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Original Research Article

Efficacy and safety of a combination of miglitol, metformin and insulin aspart in the treatment of type 2 diabetes

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Abstract

Purpose: *To study the clinical effect of combining insulin aspart with different drugs in the treatment of type 2 diabetes mellitus (T2DM).*
Methods: *Two hundred and thirty-seven T2DM patients admitted to the Endocrinology Department of the Second Affiliated Hospital of Kunming Medical University from March to September 2018 were selected as subjects in this study. Miglitol and metformin were used in combination with insulin aspart in the treatment of T2DM. In addition, data on the effectiveness and safety of different treatment options, such as patient's weight, waist circumference, blood glucose indicators, indices of heart, liver and kidney functions, and incidence of complications were recorded and compared between the two groups.*
Results: *The use of a combination of miglitol and insulin aspart produced an excellent hypoglycaemic effect, and it significantly reduced the incidence of sensory neuropathy in the eyes and distal limbs ($p < 0.05$). The use of combination of metformin and insulin aspart effectively protected the heart and kidney, and prevented hypoglycaemia ($p < 0.05$).*
Conclusion: *These results suggest that treatment with a combination of miglitol and insulin aspart is suitable for patients with T2DM whose blood sugar levels are out of control, while combined treatment with metformin and insulin aspart is more suited for patients who desire to reduce blood sugar and blood lipids through weight loss, and patients with cardiac and renal insufficiency.*

Keywords: *Type 2 diabetes, Insulin aspart, Miglitol, Metformin, Cardiac and renal insufficiency*

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex chronic metabolic disease induced by genetic and environmental factors [1,2]. The major manifestations of T2DM are insulin resistance, hyperglycaemia, and multiple complications (atherosclerosis, ocular retinopathy, acute myocardial infarction, and cerebral ischaemic stroke). These characteristics seriously endanger the health and life of T2DM patients and impose heavy burdens on the society and economy. Statistics from the International Diabetes Federation have revealed that the number of

people suffering from T2DM worldwide has increased to 416.7 million, making its prevention and treatment priority issues at the World Health Organization (WHO) [3,4]. Insulin, the greatest discovery in the 1920s, has saved the lives of many diabetic patients [5,6]. With advancements in medical science and technology, research on human insulin has gradually led to development of analogues of animal insulin and human insulin. Insulin aspart, a human insulin analogue, inhibits the synthesis of liver glycogen and promotes the absorption of blood glucose, thereby normalising blood glucose levels [7]. However, insulin aspart has some drawbacks such as rapid elimination rate and short mean residence time [8]. These impose a need for frequent application of the drug, which significantly increases the risk of hypoglycaemia. In addition, the increase in level of exogenous insulin enhances lipogenesis which is not conducive for weight control in T2DM patients [9,10]. Therefore, there is need for development of safer and more effective treatment strategies for T2DM.

Metformin is the drug of first-choice in the clinical treatment of T2DM. It improves glucose metabolism by reducing hepatic glucose output and accelerating anaerobic glycolysis, thereby enhancing glucose uptake in peripheral tissues, inhibiting glucose absorption in the gastrointestinal tract, and improving glucose metabolism [11]. Metformin reduces blood glucose levels, decreases weight gain, and protects cardiovascular health in T2DM patients. Miglitol is a new α-glucosidase inhibitor which reversibly inhibits the release of α-glucosidase and delays the tissue absorption of glucose by acting on intestinal epithelial cells, thereby eliciting hypoglycaemic effect [12,13]. Miglitol effectively balances blood glucose levels in all parts of the digestive tract, especially postprandial blood glucose levels, and prevents sharp fluctuations in glucose levels [14].

In this study, miglitol and metformin were combined with insulin aspart, and their effectiveness and reliability in the treatment of T2DM were compared.

METHODS

Patients

Two hundred and thirty-seven T2DM patients who were admitted in the Department of Endocrinology of the Second Affiliated Hospital of Kunming Medical University from March to September 2018 and were selected as subjects in this study. Type 2 diabetes patients diagnosed according to the following diagnostic criteria published by the WHO, were included in this study [20]: fasting blood glucose ≥7.00 mol/L, age >18.0 years, and body mass index (BMI) >24.0 kg/m^2. Moreover, T2DM patients who had taken the sulfonylurea hypoglycaemic drug glibenclamide for more than a year, with little effect on blood glucose, were included.

Patients in the following categories were excluded from the study: non-T2DM patients, those with severe heart disease, liver and kidney dysfunction; patients who were allergic to metformin, insulin aspart, or miglitol, as well as those who had malignant tumours. Moreover, pregnant women and breastfeeding women were excluded from the study. The patients were arbitrarily assigned to two cohorts: miglitol-insulin aspart combination group (miglitol + IA50, n = 118), and metformin-insulin aspart combination group (metformin + IA50, n = 119). The study protocol was vetted and endorsed by the ethical committee of the Second Affiliated Hospital of Kunming Medical University. All participants voluntarily signed informed consent, and also followed international guidelines for human studies.

The use of glibenclamide was suspended before treatment in both groups. The miglitol + IA50 group was treated with combination of miglitol and insulin aspart. The initial dose of miglitol was set at 25.0 mg to ensure clinical efficiency; maintenance dose was 50 mg, while maximum dose was fixed at 100 mg. Each dose was administered as appropriate, once before meals, 3 times/day. The initial dose of subcutaneous insulin aspart 50 injection was 0.50 U/kg/day, while the maximum dose was 1.00 U/kg/day, administered 5 min before breakfast and dinner every day. The metformin + IA50 group was treated with combination of metformin and insulin aspart. The initial dose of metformin was set at 250 mg to ensure clinical efficacy, and maintenance dose was set at 0.5 g, while maximum dose was 1,000 mg. Each dose was administered immediately after meals, twice a day. The initial dose of metformin was 250 mg, while the maintenance and maximum doses were 500 and 1,000 mg, respectively. Each dose was administered as appropriate, immediately after meals, twice a day. The dose of insulin aspart 50 injection was the same as that for the Miglitol + IA50 group.

Before and after administering the hypoglycaemic drugs, levels of relevant indicators such body weight, waist circumference, and fasting blood glucose (FPG), 2-h postprandial blood glucose (2hPBG), glycosylated haemoglobin (HbA1c), aspartate

aminotransferase (AST), alanine aminotransferase (ALT), and 24-h urinary microalbumin (UMA) levels of patients in the two treatment groups were determined and recorded for comparison. Moreover, complications of T2DM were recorded. These included diabetic retinopathy (DR), diabetic nephropathy (DKD), diabetic heart disease, and distal limb sensory neuropathy. In order to ensure the scientific relevance and safety of the two treatment strategies, the incidence of adverse events such as hypoglycaemia, nausea, rash, abdominal distention, and abdominal pain during the treatment period, were recorded.

Statistical analysis

The clinical data of subjects in the two treatment groups in this study were analysed using SPSS 23.0 software (IBM SPSS Inc, Chicago, IL, USA). Measured data are expressed as mean ± SD, and differences between the groups were statistically analysed using *t*-test. Count data are expressed as percentage (%), and the difference between the groups was determined using the *u*-test. Values of $p < 0.05$ were taken as indicative of significant differences.

RESULTS

Baseline data

A total of 237 T2DM patients met the inclusion criteria. They comprised 103 males and 134 females. The mean age of the subjects was 54.96 ± 9.98 years, and the mean duration of the disease was 6.68 ± 1.90 years. The general data of the subjects in the study are shown in Table 1. There were no significant differences in age, sex, mass, girth, glycaemic index, and other clinical data between the two groups of subjects ($p > 0.05$).

Changes in weight and waist circumference

The changes in weight and waist circumference of patients after treatment are shown in Figure 1. The weight changes are shown in Figure 1 A. After 24 months of treatment, the average weight of the subjects in the miglitol + IA50 group decreased from 85.22 ± 1.86 to 82.99 ± 1.49 kg, with a mean weight loss of 2.23 kg. In contrast, the mean weight of subjects in the metformin + IA50 group decreased from 86.03 ± 2.31 kg to 80.03 ± 2.26 kg. Changes in waist circumference are shown in Figure 1 B. The mean waist circumference of subjects in the miglitol + IA50 group decreased from 108.15 ± 4.20 to 105.29 ± 3.82 cm. The mean waist circumference of subjects in the metformin + IA50 group decreased from 107.80 ± 3.75 to 102.31 ± 2.76 cm. Clinical data showed that, compared with miglitol + IA50, the metformin + IA50 produced advantages of reductions in weight and waist circumference of the subjects, thereby enabling patients to obtain better benefits in the control of blood glucose and blood lipids.

T2DM blood glucose index

Figure 2 shows the levels of blood glucose indexes. Before treatment, there were no significant differences in levels of FPG, 2hPBG, and HbA1c between the two groups ($p > 0.05$).

Table 1: Baseline characteristics of subjects

Parameter	Miglitol + IA50 n = 118	Metformin + IA50 n = 119	*P*-value
Age (years)	55.28 ± 9.76	54.63 ± 10.19	0.1739
Course of disease (years)	6.53 ± 2.03	6.82 ± 1.77	0.1127
Sex *Male*	52 (44.07%)	51 (42.86%)	0.2366
Sex *Female*	66 (55.93%)	68 (57.14%)	0.2187
Weight (kg)	85.22 ± 4.86	86.03 ± 4.31	0.1528
BMI (kg/m^2)	36.62 ± 2.27	36.89 ± 1.84	0.3342
Waistline (cm)	108.15 ± 14.20	106.8 ± 13.75	0.1273
SBP (mmHg)	137 ± 6	135 ± 7	0.0708
DBP (mmHg)	90 ± 4	87 ± 5	0.0916
FPG (mM)	10.69 ± 2.03	11.17 ± 1.84	0.8524
2hPBG (mM)	15.83 ± 1.98	16.57 ± 2.44	0.6413
HbA1c (%)	8.76 ± 1.58	9.23 ± 1.17	0.7975
TG (mg/dL)	2.69 ± 0.59	2.54 ± 0.61	0.7280
TC (mg/dL)	5.73 ± 1.18	5.96 ± 1.07	0.8014
HDL-C (mg/dL)	0.88 ± 0.13	0.92 ± 0.20	0.9672
LDL-C (mg/dL)	3.48 ± 0.76	3.32 ± 0.69	0.6229
CRP (mg/L)	2.41 ± 0.27	2.28 ± 0.19	0.7581
UMA (mg/24 h)	35.69 ± 3.37	37.55 ± 2.81	0.2133

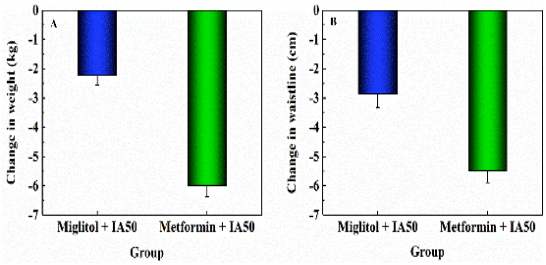

Figure 1: Changes in body weight and waist circumference between the two groups. (A) Body weight of subjects. (B) Waist circumference of subjects

However, 24 months after receiving the different treatments, the mean FPG level in the miglitol + IA50 group decreased to 6.99 ± 0.23 mmol/L (Figure 2 A). The mean level of 2-h PBG was 11.33 ± 0.65 mmol/L (Figure 2 B), while the mean HbA1c level was 6.32 ± 0.23 % (Figure 2 C). In the metformin + IA50 group, the mean FPG level was 7.91 ± 0.37 mmol/L; mean 2-h PBG level was 12.61 ± 0.42 mmol/L, while HbA1c level decreased to 6.91 ± 0.22 %. Although the two groups (miglitol + IA50 and metformin + IA50) effectively controlled blood glucose levels, the miglitol + IA50 group had better blood glucose-lowering effect (p < 0.05), with patients' blood glucose levels closer to ideal values.

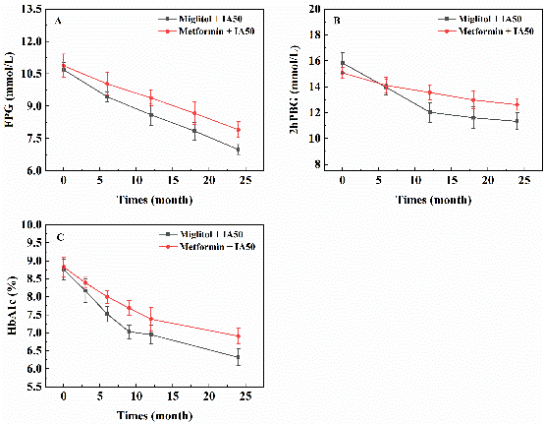

Figure 2: Changes in blood glucose levels in each group of subjects. (A) FPG levels. (B) 2-h PBG levels. (C) HbA1c levels

Heart, liver, and kidney functions

The levels of indexes of heart, liver, and kidney functions are shown in Figure 3. Compared with the miglitol + IA50 group, the metformin + IA50 group had lower AST concentration (Figure 3 A), indicating that metformin + IA50 was more effective in preventing heart and liver complications than the miglitol + IA50 group. As shown in Figure 3 B, both treatment groups had marked and time-dependent reductions in the serum ALT concentrations in the subjects (p < 0.05). The post-treatment levels of UMA in the miglitol + IA50 group and metformin + IA50 group were lower than their corresponding pre-treatment values (Figure 3 C). However, the post-treatment level of UMA in the metformin + IA50 group was closer to the normal value, indicating that the treatment of T2DM patients with metformin + IA50 also produced protective effects on kidney function.

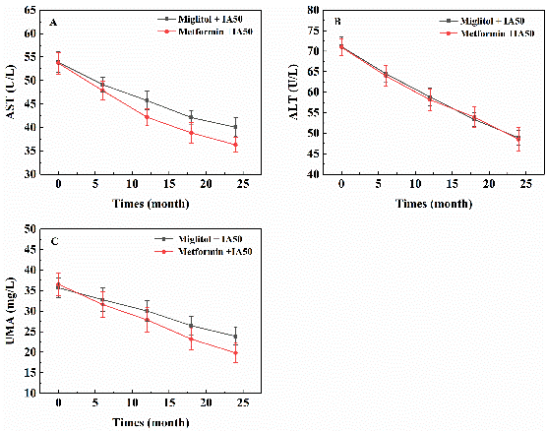

Figure 3: Indices of heart, liver and kidney functions in subjects in the two groups. (A) AST levels. (B) Serum alanine aminotransferase levels. (C) UMA levels

Complications

The complications seen in the T2DM subjects in the two groups during treatment are shown in Figure 4. In the miglitol + IA50 group, 10 subjects had DR, 9 subjects had DKD, 8 patients had diabetic heart disease, while 3 subjects developed diabetic feet, all of which accounted for 25.42 % incidence of complications (Figure 4 A). In the metformin + IA50 group, 14 subjects had DR, 4 patients had DKD, 6 subjects developed diabetic heart disease, while 5 patients had diabetic feet, accounting for 24.37 % incidence of complications (Figure 4 B). The overall incidence of complications in both groups was similar (p > 0.05). However, the two treatment options differed significantly in capacity to prevent various complications. Metformin + IA50 produced excellent protective effects on the heart and kidney functions of T2DM patients. Thus, there were lower prevalence of DKD and diabetic heart disease in the metformin + IA50 group than in miglitol + IA50 group. In contrast, there were lower cases of DR and diabetic foot in the miglitol + IA50 group. Thus, the miglitol + IA50 group produced very effective control of blood glucose.

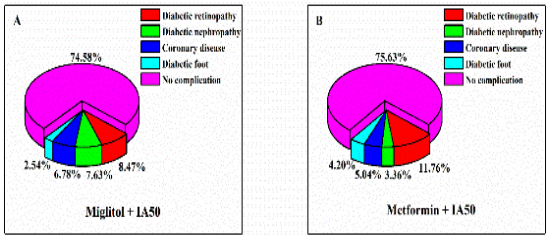

Figure 4: Potential of each treatment to prevent diabetic complications. (A) Miglitol + IA50 group. (B) Metformin + IA50 group

Drug safety

Figure 5 shows the incidence of adverse events in the two groups. In the miglitol + IA50 group, there were 7 cases of hypoglycaemia, 2 cases of nausea and vomiting, 3 cases of rash, and 4 cases of abdominal pain, accounting for 13.56 % incidence of adverse events (Figure 5 A). In the metformin + IA50 group, there were 3 cases of hypoglycaemia, 5 cases of nausea and vomiting, 1 case of rash, and 9 cases of abdominal pain, with 15.13 % incidence of adverse reactions (Figure 5 B). These results indicate that the miglitol + IA50 combination was marginally safer than metformin + IA50. However, there was a significant difference in the frequency of adverse effects between the two treatment options. The number of hypoglycaemic events and incidence of rashes were considerably higher in the miglitol + IA50 group than in the metformin + IA50 group, while there were less incidents of nausea, vomiting, and abdominal pain in the latter group.

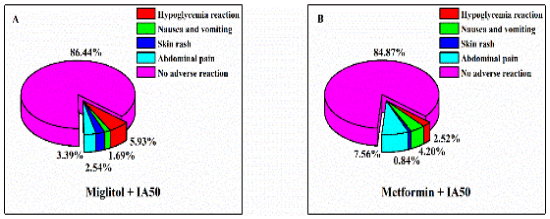

Figure 5: Safety of the two treatment options. (A) Adverse events in miglitol + IA50 group. (B) Adverse events in metformin + IA50 group

DISCUSSION

Although the widespread use of insulin effectively reduces blood glucose levels, frequent use of insulin may easily increase the risk of hypoglycaemia. Therefore, there is need for a more effective and low-risk treatment scheme for T2DM. In this study, the combination of miglitol and metformin with insulin aspart was used to design two treatment plans for T2DM, and their efficacy and safety were compared.

Studies have shown that obesity is a high-risk factor for T2DM. Excess body weight impairs the function insulin receptors, leading to diminished hypoglycaemic effect. In a compensatory attempt to sustain adequate blood glucose lowering effect, the pancreatic islets work continuously to secrete insulin. The resultant stress eventually damages the islet cells, leading to T2DM. Metabolic disorders in T2DM patients lead to aggravation of the degree of obesity. So far, obesity and T2DM have formed a vicious circle [15]. Based on this, weight control has become an important part of the treatment of T2DM patients. The results of the present study showed that metformin + IA50 significantly reduced the body weights of the subjects and decreased their insulin resistance. These effects are beneficial for improvement of the blood glucose lowering effects of the drugs, and for reduction of side effects.

It is known that HbA1c, a product formed by reaction between haemoglobin and blood glucose, is an index that directly reflects the effectiveness of blood glucose control within 8 weeks [16]. In this study, miglitol + IA50 produced significant lowering of levels of blood glucose and HbA1c, increased the oxygen affinity of red blood cells, reduced the occurrence of hypoxia in cells and tissues, and it was beneficial in the prevention of cardiovascular diseases.

Existing data show that complications are the major cause of death in T2DM patients. Therefore, the prevention of complications by control of blood glucose levels can effectively prolong the life of T2DM patients. The transaminases AST and ALT are present in cardiomyocytes, liver cells, and kidneys. Thus, sharp increases in levels of AST and ALT are seen in heart damage and liver damage [17]. The clinical data showed that the two different treatment schemes effectively reduced the levels of AST and ALT and prevented organ damage. Urinary microalbumin is an important index for evaluating DKD, and its values are higher than normal in diabetes patients, indicating that kidney function is affected due to aggravated leakage of urine protein [18]. The results of this study also showed that the combination of metformin + IA50 significantly reduced the growth of renal tubular cells and prevented renal tubular damage.

Safety assessment is a prerequisite for the use of a wide application of drugs in clinical practice. Although insulin aspart alone efficiently lowers blood glucose, hypoglycaemia in diabetic patients is a serious adverse reaction associated with it. The results of this study showed that both

treatments reduced the occurrence of hypoglycaemia in T2DM patients. However, the metformin + IA50 combination lowered blood glucose in a more stable manner, and it reduced the risk of arrhythmia, myocardial ischemia, or myocardial infarction caused by abnormal autonomic nervous system function.

Limitations of the study

In this study, a total of 237 patients with T2DM were included. For a complex disease like T2DM, this sample size is relatively small. Therefore, there is need for more studies with larger population of patients. In addition, not much is known on the mechanism involved in drug responses arising as a result of combination of different drugs. This area requires further research.

CONCLUSION

The results obtained in this study have demonstrated that miglitol + IA50 combination and metformin + IA50 combination produced significant therapeutic benefits in T2DM patients. The miglitol + IA50 combination treatment produced very effective blood glucose-lowering potential. At the same time, it reduced DR and distal limb sensory neuropathy in T2DM patients. Thus, miglitol + IA50 combination treatment is suitable for T2DM patients with uncontrolled blood glucose levels. Metformin + IA50 produced very good weight-loss effect. Thus, this treatment regimen can effectively reduce the occurrence of heart and kidney complications in T2DM patients, while preventing the occurrence of hypoglycaemia. It is suitable for patients who desire to reduce levels of blood glucose and blood lipids through weight loss, and patients with cardiac and renal insufficiency.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Tingyu Ke, Guoliang Cheng, Liping Tan, and Ling Zhao conceived and designed the study. Tingyu Ke, Xiangming Zhou, Yuanyuan Miao, Shigang Du, Jia Wang, Yi Pan, Jingjie Bi, Lin Zhao and Yunxia Zhi collected and analyzed the data, and wrote the manuscript. All authors read and approved the manuscript for publication.

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