Analysis on the Effect of Metformin Hydrochloride Combined with Insulin Pump for Gestational Diabetes Mellitus

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Abstract

**Background:** To analyze the effect of metformin hydrochloride combined with insulin pump for gestational diabetes mellitus (GDM).

**Methods:** Overall, 216 patients with GDM in Zhangqiu Maternity and Child Care Hospital, Jinan, China from Aug 2018 to Dec 2020 were enrolled and randomized into research and control groups. Patients in the control group were treated with insulin pump, while those in the research group were treated with metformin hydrochloride combined with insulin pump. The clinical efficacy, blood glucose levels, serum Betatrophin, C reactive protein (CRP), Cystatin C (Cys-C), homocysteine (Hcy), adiponectin, tumor necrosis factor (TNF-α), interleukin-6 (IL-6) content, incidence of adverse pregnancy outcomes and incidence of adverse newborns of patients in the two groups were compared.

**Results:** After treatment, the total clinical efficiency of the research group was 84.26%, significantly higher than that of the control group (68.52%). The levels of FPG, 2hPG, HbA1c, serum Betatrophin, CRP, Cys-C, Hcy, adiponectin factors, TNF-α, and IL-6 in the research group were lower than those in the control group, with statistically significant differences (P<0.05). The overall incidence of adverse pregnancy outcomes was 10.19% in the research group, and 25.93% in the control group. The comparative differences between the two groups were statistically significant (P<0.05). The overall incidence of adverse newborns was 9.26% in the research group, and 21.30% in the control group. The comparative differences between the two groups were statistically significant as well (P<0.05).

**Conclusion:** Metformin hydrochloride combined with insulin pump for GDM can significantly reduce blood glucose level, regulate serum protein factor levels, and improve adverse outcomes for mother and child, which deserves clinical promotion.

**Keywords:** Metformin hydrochloride; Insulin pump; Gestational diabetes mellitus; Clinical efficacy

Introduction

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Gestational diabetes mellitus (GDM) refers to the phenomenon of normal glucose metabolism or potential decreased glucose tolerance in pregnant women in the early gestation period, with first diabetes and blood glucose abnormalities after entering the pregnancy (1).

The symptoms of patients with the disease are similar to symptoms of ordinary diabetes mellitus, manifested as large amount of drinking water, increased amount of food and increased amount of urine volume (2). After giving birth, patients are prone to have pruritus vulvae, repeated pseudosilk saccharomyces infection and other situations. In some patients, these symptoms will gradually return to normal as glucose metabolism until it disappears, which lead to an increased risk of type 2 diabetes mellitus in the future (3,4).

According to statistics, the incidence of GDM in China is 2%~5%. It can be seen that GDM is a high incidence of complication in women during pregnancy, and it shows an increasing trend year-by-year (5).

Changes in the metabolic environment in utero also have more adverse effects on the pregnancy outcome (6-8), such as macrosomia, stillbirth, premature delivery, respiratory distress, abnormal fetal intelligence and physical development.

Controlling blood glucose is the key to reducing the harm of this disease to patients’ health and improve pregnancy outcomes (9). The blood glucose of patients with GDM should be strictly monitored in clinic. Insulin is commonly used for this disease, but insulin alone is not ideal (10).

Metformin hydrochloride is widely used, enhancing the sensitivity of patients with GDM to insulin, improving glucose metabolism in extrahepatic tissues, and controlling the speed of glucose absorption in the intestinal tract, with significant glucose control in this process (11,12).

We aimed to analyze the effect of metformin hydrochloride combined with insulin pump for gestational diabetes mellitus (GDM).

Materials and Methods

General data

A total of 216 patients with GDM hospitalized in Zhangqiu Maternity and Child Care Hospital, Jinan, China from Aug 2018 to Dec 2020 were enrolled in this study. They were randomized into research and control groups, with 108 patients for each group, with the approval from the Ethics Committee of our hospital.

The patients in the research group aged 25~46 yr old, averaged (35.5 ± 10.5) yr old, pregnant for 21~32 weeks, averaged (24.56 ± 4.81) weeks, being pregnant 1~4 times, averaged (2.41 ± 1.07) times, giving birth 0~3 times, averaged (1.14 ± 0.31) times. Among them, there were 67 primiparas and 41 multiparas, with the body mass of 59~91 kg, averaged (78.23 ± 9.41) kg. The patients in the control group aged 23~45 yr old, averaged (34.5 ± 10.5) yr old, pregnant for 20~34 weeks, averaged (25.66 ± 5.01) weeks, being pregnant 1~5 times, averaged (3.26 ± 1.42) times, giving birth 0~3 times, averaged (1.39 ± 0.36) times. Among them, there were 69 primiparas and 39 multiparas, with the body mass of 62~89 kg, averaged (77.67 ± 8.21) kg.

General data of the two groups were not statistically significant (P> 0.05), which were comparable. Inclusion criteria: ① All patients met the diagnostic criteria for GDM in the Guidelines for Diagnosis and Treatment of Pregnancy with Diabetes (2018) (13); ② Blood glucose was still not effectively decreased after diet and exercise therapy; ③ Age ≥ 20 yr old; ⑤ With complete and integrated medical records; ⑥ No precursor to premature birth, placenta previa and other symptoms; ⑦ Patients and their family members have been informed of the content of this study, and signed the consent form. Exclusion criteria: ① Patients combined with other pregnancy complications, such as pregnancy-induced hypertension; ② Combined with malignancies; ③ With artificial fecundation and multiple pregnancies; ④ With poor compliance and ineffective drug guidance in this study; ⑤ With drug allergy; ⑥ With
major organ dysfunction and failure; (7) Coagulation disorders.

Treatment Methods
Both groups were treated with insulin injection (SFDA approval number J20160006, SFDA approval number J20160006), administered at 30 min before breakfast and dinner, with an initial dose of 0.2~0.3 IU/(kg·d). It could be increased by 2IU according to the patient's blood glucose value for 12 weeks continuously. On this basis, the routine nursing process was strictly implemented to timely find to solve the arising problems. Routine nursing process included nutrition management, with detailed physical examination and inquiries of patients, to understand the basic situation of the patient’s body and conditions, convenient for doctors to customize the patient's personalized diet and meal and to make scientific and healthy diet under the premise of satisfying the patient's taste as far as possible. In this process, the blood glucose level of patients was closely monitored and constantly adjusted according to the specific situation for better treatment. Personal diet file was set up for the patient. The total amount of various nutrients for the patient to consume every day was calculated according to the results of patient’s physical examination, with more fruits and vegetables and other foods rich in vitamins, as well as a certain amount of protein, fat food, to make the patient nutrition balanced. At the same time, the pregnant woman and family members were given necessary diet lessons, including the nutrition contained in the food. They were taught to pay attention to the daily diet, science and reasonable eating, etc., to improve the patient’s attention to diet, and to increase the patient’s confidence on recovery. Meanwhile, on the premise of safety, the patient was able to take an amount of scientific aerobic exercise properly. On the basis of the above treatment, the research group was given metformin hydrochloride tablets (SFDA approval number H13020586, Beijing Zhongxin Pharmaceutical Factory), oral, 1 tablet daily, 2 times a day, the amount could be increased or decreased according to the change of blood glucose value in the pregnant woman according to the doctor's advice.

Observation index
After 3 months of treatment, both groups were observed for clinical treatment effect. The observation indexes included: (1) Clinical criteria for efficacy: The decrease of FPG (fasting blood glucose) ≥ 30% was excellent, 10~30% for effective, ≤ 10% for ineffective. Total effective rate = (number of excellent + number of effective)/total number (14). (2) Changes in blood glucose indexes: Including HbAlc (glycosylated hemoglobin), FPG, 2hPG (2h postprandial blood glucose). The normal range of FPG was 3.3~5.3 mmol/L, the normal range of 2hPG was 4.4~6.7 mmol/L, and the normal range of HbAlc was less than 6.0%. (3) Levels of serum Betatrophin, CRP, CysC, Hey, adiponectin factors, TNF-α, and IL-6: 5 mL of fasting venous blood was extracted from patients, after 3000r/s centrifugation for 10min, the supernatant was taken to detect serum Betatrophin, CRP, Cysc, Hey, adiponectin and serum inflammatory factor content of TNF-α and IL-6 by ELISA. Blood detection should be completed within 2 h after collection. (4) Incidence of adverse pregnancy outcomes: The total incidence of postpartum hemorrhage, hyperhydramnios, pregnancy hypertension and intrauterine distress were analyzed. (5) Incidence of adverse newborns: The total incidence of neonatal hypoglycemia, neonatal jaundice, premature delivery, fetal malformation and macrosomia were analyzed.

Statistical methods
The data were analyzed by SPSS 23.0 (Chicago, IL, USA) statistical software. Measurement data were represented with (x±s), and the counting data with [n (%)]. The comparison between groups were performed with two independent sample χ2 test, as well as the comparison between groups before and after treatment. P<0.05 shows statistical significance.
Results

**Comparison of clinical efficacy between the two groups**

The total treatment efficiency was 84.26% in the research group, and 68.52% in the control group, with statistical significant difference ($X^2=11.261$, **$P<0.01$**), as shown in Fig. 1.

![Fig. 1: Comparison of clinical efficacy between the two groups](image)

**Comparison of blood glucose level changes between the two groups**

There was no statistical significant differences in the levels of FPG, 2hPG and HbAlc between the two groups before treatment ($P>0.05$). The levels were lower in the research group than those in the control group were after treatment, with statistically significant difference ($^*P<0.05$). In addition, blood glucose levels in both groups were lower than those before treatment, with statistically significant difference ($P<0.05$), as shown in Fig. 2-4.

![Fig. 2: Comparison of FPG levels before and after treatment between the two groups](image)
Comparison of various cytokinine indexes between the two groups

There was no statistical significant differences in the levels of serum Betatrophin, CRP, CysC, Hcy, and adiponectin factors in both groups. Compared with the control group, the levels of all indexes decreased more significantly after treatment in the research group, with statistically significant differences ($P<0.05$). And comparing within the groups, the levels of serum Betatrophin, CRP, CysC, Hcy, and adiponectin factors significantly decreased after treatment, with statistically significant differences ($P<0.05$), as shown in Table 1.
Table 1: Comparison of various cytokinine indexes between the two groups (\( \bar{x} \pm s \))

| Cytokine               | Research Group                       | Control Group                      |
|------------------------|--------------------------------------|-----------------------------------|
|                        | Before treatment | After treatment | Before treatment | After treatment |
| Number of cases        | 108                  |                  | 108               |                  |
| Betatrophin (pg/mL)    | 736.74±61.86         | 552.63±15.14     | 739.12±62.85      | 703.71±45.66     |
| CRP (pg/L)             | 4.51±0.58            | 1.27±0.16        | 4.56±0.61         | 3.22±0.23        |
| CysC (mg/L)            | 1.52±0.41            | 0.84±0.12        | 1.49±0.43         | 1.17±0.24        |
| Hcy (μmol/L)           | 17.49±6.23           | 8.31±3.12        | 17.56±6.21        | 11.14±3.36       |
| Apoponectin (μ/L)      | 51.66±8.64           | 29.87±5.13       | 51.37±8.78        | 36.34±5.08       |

Comparison of serum TNF-\( \alpha \) and IL-6 between the two groups

There was no significant difference in serum TNF-\( \alpha \) and IL-6 between the two groups before treatment. After treatment, the indexes of both groups decreased, which was more significant in the study group (** \( P <0.01 \), * \( P <0.05 \)).

Comparison of adverse pregnancy outcomes and neonatal conditions between the two groups

Table 2: Comparison of adverse pregnancy outcomes between the two groups

| Group      | Number of cases | Pregenational hypertension | Hyperhydramnios | Postpartum hemorrhage | Intrauterine distress | Total incidence of (%) |
|------------|-----------------|-----------------------------|------------------|-----------------------|-----------------------|------------------------|
| Research Group                     | 108            | 2                           | 4                | 2                     | 3                     | 10.19                  |
| Control group                         | 108            | 8                           | 7                | 6                     | 7                     | 25.93                  |
| X2                                   |                |                             |                  |                       |                       | 4.632                  |
| \( P \) value                        |                |                             |                  |                       |                       | 0.037                  |

Table 3: Comparison of neonatal conditions between the two groups

| Group      | Number of cases | Neonatal hypoglycemia | Neonatal jaundice | Premature birth | Fetal malformation | Macrosomia | Total incidence of (%) |
|------------|-----------------|------------------------|-------------------|-----------------|---------------------|------------|------------------------|
| Research Group                     | 108            | 2                       | 2                 | 3                | 1                   | 2          | 9.26                   |
| Control group                         | 108            | 4                       | 6                 | 5                | 3                   | 5          | 21.30                  |
| X2                                   |                |                         |                   |                  |                     | 3.891      | 0.041                  |
| \( P \) value                        |                |                         |                   |                  |                     |            |                        |
Discussion

GDM is a clinically common pregnancy complication due to protein metabolism, fat metabolism disorders and glucose metabolism disorders caused by insufficient insulin secretion (15). In recent years, due to the change of birth policy in China, the number of elderly parturients increased, and the incidence of GDM increased year-by-year (16). If blood glucose is not controlled in patients with GDM, it not only poses a serious threat to maternal and infant outcomes, but also increases the long-term incidence of diabetes mellitus in patients and affect the quality of life and life safety (17). Therefore, patients with GDM must be given timely and efficient interventions to control strictly blood glucose to maintain it within the normal threshold, which is of great significance to improve adverse outcomes and reduce the risk of complications (18).

Currently, clinical treatments for GDM, such as cineisiotherapy (19) and alimentary control (20), have poor effect on improving blood glucose level, which often require combined therapy with drugs (21). Insulin, the preferred drug for diabetes mellitus, can promote the synthesis of glycogen, protein and fat, which can also regulate metabolism in body, improve the intake and utilization rate of glucose, promote protein synthesis, inhibit fat decomposition, and thereby reduce blood glucose. However, it cannot affect the fetal growth and development with high safety (22-24). Combination with metformin (DMBG) not only improves the sensitivity of surrounding tissues to insulin, as well as the utilization rate of glucose, but also increases the utilization rate of glucose in noninsulin-dependent tissues (25,26). In addition, metformin can inhibit hepatoglycogen heteroplasia, and reduce liver sugar output, with glucose-lowering effect (27).

The levels of serum Betatrophin, CRP, CysC, Hey and adiponectin in patients with GDM were different from those in healthy people (28-31). CysC is produced by nuclear cells, which can maintain the balance of sulfur amino acids. It can damage the vascular endothelium with its high expression. Then the inflammatory mediators such as interin, promoting inflammatory factor expression were further released, and the sensitivity to insulin in body decreases, leading to poor pregnancy outcome (28).

CRP is a common clinical pro-inflammatory factor. Elevated blood glucose in GDM patients will promote the increase of CRP content, which can remove necrotic cells and pathogenic microorganisms that invade the body and play an important role in the immune process (28). Betatrophin can ameliorate insulin resistance, promote islet β cell proliferation and development of GDM, and the abnormal elevation of Betatrophin in body can be one of the important factors for predicting poor prognosis in patients with GDM (29). Hey is a factor produced by methionine and cysteine that can be decomposed in body to maintain its concentration, and a high expression of Hey can reduce the sensitivity to insulin (30).

TNF-α is a multi-potent cytokinine regulating inflammatory and cytotoxic, which interferes the conduction of insulin signals, and then leads to the occurrence of insulin resistance (31). IL-6 is mainly produced by lymphocytes and fibroblasts, which can regulate immune and inflammatory response, of which, low concentration IL-6 can stimulate insulin secretion and reduce blood glucose, while high concentration IL-6 can destroy islet B cells, reduce insulin secretion, resulting in increased blood glucose (31,32). The results showed that the total clinical efficiency was 84.26% in the research group, and 68.52% in the control group, with statistically significant differences (P<0.01). The levels of HbA1c, FPG, and 2hPG decreased in both groups after treatment, which was more significant in the research group (P<0.05).

The levels of serum Betatrophin, CRP, CysC, Hey, adiponectin factors, TNF-α and IL-6 showed the same changing trend as above in both groups after treatment, which was more significant in the research group (P<0.01). It sug-
gested that insulin pumps combined with metformin for GDM could effectively regulate inflammatory factor levels in patients. The total incidence of adverse pregnancy outcomes and neonatal outcomes were 10.19% and 9.26% in the research, 25.93% and 21.30% in the control group, respectively, indicating that metformin combined with insulin pump has obvious effect in the treatment of GDM. The insulin pump can release insulin in a certain time, which can effectively reduce high sugar toxicity, promote body to timely repair damaged β cells, and then control blood glucose.

However, the effect of insulin pump is not ideal and other drugs are still needed. Metformin, as an insulin sensitizer, can improve the sensitivity to insulin and the utilization rate of glucose, thus reducing blood glucose. Combined use of metformin on the basis of insulin pump therapy can achieve effective hypoglycemic effects, improve maternal and infant outcomes, and have high safety, making up for the deficiency of single use of insulin pump therapy.

Conclusion

Metformin combined with insulin pump treatment can effectively reduce blood glucose level, regulate serum protein factor indexes, as well as the incidence of adverse pregnancy outcomes and neonatal conditions, with fewer adverse reactions in combined treatment and high safety.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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