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Effects of metformin and insulin on gestational diabetes mellitus: A dual drugs therapy approach

Yalou Jiao[1]*, Zhe Qiao[1], Ruiying Han[1], Jie Du[2], Jian Zhang[3] and Sheng Zhang[4]
[1]Xingtai People's Hospital Department of Reproductive Medicine, HeBei, PR China
[2]Xingtai People's Hospital Department of Pharmacy, HeBei, PR China
[3]Xingtai People's Hospital Department of Endocrinology, HeBei, PR China
[4]Xingtai People's Hospital Department of Emergency, HeBei, PR China

Abstract: This study was aimed to investigate the combined effects of metformin hydrochloride and insulin during gestational diabetes mellitus. A total 136 patients were randomly divided into study and control group. The control group was treated with insulin only while the study group was additionally treated with metformin hydrochloride. Maternal-infant outcomes and the levels of fasting blood glucose (FBG), 2h postprandial blood glucose (2hPG), glycosylated hemoglobin (HbA1c), total cholesterol (TC), total bilirubin (TBil), uric acid (UA) and microalbunminuria (mAlb) before and after treatment were compared. In post-treatment, the levels of FBG, 2h PG and HbA1c were decreased significantly ($p<0.05$) in both groups compared with pre-treatment. The levels of TC, TBil, UA and mAlb in both groups were significantly improved compared with pre-treatment. Levels of TC, UA and mAlb in the study group were significantly lower while TBil level was higher than control group. Compared to the control group, the incidence of gestational hypertension and premature delivery were significantly lower in the study group. There was no significant difference in the incidence of neonatal respiratory distress. The combination of metformin hydrochloride and insulin has significant effect in the treatment of gestational diabetes mellitus.

Keywords: Insulin aspart, metformin hydrochloride, pregnancy outcome.

INTRODUCTION

Gestational diabetes mellitus (GDM) is the initiated occurrence during pregnancy with abnormal glucose tolerance and its incidence has been increasing globally in recent years. The incidence of GDM is 27.5% in India (Guariguata *et al.,* 2014*),* 15%-20% in the US *(*Diabetes Care, 2014*)*, 8%-18% in Canada (Alice*,* 2013) 6.8%-10.4% in China (Hirst *et al.,* 2012*)*, 9.9% in Sri Lanka and 9.8% in Bangladesh (Subrina *et al*., 2014). GDM is closely related to long/short term complications in mother and baby. The short-term effects include that gravidas with GDM have increased risks of preeclampsia and cesarean section with high possibilities of macrosomia, shoulder dystocia as well as neonatal hypoglycemia and in the long run, GDM relates to the rising risks of maternal obesity, metabolic disorder as well as cardiovascular diseases (Carr *et al.,* 2011; Malcolm*,* 2008). At present, GDM is mainly treated by lifestyle intervention and drug intervention in which the latter is mainly conducted by application of insulin, but it is difficult to achieve satisfactory results by single medication, especially for those with insulin resistance (French, 2015). According to some research, metformin hydrochloride has been applied to treat polycystic ovary syndrome (PCOS) and it is found that going on to the metformin after pregnancy can reduce not only the risks of GDM and pregnancy-induced hypertension syndrome but also rate of abortion at early pregnancy, making the application of metformin hydrochloride be attached importance in clinical practices. However, there are few reports on the combination of metformin with insulin aspart in the treatment of pregnancy associated with diabetes (Rotondi *et al.,* 2011).

**Corresponding author:* e-mail: runua.tian2@gmail.com

MATERIALS AND METHODS

General information

A total of 136 patients with gestational diabetes mellitus treated in Second People's Hospital of Dongying city from July 2015 to January 2017 were selected as the objects. The patients were randomly divided into study group and control group with 68 cases in each group. Patients in the study group were aged 22~40 with an average of 30.6±1.5 years; having a gestational age of 24~38 weeks, 31.1±1.4 weeks on average; and including 48 primipara while 20 pluripara cases. Patients in the control group were aged 23~40 with an average of 30.7±1.2 years; having a gestational age of 24~39 weeks with 31.7±1.5 weeks on average; and including 47 primipara while 21 pluripara cases.

Inclusion criteria

Patient was diagnosed with the standard; blood glucose fails to be obviously controlled in patients after conventional interventions on diet, exercise and health education, leading to need of drug therapy; patient was with single ton pregnancy; patient agreed to participate in the study.

Exclusion criteria

Patients with serious diseases of organs such as heart, liver, lung, brain and kidney, hereditary diseases or endocrine diseases; patients who were not ready to be research objects.

Treatment methods

The two groups of pregnant women were given routine interventions on health education, diet control and exercise. The control group were injected with insulin aspart (Novo Nordisk Pharmaceutical Co. Ltd, China) in the subcutaneous tissue before dinner at the initial dose of $0.2\sim0.3IU\cdot kg^{-1}\cdot d^{-1}$ followed by an increase or decrease of 2IU according to the blood glucose level. The study group were treated with metformin hydrochloride (Qilu Pharmaceutical Co., Ltd.) in addition to insulin aspart, at the dose of 0.5g/times, 2 times/d. All pregnant women were treated until the birth of the fetus.

Observation index

(1) The fasting blood glucose (FBG), 2h postprandial blood glucose (2hPG) and glycosylated hemoglobin (HbA1c) were detected; (2) Fasting venous blood (5ml) were collected from patients, the concentrations of total cholesterol (TC), total bilirubin (TBil) and uric acid (UA) were measured using the Backman AU680 automatic biochemical analyzer and the urine was collected with the microalbunminuria level determined by immuno-turbidimetry (ITM); (3) Such complications as gestational hypertension, hypoglycemia, proteinuria, poly-hydramnios, preterm birth and cesarean section in the two groups were recorded; (4) The incidence rates of macrosomia, neonatal hypoglycemia, jaundice and respiratory distress in the two groups were recorded.

STATISTICAL ANALYSIS

Statistical software SPSS (v=21) was used for data analysis, the measurement data was expressed by mean, standard deviation and assessed by t-test, and the count data was analyzed by χ^2 test. P=5% (P<0.05) was considered statistically significant difference.

RESULTS

Pre and post treatment comparison of blood glucose level

After treatment, the levels of FBG, 2h PG and HbA1c were decreased significantly (P<0.05) in both groups compared with before treatment, more significantly in the study group than in the control group, as shown in table 1.

Pre and post treatment comparison of TC, TBil, UA and mAlb levels

After treatment, the levels of TC, TBil, UA and mAlb in the two groups were significantly (P<0.05) improved compared with those before treatment and the levels of TC, UA and mAlb in the study group were significantly lower than those in the control group and the TBil level was significantly higher than that in the control group, with the difference being statistically significant, as shown in table 2.

Comparison of the complications after treatment

The incidence rates of gestational hypertension, polyhydramnios, premature delivery, macrosomia and cesarean section in the study group were significantly lower than those in the control group, and the differences were statistically significant (P<0.05), as shown in table 3.

Comparison of neonatal status

The incidence rates of neonatal hypoglycemia and jaundice in the study group were significantly lower than those in the control group and the difference was statistically significant (P<0.05). There was no significant difference in the incidence rate of neonatal respiratory distress between the two groups (P>0.05), as shown in table 4.

DISCUSSION

Recent epidemiological studies propose that the incidence of diabetes has shown a sharp increase in world population, including the women in childbearing age. Domestic survey results demonstrate that the average incidence of gestational glycometabolism abnormality [including gestational diabetes mellitus (GDM) and impaired glucose tolerance] is 6.6%, with 7.2% in the south and 5.1% in the north GDM leads to a high-risk pregnancy. Besides increasing the incidence of cesarean section, other complications include macrosomia and shoulder dystocia, which can affect the health of the second generation and even their offspring (Shalayel *et al.,* 2013). The etiology of GDM is unknown and it is traditionally thought that GDM is attributed to the increase of insulin-resistant hormones like placental lactogen, prolactin and glucocorticoid as well as progesterone hormone during pregnancy and the resulting insulin resistance condition (Brelje *et al.,* 1993). It has been indicated that hyperglycemia is a key factor of GDM induced poor maternal-infant outcomes, so the early and active intervention on blood glucose control can effectively improve pregnancy results (Young *et al.,* 2016). Insulin aspart has similar activity with insulin and better absorption effect. It can better control postprandial blood sugar and reduce the incidence of hypoglycemia. Nevertheless, some patients may have insulin resistance, always needing insulin sensitizer as supplementary therapy (Deepaklal *et al.,* 2015). Metformin hydro-chloride, as the earliest insulin sensitizer, is commonly used in the treatment of type 2 diabetes and the reproductive abnormalities associated with insulin resistance. It can reduce the synthesis of liver glucogen and lipolysis of fatty tissue, enhance the utilization of

Table 1: Blood glucose level in the two groups before and after treatment (n=68)

Group	FBG (mmol/L)		2h PG (mmol/L)		HbA1c (%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study	8.52±1.63	4.03±0.75	11.57±2.32	5.69±0.5	7.76±1.42	5.27±0.54
Control	8.57±1.68	5.54±1.21	11.59±2.41	8.26±0.6	7.74±1.51	6.31±0.96
t	0.317	11.125	0.204	10.562	0.249	11.005
P	0.562	0.012	0.793	0.016	0.605	0.014

Table 2: TC, TBil, UA and mAlb levels before and after treatment between the two groups (x±s) (n=68)

Group	TC (mmol/L)		TBil (μoml/L)		UA (μoml/L)		mAlb (mg/L)	
	Before Treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study	4.61+0.6	2.57+0.4	8.5±0.5	12.5±0.5	281.7±2	210.1±1	18.05±2	9.41±1.2
Control	4.62+0.6	3.25+0.3	8.46±0.5	10.5±0.5	282.92±1	248±12	18.1±1.2	13.4±1.5
t	1.306	9.233	0.405	9.307	1.448	11.192	0295	9.188
P	0.146	0.011	0.701	0.012	0.157	0.009	0.232	0.016

Table 3: The incidence of complications in the two groups after treatment [case (%)] (n=68)

Group	Gestational hypertension	Macrosomia	Polyhydramnios	Premature delivery	Cesarean section
Study	4(5.9)	0(0)	2(2.9)	1(1.5)	5(7.4)
Control	10(14.7)	6(8.8)	13(19.1)	8(11.8)	12(17.6)
X^2	9.652	6.114	5.933	5.016	5.247
P	0.008	0.019	0.025	0.034	0.038

Table 4: Neonatal status in the two groups [cases (%)] (n=68)

Group	Hypoglycemia	Jaundice	Respiratory distress
Study	3(4.4)	5(7.4)	3(4.4)
Control	7(10.3)	16(23.5)	4(5.9)
X^2	5.993	6.041	1.168
P	0.021	0.019	0.724

glucose in peripheral tissues, delay the glucose absorption into the small intestine and thus improve the sensitivity to insulin (Niromanesh *et al.,* 2012). The results of this study show that FBG, 2hPG and HbA1c levels were significantly decreased, suggesting that metformin has the effect of increasing insulin sensitivity and control blood glucose effectively and comprehensively by interacting with insulin aspart. The maternal-infant outcome in patients with gestational diabetes depends on the degree of glucose control. Adequate control of blood sugar can reduce the maternal and infant complications. According to the present research, the incidence rates of hypertension, polyhydramnios, premature birth, cesarean section, fetal macrosomia and neonatal jaundice were significantly lower, further suggesting that combination of insulin aspart and metformin can improve the pregnancy outcome with effective control of blood glucose.

Because of insulin deficiency or resistance, patients with gestational diabetes may suffer from lipid metabolism disorder, which will decrease the activity of lipoprotease and increase the level of TC. An existing study has shown a close relationship between the level of blood lipid and the maternal-infant outcome in patients with gestational diabetes (Trout *et al.,* 2016). TBil helps to protect cardiovascular system with the inhibitory effect on atherosclerosis. Studies have shown that TBil concentration tends to decrease in GDM patients with the damages to endothelial cells and renal function caused by glycometabolism. Serum uric acid is the metabolite of purine compounds in the body. Its increase may indicate a weakened kidney function and can also indirectly reflex the level of oxygen free radicals. Studies suggest that patients with gestational diabetes have decreased UA excretion from kidney tubules with the resulting increase of UA level, while high-concentrated UA will lead to microvascular and macrovascular injury in diabetic patients. The excretion of micro-albumin (mALB) is very low in the normal population and a slight damage to the glomeruli will obviously increase the level of urine mALB, enabling to reflect the degree of glomerular damage. According to a previous research, the increases

in blood volume, kidney blood flow and glomerular filtration rate during pregnancy will induce the elevation of urinary protein excretion. Furthermore, the hyperglycemic state in patients with gestational diabetes will affect the release of vasoactive substances by endothelial cells, resulting in glomerular hyperfiltration with renal injury and exerting certain effects on maternal - neonatal outcomes (Tynkevich *et al.,* 2015).

The results of this study show that compared with before treatment and the control group, in the study group the levels of TC, TBil, UA and mAlb were significantly improved, the levels of TC, UA and mAlb significantly lower, and the TBil level significantly higher, indicating that metformin combined with insulin aspart can actively improve the levels of TC, TBil, UA and mAlb in patients, but its mechanism still needs to be further studied as a possible important reason for improvement of maternal and infant outcomes.

CONCLUSION

From the findings of this study, it can be concluded: the combination of metformin hydrochloride and insulin aspart has significant effect in the treatment of gestational diabetes mellitus. It can effectively control blood glucose level, reduce the levels of TC, UA and mAlb and improve pregnancy outcome in patients with gestational diabetes mellitus.

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