Clinical Efficacy of Polyethylene Glycol Loxenatide in the Treatment of Obese or Overweight Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objective: To determine the clinical efficacy of Polyethylene Glycol Loxenatide in the treatment of obese or overweight Type 2 Diabetes mellitus (T2DM) patients.

Study Design: A randomised-controlled trial.

Place and Duration of the Study: Department of Endocrinology, Baoding No. 1 Central Hospital, Hebei, China, from January 2020 to January 2022.

Methodology: One hundred overweight and obese patients who were diagnosed with T2DM were prospectively included. They were randomly divided into two groups, with 50 cases in each group. The control group was given oral metformin + subcutaneous insulin injection. The combined treatment group was also given Polyethylene Glycol Loxenatide in addition to the control treatment. The duration of treatment was 6 months for both groups. The clinical efficacy of the two group treatments was compared. The height, body mass, weight index (body mass index (BMI)), total cholesterol (TC), 2-h postprandial blood glucose (2hPBG), high-density lipoprotein cholesterol, fasting insulin (FINS), lipids (triglycerides (TG), low-density lipoprotein cholesterol, homeostasis model assessment of insulin resistance (HOMA-IR) levels, fasting blood glucose (FPG), and glycosylated haemoglobin (HbAlc) were evaluated before and 6 months after the treatment. In addition, any adverse reactions in the two groups were observed.

Results: The overall effective rate of clinical therapy was 92% (46/50) in the combined treatment group, which was higher than that of the control group (76%, 38/50, $p = 0.029$). The weight and BMI levels of the combined treatment group became considerably lower than those of the control group (weight $p = 0.004$; BMI $p < 0.001$), and the levels of FPG, 2hPBG, FINS, HbAlc and HOMA-IR (all $p = <0.001$), and the TG and TC values decreased in both groups (TG $p = 0.001$; TC $p = 0.016$).

Conclusion: PEG Loxenatide considerably affects obese and overweight T2DM patients. With no noticeable adverse reactions, this drug is highly recommended for application and clinical promotion.

Key Words: *Polyethylene Glycol Loxenatide, Type 2 Diabetes mellitus, Obesity, Overweight, Clinical efficacy.*

How to cite this article: Song X, Yao M, Li Z, Guo S, Yin F, Li R. Clinical Efficacy of Polyethylene Glycol Loxenatide in the Treatment of Obese or Overweight Patients with Type 2 Diabetes Mellitus. *J Coll Physicians Surg Pak* 2023; **33(12)**:1390-1394.

INTRODUCTION

Patients with Type 2 Diabetes mellitus (T2DM) are at high risk of suffering from obesity and overweight, which manifest as increased body weight and body mass index (BMI), abdominal obesity, etc.[1,2] Coupled with the administration of insulin, patients suffer from notably increased obesity rates, which can lead to a series of metabolic disorders and cardiovascular complications that affect physical and mental health.[3] Thus, effective therapeutic interventions should be implemented for obese and overweight patients with T2DM.

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Received: August 01, 2022; Revised: October 13, 2023; Accepted: November 25, 2023
DOI: https://doi.org/10.29271/jcpsp.2023.12.1390

Although insulin and glinide present good hypoglycaemic effects, they are ineffective in obese or overweight T2DM patients, and their application is limited.[4,5] Human glucagon like peptide-1 receptor agonists (GLP-1-RAs) exhibit high hypoglycaemic effects and can reduce body weight and regulate glycolipid metabolism in patients.[6,7] Polyethylene Glycol (PEG) Loxenatide is an upgraded drug based on exenatide modified by PEG. It reduces the rate of drug degradation and prolongs the efficacy of a therapeutic agent to achieve the desired therapeutic effect.[8] Currently, limited literature is available on the use of PEG loxenatide in the treatment of obese and overweight patients with T2DM. In this regard, this study aimed to investigate PEG loxetine's clinical efficacy in the treatment of obese or overweight T2DM patients.

METHODOLOGY

This study was a randomised-controlled trial. In accordance with the inclusion and exclusion criteria, 100 obese and overweight patients diagnosed with T2DM in the Department of Endocrinology, Baoding No. 1 Central Hospital, from January 2020 to

January 2022 were selected as the study subjects. They were randomly divided into a combination and a control group using the random number table method. The patients included in this work were followed up for 6 months. This study was approved by the Institutional Ethics Committee of the hospital, and written informed consents were acquired from all participants.

Inclusion criteria were patients who met the diabetes diagnostic criteria of the Chinese guidelines for the prevention and treatment of Type 2 Diabetes (2017 Version);[9] aged 25-65 years; BMI of 24-35 kg/m^2 or waist circumference >90 cm for males and >85 cm for females; glycosylated haemoglobin (HbA1c) of 7-14%; patients who had received Diabetes and obesity-related health education and participated in the standard diet and exercise programmes; without mental diseases; and patients who understood and agreed to participate in this study and signed informed consent form. The exclusion criteria were pregnancy, cognitive impairment, malignant tumour, contraindications or allergies, adult-onset autoimmune diabetes and Type 1 Diabetes, severe or acute chronic diabetes complications, patients who recently used medicines that could affect bone metabolism and those with orthopaedic disease history, and patients with severe organ dysfunction.

The patients included in this study were divided into the combination and control groups at a 1:1 ratio, and the main efficacy index, that is, fasting blood glucose (FPG), was calculated using the formula for estimating the mean sample size of the two groups. Referring to the relevant literature, FPG's $\sigma = 0.83$, $\delta = 0.64$, $\alpha = 0.05$ (two-sided), and $\beta = 0.10$ (one-sided). Thus, $Z_\alpha = 1.96$, and $Z_\beta = 1.28$. The minimum sample size for each group was 35 cases, and 50 patients were finally collected for each group, with a total of 100 patients being included in the study.

$$n = 2 \times (Z_\alpha + Z_\beta)^2 \times \sigma^2/\delta^2$$

Both groups were subjected to lifestyle intervention measures, such as routine diabetic diet control and appropriate functional exercise. In the control group, patients took 1.5 g/day to 2.0 g/day metformin orally and received a subcutaneous injection of insulin before the breakfast, lunch, and dinner. The initial dose was 12 U/day, adjusted based on the specific blood glucose status. In the combination groups. The patients were subcutaneously treated with 0.2 mg PEG Loxenatide once weekly, in addition to the control treatment.

Clinical efficacy was assessed as follows:[10] excellent = FPG and 2-h postprandial blood glucose (2hPBG) levels decreased by >30% and returned to normal values; good = FPG and 2hPBG levels decreased by 10–30% and poor = FPG and 2hPBG levels decreased by <10%. Total effective rate was calculated as significantly excellent + good/n × 100%.

The general data of all patients were collected which comprised of the height, weight, BMI, FPG, 2hPBG, blood lipid indexes (triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting insulin (FINS), HbAlc, homeostasis model assessment of insulin resistance (HOMA-IR), 25 (OH) D3 and BGP levels. A Siemens ADVIA Chemistry XPT automatic biochemical analyser was used to detect glucose metabolism-related indicators, where HOMA-IR = HbAlc * FINS/22.5, and high-performance liquid chromatography was used to determine the HbAlc levels.

Adverse reactions, such as gastrointestinal reactions, liver and kidney damage, pancreatitis, nausea, headache, and hypoglycaemia, were observed.

All were analysed on SPSS 22.0. Enumerated data were expressed *via* n (%) and χ^2 test was performed. The Shapiro-Wilk method was used to detect the normality of data. The data with a continuous normal distribution were expressed as the mean ± standard deviation ($\bar{x} \pm s$). An independent Student's t-test was used for intergroup comparisons, and non-continuous normal data were expressed as the M(P_{25}, P_{75}) and tested using the Mann-Whitney U test. The value of $p < 0.05$ indicated a statistically significant difference.

RESULTS

All patients completed the study, and none were lost to the follow-up. A total of 50 patients were included per group. The combined treatment group comprised of 26 males and 24 females aged 25-62 years old, with an average age of 51.38 ± 6.39 years. The duration of their disease was 1-6 years, and the average disease course was 3.65 ± 1.28 years. The control group consisted of 27 males and 23 females aged 27-65 years, with a mean age of 51.49 ± 6.67 years. The duration of their disease was 1-8 years, with a mean disease duration of 3.77 ± 1.32 years. The differences between the general information on both groups were not statistically significant ($p > 0.05$) but were comparable.

In the combined treatment group, the general effective rate of clinical treatment was 92%, which has considerably higher than that of the control group (76%), and the difference was statistically significant ($p < 0.05$, Table I).

The frequency of adverse reactions was 12% in the combined treatment group, and it was higher than that in the control group (8.00%). The difference was not statistically significant ($p > 0.05$). The duration of adverse reaction symptoms was short in both groups, and they all resolved on their own (Table II).

Prior to the treatment, the differences in body mass, weight and height index levels between both groups were not statistically meaningful ($p > 0.05$). After 6 months of treatment, both groups experienced a decrease in body weight and BMI levels, but the decrease in the combined treatment group was significantly lower than that in the control group. The difference was statistically significant ($p < 0.05$). No significant difference was observed in terms of height between the two groups ($p > 0.05$, Table II).

Before the treatment, no statistically significant differences were observed in the FPG, 2hPBG, FINS, HbAlc, and HOMA-IR

levels between both groups (p>0.05). After 6 months of treatment, the levels decreased in both groups. The difference was statistically significantly lower in the combined treatment group than in the control group (p<0.05, Table II).

The differences in the TG, TC, LDL-C, and HDL-C levels between both groups were not statistically significant before the treatment (p>0.05). After 6 months of the therapy, the LDL-C, TC, and TG levels decreased in both groups, and the values were lower in the combined treatment group than the values in the control group. By comparison, the levels of HDL-C increased and were higher in the combined treatment group than in the control group, with statistically significant differences (p<0.05, Table II).

Table I: Contrasts of clinical efficacy and adverse reactions between the two groups [n (%)].

	Combined group	Control group	χ^2	p*
Clinical efficacy			4.762	0.029
Excellent	31 (62.00)	14 (28.00)		
Good	15 (30.00)	24 (48.00)		
Poor	4 (8.00)	12 (24.00)		
Total effective rate	46 (92.00)	38 (76.00)		
Adverse reactions			0.444	0.505
Gastrointestinal reactions	1 (2.00)	1 (2.00)		
Liver and kidney damage	1 (2.00)	1 (2.00)		
Pancreatitis	0 (0.00)	0 (0.00)		
Nausea	2 (4.00)	1 (2.00)		
Headache	2 (4.00)	1 (2.00)		
Hypoglycaemia	0 (0.00)	0 (0.00)		

$^{\triangle}\chi^2$ test, p <0.05.

Table II: Contrast of height, body weight, BMI, glucose metabolism-related indicators and lipid metabolism indicators between both groups [M(P_{25},P_{75})].

	Combined group	Control group	t	Z*
Height (cm)				
Before treatment	168.00(158.00,174.25)	164.50(152.00,174.25)	0.498	0.498
6 months after treatment	168.00(158.50,174.25)	164.50(153.75,174.25)	0.801	0.423
Body weight (kg)				
Before treatment	82.50(75.00,87.50)	81.50(75.75,86.00)	0.518	0.604
6 months after treatment	74.50(67.00,79.00)*	76.50(71.75,80.25)*	2.498	0.012
BMI (kg/m^2)				
Before treatment	28.50(25.25,30.10)	27.40(24.88,29.05)	0.501	0.616
6 months after treatment	25.80(23.30,26.50)*	26.40(24.15,27.90)*	2.035	0.042
FPG (mmol/L)				
Before treatment	7.25(6.90,7.95)	7.90(6.30,8.40)	1.094	0.274
6 months after treatment	5.40(5.00,6.05)*	7.10(5.50,7.60)*	4.364	<0.001
FPG (mmol/L)				
Before treatment	11.55(9.98,13.53)	11.10(9.98,13.03)	0.221	0.825
6 months after treatment	8.50(6.90,9.63)*	0.05(8.18,11.00)*	3.539	<0.001
FINS (μu/L)				
Before treatment	12.60(11.78,14.70)	12.90(11.05,14.73)	0.166	0.869
6 months after treatment	7.90(7.20,9.03)*	9.90(8.90,11.10)*	5.004	<0.001
HbAlc (%)				
Before treatment	7.60(6.90,8.13)	7.60(6.90,8.13)	0.141	0.887
6 months after treatment	5.60(5.00,6.13)*	6.40(5.60,7.10)*	4.924	<0.001
HOMA-IR				
Before treatment	4.24(3.73,4.93)	4.03(3.66,5.06)	0.300	0.764
6 months after treatment	1.98(1.66,2.41)*	2.75(2.39,3.47)*	6.225	<0.001
TG (mmol/L)				
Before treatment	2.25(1.70,2.83)	2.20(1.58,2.73)	0.024	0.981
6 months after treatment	1.70(1.10,2.20)	2.00(1.38,2.50)	2.932	0.003
TC (mmol/L)				
Before treatment	5.20(4.60,5.50)	5.05(4.50,5.70)	0.204	0.839
6 months after treatment	4.60(4.00,4.90)	4.85(4.30,5.33)	2.074	0.038
LDL-C (mmol/L)				
Before treatment	2.80(2.20,3.10)	2.75(2.30,3.33)	0.428	0.669
6 months after treatment	2.60(2.08,2.90)	2.45(2.00,3.10)	0.383	0.702
HDL-C (mmol/L)				
Before treatment	1.20(0.90,1.40)	1.30(0.98,1.53)	0.516	0.606
6 months after treatment	1.40(1.20,1.75)	1.40(1.08,1.63)	1.499	0.134

*$^{\triangle}$Mann-Whitney U test, *p<0.05 compared with this group before the treatment.*

DISCUSSION

Weight reduction is one of the keys to treat overweight and obese T2DM patients. Obese or overweight T2DM patients suffer from high levels of adipocytes and abnormal metabolism in the body. If no effective weight loss intervention is carried out for a long period, the expression level of adipocyte-derived hormones will be affected, and insulin sensitivity will be reduced, failing to achieve the ideal hypoglycaemic effect.[11,12] Traditionally, metformin has been the primary hypoglycaemic agent for weight loss, but it has limited effects if used alone.[13] PEG Loxenatide, as a novel, long-acting GLP-1-RA, exerts a hypoglycaemic effect while reducing gastrointestinal motility. Affected by this property, the central appetite of patients is suppressed, thereby reducing their food consumption and weight.[14] Cai *et al*. showed that in overweight or obese patients with T2DM, a once-weekly subcutaneous administration of PEG Loxenatide for 16 weeks,[15] in addition to lifestyle interventions or oral antidiabetic medical therapy, resulted in substantially greater weight loss as compared to what was observed with metformin. In this study, PEG Loxenatide was administered to obese and overweight patients with T2DM, and relatively ideal results were observed.

The total effective rate of patients in the combined treatment group was considerably more noticeable than that in the control group. After 6 months of the therapy, the weight and BMI levels in patients in the combined treatment group were lower than those in the control group, indicating that the overweight and obesity of the patients in the combined group were notably improved. Through 6 months of the therapy, the levels of glucose metabolism and insulin function indicators, such as FPG, 2hPBG, FINS, HbAlc, and HOMA-IR, in the combined group were lower than those in the control group. The lipid metabolism indexes, namely the TG and TC levels, were lower than those in the control group, which indicated that the symptoms of glucose and lipid metabolism disorder in the combined treatment group were dramatically changed. Insulin function recovered well. Exenatide is a GLP-1-RA that promotes glucose-dependent insulin secretion and reduces glucagon secretion. This drug also reduces the patient's postprandial blood sugar level and gastric acid secretion and has a protective effect on islet function, which allows patients to reduce their diet. Furthermore, exenatide reduces the patient's body weight and BMI to a certain extent. The pharmacological mechanism of PEG Loxenatide is consistent with that of exenatide. The chemical structure of PEG Loxenatide is changed by amino acid modification, which is completed based on PEG. In addition, this drug becomes a long-acting agent, prolonging its efficacy. In this manner, the number of medications can be reduced. In addition, no statistically significant difference was observed in the incidence of adverse reactions between the two groups, implying that the addition of PEG Loxenatide did not cause significant adverse reactions and had a high safety profile.

Nevertheless, this study encountered shortcomings, such as the small number of samples. In response to this limitation, the inclusion and exclusion criteria will be improved in a future study, and the number of samples will be further expanded for more scientific results.

CONCLUSION

PEG Loxenatide had an ideal therapeutic effect on obese and overweight patients with T2DM, with no evident adverse reactions, hence, presenting a high safety profile.

ETHICAL APPROVAL:
An approval was taken from Ethics Review Committee of Baoding No. 1 Central Hospital, China.

SOURCE OF FUNDING:
This study is supported by the Hebei Province Medical Application Technology Tracking Project (No. GZ2021055).

COMPETING INTEREST:
The authors declared no conflict of interest.

PATIENTS' CONSENT:
Informed, written consents were obtained from the patients.

AUTHORS' CONTRIBUTION:
XS, MY: Designed the study, prepared the manuscript, responsible and accountable for the accuracy or integrity of the work.
ZL: Collected and analysed the data.
SG: Analysed the data and prepared the manuscript.
FY, RL: Participated in acquisition, analysis, and interpretation of data and drafted the manuscript.
All authors read and agreed to the final version of the manuscript to be published.

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