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Effect of continuous subcutaneous insulin pump infusion on glucolipid metabolism as well as inflammation and oxidative stress in placenta of patients with GDM

Liu Jie✉

Pharmacy Department, Zigong Maternal and Child Health-Care Hospital in Sichuan Province, Zigong City, Sichuan Province, 643000

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ABSTRACT

Objective: To study the effect of continuous subcutaneous insulin pump infusion on glucolipid metabolism as well as inflammation and oxidative stress in placenta of patients with gestational diabetes mellitus (GDM). **Methods:** Patients with GDM who received insulin therapy between March 2013 and May 2016 were selected as the research subjects and randomly divided into multiple subcutaneous insulin injection (MSII) group and continuous subcutaneous insulin pump infusion (CSII) group. Before and after treatment, serum glucolipid metabolism as well as inflammation and oxidative stress inexes in placenta were determined respectively. **Results:** 2 weeks and 4 weeks after treatment, FBG, 1hPBG, 2hPBG, Chemerin, Vaspin and Visfatin levels of both groups of patients were significantly lower than those before treatment and FBG, 1hPBG, 2hPBG, Chemerin, Vaspin and Visfatin levels of CSII group were significantly lower than those of MSII group; after delivery, TNF-α, IL-6, ROS and AGEs levels in placenta of CSII group were significantly lower than those of MSII group. **Conclusion:** Continuous subcutaneous insulin infusion can more effectively improve the glucolipid metabolism and inhibit the inflammation and oxidative stress in placenta of patients with GDM than multiple subcutaneous insulin injection.

1. Introduction

Gestational mellitus (GDM) is the common complication during pregnancy, it is with insulin resistance as the main characteristic, and it will increase the occurrence risk of type 2 diabetes in puerperal after childbirth and the risk of neonatal metabolic disease in adulthood[1]. During pregnancy, the prolactin, estradiol, progesterone and other hormones secreted by the placenta have anti-insulin effect and can cause maternal insulin resistance; in addition, the inflammatory factors and adipokines synthesized by the placenta may also affect maternal sensitivity to insulin and worsen insulin resistance[2,3]. Exogenous supplementation of insulin is the preferred treatment for GDM patients with poor blood sugar control after diet and exercise intervention. Traditional multiple subcutaneous insulin injection (MSII) requires the insulin injection in different parts for many times, the insulin absorption by different parts is different, which can cause increased blood sugar volatility and is not conducive to stable control of blood sugar[4]. Continuous subcutaneous insulin pump infusion (CSII) is the new way of insulin injection developed in recent years, which can simulate the physiological insulin secretion of human body to realize accurate control of blood sugar levels[5]. In order to define the effects of CSII and MSII for GDM, the glucolipid metabolism indexes as well as inflammation and oxidative stress indexes in placenta of patients with GDM were analyzed.

2. Research subjects and methods

2.1Inclusion and exclusion criteria for research subjects

Patients with GDM who were treated in Zigong Maternal and Child Health-Care Hospital between March 2013 and May 2016 were selected as the research subjects, and the inclusion criteria were as follows: (1) diagnosed with diabetes after OGTT at 24-28

✉Corresponding author: Jie Liu, Pharmacy Department, Zigong Maternal and Child Health-Care Hospital in Sichuan Province, Zigong City, Sichuan Province, 643000.
Tel: 0813-2302227; 18081660930
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weeks of gestation; (2) with normal blood sugar before pregnancy; (3) with substandard blood glucose control after nutrition and exercise intervention, and conforming to the insulin treatment indications; (4) signing the informed consent. Exclusion criteria were as follows: (1) associated with hypertensive disorder complicating pregnancy and cholestasis; (2) associated with fetal malformation. A total of 95 puerperae were included, 48 cases were primiparae, 47 cases were multiparae, and the initial time of insulin treatment was at (32.5±5.20) weeks of gestation.

2.2Implementation method of the research

2.2.1Grouping methods

The medical data of 95 patients with gestational diabetes mellitus were retrospectively analyzed, they were divided into multiple subcutaneous insulin injection (MSII) group and continuous subcutaneous insulin pump infusion (CSII) group according to different insulin treatments, MSII group received multiple subcutaneous insulin injection to reduce blood glucose, and CSII group received continuous subcutaneous insulin pump infusion to reduce blood glucose. MSII group, a total of 56 patients, included 29 primiparae and 27 multiparae, the initial time of insulin treatment was at (32.3±5.4) weeks of gestation; CSII group, a total of 39 cases, included 19 primiparae and 20 multiparae, the initial time of insulin treatment was at (32.7±5.1) weeks of gestation. The two groups of patients were not significantly different in general data (P>0.05).

2.2.2 Therapy

CSII group received insulin infusion through two-way trace injection pump WZS-50F6, insulin was NovoRapid insulin aspart, the insulin pump needle was subcutaneously buried in abdomen, 0.4 IU/kg/d was referred to calculate the total amount of insulin, 50% of the total amount was as the base amount and 50% was as the preprandial additional amount, then the blood sugar was monitored and the blood glucose levels were referred to adjust the base amount and preprandial additional amount of insulin. MSII group received preprandial injection of NovoRapid insulin aspart and subcutaneous injection of insulin glargine before sleeping at night, the volume calculation method was the same as that of CSII group, and the blood glucose levels were referred to adjust the base amount and preprandial additional amount of insulin.

2.2.3 Clinical index detection methods

Before treatment as well as 2 weeks and 4 weeks after treatment, fasting venous blood as well as postprandial 1 h and 2 h venous blood was collected from two groups of patients, automatic biochemical analyzer was used to determine FBG, 1hPBG and 2hPBG contents, enzyme-linked immunosorbent assay kits were used to determine the fasting Chemerin, Vaspin and Visfatin contents; after delivery, placental tissue was collected, RIPA lysis buffer was used to extract protein, and enzyme-linked immunosorbent assay kits were used to determine the contents of TNF-α, IL-6, ROS and AGEs.

2.3Statistical methods

SPSS 18.0 software was used to input glucolipid metabolism indexes and placenta indexes, comparison of above data between two groups was by t test and P<0.05 was the standard of statistical significance in differences between two groups.

3.Results

3.1Blood glucose metabolism indexes of two groups of patients

Before treatment as well as 2 weeks and 4 weeks after treatment, analysis of blood glucose metabolism indexes FBG, 1hPBG and 2hPBG between two groups of patients was as follows: before treatment, FBG, 1hPBG and 2hPBG levels were not significantly different between two groups of patients (P>0.05); 2 weeks and 4 weeks after treatment, FBG, 1hPBG and 2hPBG levels of both groups of patients were significantly lower than those before treatment (P<0.05) and FBG, 1hPBG and 2hPBG levels of CSII group were significantly lower than those of MSII group. Differences in above blood glucose metabolism indexes were statistically significant within group before and after treatment as well as between groups after treatment (P<0.05).

3.2 Serum adipocytokine levels of two groups of patients

Table 1.

Comparison of blood glucose metabolism indexes of two groups of patients before and after treatment (mmol/L).

Groups	*n*	Time	FBG	1hPBG	2hPBG
CSII group	56	Before treatment	7.61±0.93	12.57±1.76	10.23±1.52
		2 weeks after treatment	5.14±0.76$^{*\#}$	7.92±0.93$^{*\#}$	6.85±0.91$^{*\#}$
		4 weeks after treatment	5.02±0.71$^{*\#}$	7.73±0.95$^{*\#}$	6.72±0.98$^{*\#}$
MSII group	39	Before treatment	7.57±0.96	12.73±1.92	10.18±1.45
		2 weeks after treatment	6.11±0.78$^{\#}$	9.31±1.13$^{\#}$	8.21±1.02$^{\#}$
		4 weeks after treatment	5.76±0.71$^{\#}$	9.14±1.07$^{\#}$	8.03±0.97$^{\#}$

$^{\#}$: comparison within group before and after treatment, P<0.05; *: comparison between groups after treatment, P<0.05.

Table 2.

Comparison of serum adipocytokine levels of two groups of patients before and after treatment.

Groups	*n*	Time	Chemerin	Vaspin	Visfatin
CSII group	56	Before treatment	9.68±1.14	35.52±5.21	6.78±0.93
		2 weeks after treatment	6.76±0.89*#	25.75±3.26*#	2.87±0.36*#
		4 weeks after treatment	6.23±0.83*#	22.18±2.94*#	2.74±0.32*#
MSII group	39	Before treatment	9.91±1.07	35.91±5.71	6.91±0.89
		2 weeks after treatment	7.98±0.84#	31.21±3.52#	4.52±0.61#
		4 weeks after treatment	7.64±0.77#	27.65±3.42#	4.27±0.55#

#: comparison within group before and after treatment, $P<0.05$; *: comparison between groups after treatment, $P<0.05$.

Before treatment as well as 2 weeks and 4 weeks after treatment, analysis of serum adipocytokines Chemerin (ng/mL), Vaspin (ng/mL) and Visfatin (pg/mL) between two groups of patients was as follows: before treatment, serum Chemerin, Vaspin and Visfatin levels were not significantly different between two groups of patients ($P>0.05$); 2 weeks and 4 weeks after treatment, serum Chemerin, Vaspin and Visfatin levels of both groups of patients were significantly lower than those before treatment ($P<0.05$) and serum Chemerin, Vaspin and Visfatin levels of CSII group were significantly lower than those of MSII group. Differences in above adipocytokines were statistically significant within group before and after treatment as well as between groups after treatment ($P<0.05$).

3.3 Inflammatory response and oxidative stress response indexes in placenta of two groups of patients

After delivery, analysis of inflammatory response indexes TNF-α (ng/mg) and IL-6 (ng/mg) as well as oxidative stress response indexes ROS (IU/mg) and AGEs (nmol/mg) in placenta between two groups of patients was as follows: TNF-α, IL-6, ROS and AGEs levels in placenta of CSII group were significantly lower than those of MSII group. Differences in TNF-α, IL-6, ROS and AGEs levels in placenta were statistically significant between two groups of patients ($P<0.05$).

4.Discussion

Insulin infusion is the preferred treatment for GDM patients with substandard blood sugar control after diet and exercise intervention, the insulin will not cross through the placenta, so using insulin to control prenatal blood glucose is with good security. MSII is currently the most widely used clinical insulin infusion method, but different subcutaneous injection sites can cause differences in insulin absorption into the bloodstream and onset time, and will cause varying degrees of blood glucose fluctuations[6]. CSII is the new insulin infusion method developed in recent years, which uses insulin pump for continuous insulin infusion, can furthest simulate physiological insulin release curve and realize the precise control of blood sugar level, and is conducive to reducing the blood glucose fluctuations in GDM patients and increasing the success rate of blood glucose control[5]. In order to define the effect of two types of insulin infusion on glucose metabolism in patients with GDM, blood sugar levels of two groups of patients before and after treatment were analyzed, and the results showed that FBG, 1hPBG and 2hPBG levels of both group of patients after treatment were significantly lower than those before treatment and FBG, 1hPBG and 2hPBG levels of CSII group after treamtent were significantly lower than those of MSII group. This means that both MSII and CSII can effectively reduce the blood sugar levels in patients with GDM, and CSII has better hypoglycemic effect than MSII.

There is obvious glucolipid metabolism disorder in GDM patients, abnormal lipid metabolism will cause the endocrine function disorder of adipose tissue, and the levels of Chemerin, Vaspin, Visfatin and various other cytokines synthesized and secreted by adipose tissue will change[7,8]. Chemerin can affect insulin receptor substrate-1 phosphorylation level in peripheral tissue so as to antagonize the insulin signaling pathway transmission, reduce the peripheral tissue uptake of glucose and cause insulin resistance[9]. Vaspin and Visfatin are the adipose cytokines that promote peripheral tissue to absorb glucose, the former is a kind of serine protease inhibitor and can increases the peripheral tissue sensitivity to insulin, and the latter can be combined with insulin receptor to start the downstream signaling pathways and simulate the biological effects of insulin[10,11]. In the occurrence and development of GDM, increased secretion of Chemerin can increase maternal insulin resistance, and the increased

Table 3.

Comparison of inflammatory response and oxidative stress response indexes in placenta between two groups of patients.

Groups	*n*	Inflammatory response		Oxidative stress response	
		TNF-α	IL-6	ROS	AGEs
CSII group	56	3.25±0.52	1.46±0.20	0.67±0.09	1.08±0.17
MSII group	39	5.52±0.78	2.18±0.27	1.13±0.13	2.21±0.34
T		8.498	7.281	9.092	11.275
P		<0.05	<0.05	<0.05	<0.05

secretion of Vaspin and Visfatin is regarded as the body's self compensate for insulin resistance. In order to define the effect of two types of insulin infusion on blood lipid metabolism in GDM patients, serum adipocyte factor levels of two groups of patients were analyzed before and after treatment, and the results showed that Chemerin, Vaspin and Visfatin levels of both group of patients after treatment were significantly lower than those before treatment, and Chemerin, Vaspin and Visfatin levels of CSII group after treatment were significantly lower than those of MSII group. This means that both MSII and CSII can effectively regulate the adipose cytokine levels in patients with GDM, and CSII has better adjusting effect on adipose cytokines than MSII.

The abnormal activation of placental inflammation and oxidative stress are thought to be closely related to the development and changes of GDM, the high blood glucose environment in GDM patients will directly affect the placental inflammation and oxidative stress, and the inflammatory factors and oxidative stress products abnormal secreted in the placenta will further promote the development and change of GDM illness[12]. TNF-α and IL-6 are the important inflammatory factors in the placenta, they are synthesized and secreted by mononuclear macrophages, trophocytes and endothelial cells, and can cause inflammation cascade amplification and increase the secretion of other inflammatory mediators in the placenta; after released into the maternal blood circulation, they can affect the insulin sensitivity and cause insulin resistance[13,14]. ROS and AGEs are the main media that mediate oxidative stress in the placenta, and high blood sugar can on the one hand, increase the electron donor in the mitochondrial respiratory chain and promote the production of ROS, and on the other hand, promote the non-enzymtic glyction and increase the generation of AGEs; excessively activated oxidative stress can influence insulin sensitivity through JNK/SAPK p38/MAPK and other ways[15,16]. In the study, analysis of inflammation indexes and oxidative stress indexes in placenta of the two groups of patients showed that TNF-α, IL-6, ROS and AGEs levels in placenta of CSII group were significantly lower than those of MSII group. This means that CSII can more effectively inhibit the inflammation and oxidative stress in the placenta than MSII.

To sum up, it is believed that the value of continuous subcutaneous insulin pump injection for the treatment of GDM is superior to that of multiple subcutaneous insulin injection, and the treatment method can more effectively improve maternal glucolipid metabolism and inhibit the inflammation and oxidative stress in the placenta.

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