed T2DM and achieved significant effect [6-8]. Saxagliptin is an efficient dipeptidyl peptidases-4 (DPP-4) inhibitor which increases endogenous glucagon-like peptide 1 and level of glucose-dependent insulinotropic polypeptide through selective inhibit DPP-4 and has some effects on glycemic adjustment [9-11].

Insulin glargine has some effects on treating T2D. Meantime, a promising application prospect has been shown when combined with other drugs in treating T2D [4-8]. Therefore, we aimed to investigate the efficacy of insulin glargine combined with Saxagliptin on treating newly diagnosed type 2 diabetes and their effect on β-cell function as well as the values of treating T2D with combination of the two drugs.

Materials and methods

General data

One hundred and two patients with newly diagnosed T2D, aged 26 to 66, who were admitted between December 2013 and December 2014 in The Affiliated Hospital of Beihua University were randomly divided into combination therapy group and monotherapy group with 30 men and 30 women respectively in each group. There was no difference on sex and age between the two groups (*P*>0.05) (**Table 1**). All patients should meet the diagnostic criteria of DM diagnostic criteria of WHO (1990) and inclusion criteria included: (1) All patients were newly diagnosed as T2D, course ≤6 months and were not given any related treatment, such as oral antihyperglycemic, antihyperlipidemic drugs, insulin and so on. (2) Fasting plasma glucose (FPG) of patients was over 11.1 mmol/L one week after life style intervention. (3) All participants were not combined with severe hepatic, kidney and cardiac diseases and had normal blood pressure.

Medication and detecting methods

Medication regimen of the two groups was: Patients in combination therapy group were administrated hypodermic injection of insulin glargine 0.3 U/kg without time limited every day. The doses were adjusted to reach the standard according to FPG statistical results and patients were administrated Saxagliptin 5 mg every day 30 minutes after breakfast at the same time. Patients in monotherapy group were administrated hypodermic injection of insulin glargine 0.3 U/kg with same time as to combination therapy group. All patients were performed dietary control and followed up 3 months. Statistical analysis was performed with unit of month. FPG, 2 hours postprandial blood glucose (PBG2 h) and concentration of glycosylated hemoglobin (HbA1-C) were detected respectively before and after treatment. Meanwhile, insulin and secretion index (FINS/HOMA-IS), the change of insulin resistant index (HOMA-IR), triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) were also detected to evaluate the efficacy of

Table 3. The comparison of detected indicators at baseline and after treatment between the two groups

Group	Time		FPG (mmol/L)	F2hPG (mmol/L)	HbA1-C %	TG (mmol/L)	TC (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)
Combined group	The first month	Baseline	8.7±1.03	16.7±2.13	8.9±1.24	2.9±1.1	6.7±1.23	4.6±1.35	1.2±0.87
		After treatment	7.7±0.93	13.6±1.65	7.7±0.83	2.8±1.3	6.5±1.15	4.5±1.43	1.2±0.69
	t		1.09	1.65	3.67	0.92	0.68	1.01	0.98
	The second month	After treatment	5.6±1.33	9.7±1.13	4.9±1.24	2.1±1.1	5.7±1.23	4.4±1.35	0.9±0.87
	t		1.98	2.09	2.25	1.67	1.62	0.68	1.01
	The third month	After treatment	4.3±0.93	5.6±1.65	3.7±0.83	2.0±1.3	4.5±1.15	4.1±1.43	0.92±0.19
	t		3.56	3.89	4.67	2.01	2.76	0.98	1.24
Monetherapy	The first month	Baseline	8.8±1.05	16.6±2.15	9.0±1.34	2.9±1.0	6.6±1.33	4.7±1.56	1.1±0.88
		After treatment	7.8±0.98	12.9±1.75	7.8±0.88	2.8±1.1	6.5±1.24	4.6±1.33	1.1±0.69
	t		1.03	1.57	1.35	0.67	0.42	0.67	0.99
	*P**		>0.05	<0.05	>0.05	>0.05	>0.05	>0.05	>0.05
	The second month	After treatment	5.9±1.33	10.3±1.13	5.4±1.24	2.3±1.1	5.9±1.13	4.4±1.25	1.0±0.84
	t		2.65	1.89	2.12	1.01	1.64	0.89	1.03
	*P**		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
	The third month	After treatment	4.8±0.93	8.0±1.65	4.5±0.83	1.9±1.3	4.5±1.05	4.2±1.33	1.12±0.49
	t		3.01	3.32	3.87	1.97	2.65	0.76	1.0
	*P**		<0.05	<0.05	>0.05	>0.05	>0.05	>0.05	>0.05

Table 4. Summary of related detection of islet β-cell

Group	FINS	HOMA-IR	HBCI	HOMA-IS
Before treatment	22.36±18.65	5.89±6.32	55.67±89.98	18.96±24.32
Combination therapy	5.86±6.45**	2.34±3.21**	90.36±38.45**	47.32±24.78**
monotherapy	8.76±4.32*	4.78±5.65*	78.47±42.58*	29.34±13.65*

*Compared with baseline, *P*<0.05; **Comparison between groups, *P*<0.05.

treatment and the effect of drugs on function of β-cells.

The safety of medication in each group

According to adverse events of DM patients after high-speed treatment, such as hypoglycemia, insulin allergic reaction (red, swollen and heat in local part and different extend of urticaria in the skin), refraction, insulin edema and hepatic and renal impairment and so on, all patients were followed up and recorded to have analysis on the safety of combination therapy.

Statistical analysis

Statistical analyses were conducted using SPSS 16.0 software. Continuous values were summarized with mean values and standard deviations ($\bar{x} \pm s$). The comparison between before and after treatment in each group was analyzed by using the Student t-test. The comparison between groups was analyzed by One-way ANOVA. The *P* value of less than 0.05 was considered to indicate a statistically significant difference.

Results

The safety of medication in each group

After medication treatment, FPG of patients in both groups reached normal level. Transient hypoglycemia occurred in 2 patients in each group, respectively. Refraction occurred in 1 patient in each group and disappeared soon. No insulin edema, renal and liver impairment occurred in both groups. Other adverse events were shown in **Table 2**. Adverse event was not occurred in most patients, which indicated that there was no severe DM complication with combination therapy or monotherapy and indicated that both treatment regimens were quite safe.

The comparison before and after treatment between the two groups

Except those patients with transient adverse events were dealt with expectant treatment, other patients were strictly treated according to medication regimen. Every month after treatment FPG, TG, PBG2h, TC, HbA1-C, LDL-C, and

HDL-C of patients in each group were detected and summarized. After 3 months treatment, as the results present in **Table 3** indicated that there was no difference on most detected indicators between the two groups. With the progress of the treatment course, all indicators reached normal level in different extend. But the comparison in each group showed that both medication regimens achieved a good efficacy.

Evaluation of β-cell function

At the end of a treatment course (3 months), fasting insulin (FINS), HOMA-IS, HOMA-IR and function index of islet β-cells (HBCI) were detected to evaluate the secretion function of β-cells. The results in **Table 4** showed that FINS, HOMA-IR were reduced after treatment in the two groups ($P<0.05$). HBCI was increased from baseline ($P<0.05$). HOMA-IS was improved and increased from baseline significantly. But between-group comparison showed that the efficacy of combination therapy was much better that monotherapy ($P<0.05$). These results indicated that there were some effects of the two medication regimens on the recovery of β-cells function.

Discussion

DM is a commonest endocrinology and metabolic disease today. With the development of economy, change of lifestyle and increasing work stress, eating too much, few physical activities and aging of population result in the increasing incident of DM every year [12-14]. According to incomplete statistics, the incidence of T2D is on the rise yearly worldwide, especially in backward economical developing countries the incidence is obviously increased fast. Thus, DM has become one the non-communicable diseases which thread our health and life and rank only second to tumor and cardiac diseases [3, 15-18]. As a progress chronic disease, the development of T2D will cause continuous recession of islet β-cells function. Because persistent hyperglycemia and hyperlipid could directly damage function of islet β-cells leading to disorder of cell function and continuous increasing of blood glucose, and finally glucose and lipid toxicity. It is reported that after insulin treatment and lifestyle intervention for a short time, function of islet β-cells in T2DM patients could be partly recovered. To date, medication therapy to control blood glucose at early period, increasing secretion function of islet β-cells, improvement of insulin resistance is the main clinical method to manage patients with T2D, which could promote the recovery of regulation and control of blood glucose in human body [19, 20].

In present study, all patients had symptoms of impaired function of islet β-cells in varying degree with FPG<11.1 mmol/L. Thus the selective patients were available for study which investigates the effect of medication therapy on function of islet β-cells. The two drugs in present study, as mentioned above, had both been proved to have better efficacy in controlling blood glucose clinically. Insulin glargine which is one of the widely used antihypercemia medications has similar effect as human insulin when combined with related receptor and can control basic insulin secretion to achieve treatment purpose with long time effect of over 24 hours. Saxagliptin which is a drug for treating T2D with good efficacy can be used with monotherapy or combination therapy with other drugs, for example, metfomin hydrochloride. But there are few studies on the effect of combination therapy on function of islet β-cells. There is no report about the effect of combination therapy with these two drugs. Whether combination therapy with these two drugs could significantly improve efficacy is the key of our concern. 120 patients with newly diagnosed T2D, were randomly divided into monotherapy group with insulin glargine and combination therapy group with insulin glargine combined Saxagliptin. With 60 patients in each group who were administrated monotherapy and combination therapy, FPG, PBG2h and concentration of HbA1-C were detected respectively before and after treatment. Meanwhile, FINS/HOMA-IS, HOMA-IR, TG, TC, LDL-C and HDL-C were also detected to evaluate the efficacy of treatment and the effect of drugs on the function of islet β-cells. The results showed that efficacy of combination therapy for controlling blood glucose was consistent with the effect of insulin. Positive effect was present in partly recovery of the function of islet β-cells. But the efficacy of combination therapy was superior to monotherapy. All in all, treating newly diagnosed T2D with insulin glargine combined Saxagliptin had a promising application prospect.

Disclosure of conflict of interest

None.

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