Am J Transl Res 2021;13(11):13010-13016
www.ajtr.org /ISSN:1943-8141/AJTR0135829

Original Article

Clinical effects of insulin glargine combined with repaglinide in the treatment of type 2 diabetes

Juan Li[1*], Min Zhao[2*], Mei Liu[3], Kaixi Tang[4], Guoxing Sun[5]

[1]Department of Critical Care Medicine, Taishan Sanatorium of Shandong Province, Tai'an 271000, Shandong Province, China; [2]Department of Pharmacy, Weifang Yidu Central Hospital, Weifang 262500, Shandong Province, China; [3]China Static Dispensing Center of Pharmaceutical and Mechanical Division, The Second People's Hospital of Dongying, Dongying 257300, Shandong Province, China; [4]Department of Pharmacy, Shizhong Maternal and Child Health Hospital of Zaozhuang City, Zaozhuang 277000, Shandong Province, China; [5]Department of Business, Cangzhou People's Hospital Yihe District, Cangzhou 061000, Hebei Province, China. [*]Equal contributors and co-first authors.

Received May 30, 2021; Accepted October 8, 2021; Epub November 15, 2021; Published November 30, 2021

Abstract: Objective: To analyze the clinical effects of insulin glargine combined with repaglinide on the treatment of type 2 diabetes (T2D). Methods: One hundred and twelve T2D patients were divided into two groups based on the treatment strategy, the control group (N=56) receiving insulin glargine and the experimental group (N=56) receiving insulin glargine combined with repaglinide. Clinical effects were analyzed and compared between the two groups. Results: After treatment, the levels of fasting blood glucose (FBG), 2h-postprandial blood glucose (2h-PBG), and glycosylated hemoglobin of the experimental group were significantly lower than those of the control group (P<0.05). The levels of fasting C-peptide (FCP) and 2h-postprandial C-peptide (2h-PCP) of the experimental group were significantly higher than those of the control group (P<0.05) after treatment. Compared with the control group, the therapeutic efficacy was significantly higher (P<0.05), the time to normal blood glucose was notably shorter (P<0.05), and the insulin dosage was considerably lower in the experimental group (P<0.05). The incidence of adverse effects of the experimental group was significantly lower than that of the control group (P<0.05), and the treatment satisfaction of the experimental group was significantly higher than that of the control group (P<0.05). Conclusion: Insulin glargine combined with repaglinide is an effective and safe regimen in clinical practice, which can effectively control the blood glucose level, lower insulin dosage, and reduce adverse effects of T2D.

Keywords: Diabetes, insulin glargine, repaglinide

Introduction

Diabetes is a common endocrine disease with high morbidity among middle-aged and elderly population in China [1, 2]. It is also a dysmetabolic disease with significantly elevated levels of blood glucose as major clinical manifestation and basic feature in chronic patients. Poor blood glucose control may lead to diabetic chronic neuropathy, fundus conjunctival disease, diabetes-related nephropathy, and various clinical complications, which greatly increase the risk of death caused by cardiovascular disease. In severe cases, hyperglycemia may even directly result in life-threatening ketoacidosis [3, 4]. The diagnosis of diabetes cannot only rely on an increase in fasting blood glucose (FBG), other indicators should also be considered for the diagnosis and therapeutic efficacy. FBG reflects the function of pancreatic β-cells and generally indicates the secretory function of basal insulin. C-peptide can reflect the secretory function of pancreatic β-cells, which is used to classify diabetic patients and identify hypoglycemia. Glycosylated hemoglobin is the glycated product of hemoglobin in red blood cells that is attached to glucose from serum. The level of glycosylated hemoglobin only depends on the blood glucose concentration and the interaction time between blood glucose and hemoglobin. Glycosylated hemoglobin can effectively reflect the average blood glucose level of diabetic patients in the past 8 to 12 weeks, which is a gold standard for the

evaluation of blood glucose control and is also an important tool for the diagnosis and treatment of diabetes [5].

Patients usually obtain therapeutic outcomes in a short time after the treatment of insulin glargine, which, however, is not ideal for the control of blood glucose fluctuations. Large doses of insulin glargine may even directly cause discomfort and hypoglycemia [6-8]. The main function and effect of repaglinide are effective control of postprandial hyperglycemia and regulation of postprandial blood glucose fluctuation. Repaglinide is not recommended to use alone to control hyperglycemia, which instead is used as an adjuvant medication to control hyperglycemia fluctuation [9]. Meanwhile, limited studies are reported regarding the efficacy and relevant adverse effects of insulin glargine combined with repaglinide on the treatment of T2D. Thus, further investigations are urgently needed.

This study focused on analyzing and comparing the effects of insulin glargine combined with repaglinide and insulin glargine alone on the blood glucose control, the efficacy of the treatment, the incidence of adverse effects, and the treatment satisfaction of T2D.

Patients and methods

Patients

The patients with T2D who were treated in our hospital from January 1, 2019 to June 30, 2020 were divided into two groups based on the treatment strategy, and their clinical data were retrospectively analyzed. The patients in the control group (N=56) were treated with insulin glargine alone, while patients in the experimental group (N=56) were given insulin glargine combined with repaglinide. The clinical effects were compared and analyzed between the two groups.

Inclusion criteria: Patients were primarily diagnosed as T2D; Patients had taken no specific drugs for controlling hyperglycemia.

Exclusion criteria: Patients with other types of diabetes; patients with complications such as diabetic neuropathy, diabetic fundus disease, or diabetic nephropathy; patients with severe functional damage of important organs; patients complicated with other endocrine diseases; patients with systemic lupus erythematosus and other autoimmune diseases; patients had taken hormones and other drugs that may affect the level of blood glucose; patients with other mental illnesses or unable to cooperate.

This study was approved by the Ethics Committee of our hospital. The patients or their family members understood their conditions and voluntarily signed the informed consent.

Intervention approaches

Both groups of patients were given personalized dietary and appropriate exercise. Meanwhile, both groups were given insulin glargine (3 ml:300 U, Beijing Sanofi Pharmaceutical Co., Ltd., China). The initial dose of insulin glargine was 0.2 U/Kg/d, which was subcutaneously injected at 22:00 every day. The drug dose was adjusted according to the 246 rule [10]. The target of FBG was set as 4.0~7.0 mmol/L. The experimental group was given additional 0.5 mg of repaglinide (0.5 mg:30 tablets, Novo Nordisk Pharmaceutical Co., Ltd., China) via oral administration on the basis of the control group, 3 times/d before meals. In addition to the subcutaneous injection of insulin glargine, the control group was given starch tablets as the placebo. A double-blind study was conducted, by which the test drugs were stored in sealed envelopes and handed over to the investigators. Therefore, neither the investigators nor the participants knew their groups. The observation period was 14 days.

Outcome measures

Primary outcome measures: FBG after treatment, 2h-PBG, glycosylated hemoglobin, FCP, 2h-PCP, therapeutic efficacy (number of patients meeting the blood glucose standard/ total number * 100% after 7 days of treatment), and time to normal blood glucose level (from the start of treatment to the time of blood glucose back to normal value). Fasting blood was collected at 7 am. The standard level of blood glucose was 4.0 to 7.0 mmol/L.

Secondary outcome measures: Insulin dosage, the incidence of adverse effects such as hypoglycemia, dizziness, nausea, vomiting, and malnutrition (number of adverse reactions/

Table 1. Comparison of general information between the two groups of patients (mean ± SD)

	Experimental group	Control group	t/χ^2	P
Case (n)	56	56	-	-
Age (year)	53.4±9.4	55.1±9.0	0.978	0.330
BMI (kg/m^2)	28.33±5.64	27.68±5.35	0.626	0.533
Body weight (kg)	74.32±11.43	73.58±12.09	0.333	0.740
Gender (n)			0.038	0.846
Male	35	34		
Female	21	22		
Combined with other underlying diseases (n)			0.169	0.681
Yes	18	16		
No	38	40		
Fasting blood glucose (mmol/L)	9.59±3.21	9.77±3.15	-0.300	0.765
Mean blood pressure (mmHg)	94.76±11.43	92.97±13.58	0.755	0.452
Malnutrition (n)			0.538	0.463
Yes	3	5		
No	53	51		

total number * 100%), and satisfaction with treatment.

Satisfaction score: Before patients were discharged from the hospital, the satisfaction questionnaire was applied with a total point of 100, in which 90-100 points were very satisfied, 70-89 points were satisfied, and <70 points were not satisfied [6]. Patients/family satisfaction = (number of very satisfied cases + number of satisfied cases)/total number of cases × 100%.

Statistical analysis

SPSS 22.0 and Graphpad Prism5 were applied to analyze the data and figures generating. The counting data were expressed as the number of cases/percentage (n/%), and χ^2 test was used to compare the differences between groups. The quantitative data following normal distribution were presented as Mean ± Standard Deviation (SD). The independent sample t test was used to compare the differences between groups. P<0.05 indicated that the difference between the two groups was statistically significant.

Results

Comparison of general information

There were no uncontrollable accidents and discharges during the treatment. All participants completed the research. The general information of the two groups of patients was compared, and the results showed that there were no significant differences in terms of age, BMI, gender, FBG, presence of other underlying diseases, blood pressure, and state of the nutrition of the body (P>0.05) (**Table 1**).

Comparison of blood glucose and glycosylated hemoglobin

After treatment, the levels of FBG, 2h-PBG, and glycosylated hemoglobin of the experimental group were significantly lower than those of the control group (P<0.001) (**Table 2**).

Comparison of C-peptide between the two groups of patients

After treatment, FCP and 2h-PCP levels in the experimental group were significantly higher than those in the control group (P<0.05) (**Table 3**).

Comparison of therapeutic efficacy between the two groups of patients

The therapeutic efficacy of the experimental group (effective in 53 patients out of 56 in total) was significantly higher than that of the control group (P<0.01), and the time to normal blood glucose level in the experimental group was significantly shorter than that in the control group (P<0.01) (**Table 4**).

Table 2. Comparison of changes in blood glucose indices between the two groups of patients after treatment

	Experimental group	Control group	t	P
Case (n)	56	56		
Fasting blood glucose (mmol/L)	7.01±1.23	8.95±1.56	7.308	<0.001
2h-postprandial blood glucose (mmol/L)	9.00±1.09	11.23±1.64	8.474	<0.001
Glycosylated hemoglobin (%)	6.28±0.56	7.85±1.03	10.021	<0.001

Table 3. Comparison of C-peptide changes between the two groups of patients after treatment

	Experimental group	Control group	t	P
Case (n)	56	56		
Fasting C-peptide (nmol/L)	2.89±0.41	2.35±0.56	5.822	<0.001
2h-postprandial C-peptide (nmol/L)	3.35±0.69	3.03±0.64	2.544	0.012

Table 4. Comparison of therapeutic efficacy and time to normal blood glucose level between the two groups of patients after treatment

	Experimental group	Control group	t/χ^2	P
Case (n)	56	56		
Therapeutic efficacy (effective-noneffective)	53/3	38/18	13.190	<0.001
Time to normal blood glucose level (d)	7.35±0.87	8.33±0.98	5.596	<0.001

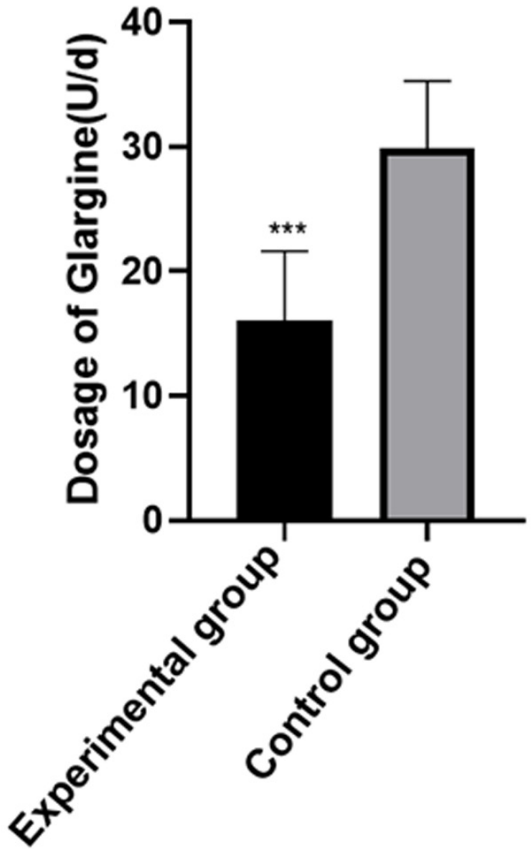

Figure 1. Comparison of insulin dosage between the two groups. Compared with the contr ol group, ***P<0.001.

Comparison of insulin dosage between the two groups of patients

The insulin dosage in the experimental group was significantly lower than that in the control group (P<0.001) (**Figure 1**).

Comparison of the incidence of adverse effects between the two groups of patients

The incidences of adverse effects such as hypoglycemia and dizziness in the experimental group were significantly lower than those in the control group (P<0.05), but there were no significant differences regarding the incidences of malnutrition, nausea, and vomiting (all P>0.05) (**Table 5**).

Comparison of treatment satisfaction between the two groups of patients

Meanwhile, compared with the control group, the treatment satisfaction was also significantly improved in the experimental group (P<0.01) (**Table 6**).

Discussion

T2D is the most common type of diabetes, and it is a metabolic disease characterized by chronic blood glucose elevation. Most T2D

Table 5. Comparison of hospital-related complications between the two groups

	Experimental group (n=56)	Control group (n=56)	χ^2	P
Hypoglycemia (n)	1	7	4.846	0.028
Dizziness (n)	3	10	4.264	0.039
Malnutrition (n)	3	6	1.087	0.297
Nausea (n)	8	10	0.265	0.607
Vomiting (n)	5	6	0.101	0.751
Incidence of adverse effects (%)	35.71	69.64	23.9	<0.001

Table 6. Comparison of treatment satisfaction between the two groups of patients/family members (n, %)

	Experimental group (n=56)	Control group (n=56)	χ^2	P
Very satisfied	36	25		
Satisfied	11	4		
Not satisfied	9	27		
Satisfaction	83.93%	51.79%	16.890	0.001

patients still have a certain insulin secretion function but the secretion of insulin may gradually decrease, resulting in elevation of the blood glucose level [11]. When diet and exercise fail to control the blood glucose level, oral medication is the first choice to treat T2D. For patients with insulin secretion disorders or insulin resistance, the medication cannot control blood glucose within the normal range, which needs exogenous insulin for the treatment [12, 13]. As patients' condition getting worse or becoming resistant to the drug, the medication dosage will be increased. In addition, when blood glucose control is compromised, complications such as coronary heart disease, atherosclerotic heart disease, high blood pressure, retinopathy, and other kidney diseases may be induced [14]. Therefore, the strategy of T2D treatment and medication regimen is of great importance. Repaglinide is a novel oral hypoglycemic drug developed in recent years, which is a derivative of dimethyl phenylacetamide and binds to the enzyme inhibitory receptor on the pancreatic β-cell membrane, thereby stimulating the pancreatic islet cells to secret insulin by [15, 16]. The main advantage of repaglinide is that it can simulate the normal postprandial insulin secretion peak. Even if taken before a meal, it will only stimulate insulin secretion during the meal, but not during fasting that will cause hypoglycemia [17]. Insulin glargine is a biosynthetic long-acting insulin. After subcutaneous injection of insulin glargine, the digestion and absorption of blood glucose can be slowed down, and blood glucose control lasts for 24 hours, which could avoid acute hypoglycemia when fasting at night and control patients' blood glucose at a relatively stable level. This exogenous insulin is much similar to the features of endogenous insulin [18]. It has been shown that the effect of insulin glargine on controlling fasting blood glucose is significantly better than other insulins. However, the control of blood glucose is relatively stable, indicating that the control of PBG is not desirable by insulin glargine [19]. According to the analysis of currently available clinical data, insulin glargine combined with repaglinide reveals high drug safety, which can effectively control both severe postprandial hypoglycemia in patients with early T2D and the elevation of the total volume of fasting and after-meal blood glucose levels as well as reduce the incidence of blood glucose complications, thereby reducing the incidence of hypoglycemia.

The results of our study demonstrate that the combination of these two drugs has advantages of regulating FBG, 2h-PBG, and glycosylated hemoglobin control compared with the group treated with insulin glargine alone. Moreover, the levels of FCP and postprandial C peptide were significantly increased, while the time to normal blood glucose level was significantly reduced in the experimental group, indicating a better therapeutic effect *via* the combined treatment. Especially for postprandial blood glucose control, the combined treatment compensated for the poor postprandial blood glucose control from insulin glargine alone. In addition, regarding the adverse effects, the incidences of hypoglycemia and dizziness in the experimental group are significantly lower than those in the control group, but there were

no significant differences as to the incidences of malnutrition, nausea, and vomiting between the two groups. The reason could be that repaglinide is rapidly absorbed by the gastrointestinal tract, which can be completely excreted after 4-6 hours of medication without any accumulation. Therefore, there are relatively few adverse effects in clinical practice, which further confirms its safety [20-22]. In this study, it has been found that the combination of two drugs can significantly improve patients' satisfaction with the treatment, which is likely due to the significant reduction of complications during the treatment. However, because the sample size is small and the follow-up time is relatively short, which may cause some bias in the results. To better validate the above results, a multi-center prospective study will be conducted with larger samples in the future.

In summary, the combination of insulin glargine and repaglinide is an effective and safe regimen in clinical practice, which can effectively control the elevated blood glucose level, decrease insulin dosage, and reduce adverse effects in the treatment of T2D.

Disclosure of conflict of interest

None.

Address correspondence to: Guoxing Sun, Department of Business, Cangzhou People's Hospital Yihe District, 100 Meters East to The Intersection of Haihe Road and Yingbin Avenue, Yunhe District, Cangzhou 061000, Hebei Province, China. Tel: +86-18131797850; E-mail: sunguoxing.123@163.com

References

[1] Kalyani RS and Raghunath V. Assessment of serum and salivary adiponectin levels in newly diagnosed Type II diabetes mellitus patients. J Oral Maxillofac Pathol 2020; 24: 245-250.

[2] Edmealem A, Ademe S and Tegegne B. Level of physical activity and its associated factors among type II diabetes patients in dessie referral hospital, northeast ethiopia. Diabetes Metab Syndr Obes 2020; 13: 4067-4075.

[3] Hsieh MS, Hung PS, Hsieh VC, Liao SH and How CK. Association between thiazolidinedione use and rheumatoid arthritis risk in patients with type II diabetes, a population-based, case-control study. Int J Clin Pract 2021; 75: e13804.

[4] Lee RSB, Hamlet SM, Moon HJ and Ivanovski S. Re-establishment of macrophage homeostasis by titanium surface modification in type II diabetes promotes osseous healing. Biomaterials 2021; 267: 120464.

[5] Guo F, Zhang Q, Jiang H, He Y, Li M, Ran JJ, Lin J, Tian LW and Ma L. Dietary potato intake and risks of type 2 diabetes and gestational diabetes mellitus. Clin Nutr 2021; 40: 3754-3764.

[6] Arabiat D, Whitehead L, Abu Sheikh B and Afrifa-Yamoah E. Confirmatory factor analysis and reliability of the diabetes treatment satisfaction questionnaire (DTSQ) for arabic speaking patients with type II diabetes. J Multidiscip Healthc 2020; 13: 953-961.

[7] Sulway S and Whitney SL. Advances in vestibular rehabilitation. Adv Otorhinolaryngol 2019; 82: 164-169.

[8] Cetin YS, Ozmen OA, Demir UL, Kasapoglu F, Basut O and Coskun H. Comparison of the effectiveness of Brandt-Daroff vestibular training and Epley Canalith repositioning maneuver in benign Paroxysmal positional vertigo long term result: a randomized prospective clinical trial. Pak J Med Sci 2018; 34: 558-563.

[9] Scholtz AW, Hahn A, Stefflova B, Medzhidieva D, Ryazantsev SV, Paschinin A, Kunelskaya N, Schumacher K and Weisshaar G. Efficacy and safety of a fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg vs betahistine dihydrochloride 16 mg in patients with peripheral vestibular vertigo: a prospective, multinational, multicenter, double-blind, randomized, non-inferiority clinical trial. Clin Drug Investig 2019; 39: 1045-1056.

[10] Russell-Jones D, Dauchy A, Delgado E, Dimitriadis G, Frandsen HA, Popescu L, Schultes B, Strojek K, Bonnemaire M, Roborel de Climens A and Davies M. Take control: a randomized trial evaluating the efficacy and safety of self- versus physician-managed titration of insulin glargine 300 U/mL in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab 2019; 21: 1615-1624.

[11] Vuong Chaney H, Rohmer D and Charpiot A. How to manage vertigo in adult?. Presse Med 2017; 46: 1055-1063.

[12] Baumgartner B and Taylor RS. Peripheral vertigo. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.

[13] Hain T and Cherchi M. Migraine associated vertigo. Adv Otorhinolaryngol 2019; 82: 119-126.

[14] Karatas M. Central vertigo and dizziness: epidemiology, differential diagnosis, and common causes. Neurologist 2008; 14: 355-364.

[15] Sennaroglu L. Treatment algorithm for vertigo. Eur Ann Otorhinolaryngol Head Neck Dis 2020; 137: 237-238.

[16] Zwergal A, Feil K, Schniepp R and Strupp M. Cerebellar dizziness and vertigo: etiologies, di-

agnostic assessment, and treatment. Semin Neurol 2020; 40: 87-96.
[17] Jahn K, Saul AK, Elstner M, Sapa K and Kelleer S. Vestibular rehabilitation therapy and Nintendo Wii balance board training both improve postural control in bilateral vestibulopathy. J Neurol 2018; 265: 70-73.
[18] Walther LE and Blödow A. Current aspects of vertigo and dizziness in advanced age. Hno 2020; 68: 191-198.
[19] Hsu SY, Fang TY, Yeh SC, Su MC, Wang PC and Wang VY. Three-dimensional, virtual reality vestibular rehabilitation for chronic imbalance problem caused by Ménière's disease: a pilot study. Disabil Rehabil 2017; 39: 1601-1606.
[20] Sun LB, Zheng ZY, Wang BQ, Yu WY, Yang J, Guo WJ and Ren HJ. Curative effect analysis of the vestibular rehabilitation training on residual dizziness after successful canalith repositioning maneuvers in patients with benign paroxysmal positional vertigo. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2017; 31: 897-900.
[21] Tramontano M, Medici A, Iosa M, Chiariotti A, Fusillo G, Manzari L and Morelli D. The effect of vestibular stimulation on motor functions of children with cerebral palsy. Motor Control 2017; 21: 299-311.
[22] Boudreau CE, Dominguez CE, Levine JM, Mankin J, Anderson KM, Voges AK and Fosgate GT. Reliability of interpretation of neurologic examination findings for the localization of vestibular dysfunction in dogs. J Am Vet Med Assoc 2018; 252: 830-838.