Original Article

Metformin combined with insulin aspart for ameliorating blood glucose levels and maternal and neonatal outcomes in women with gestational diabetes mellitus and chronic hypertension

Wei Wang¹, Yanchun Fan², Qun Lin³

¹Department of Pharmacy, Yantai Yuhuangding Hospital, Yantai, Shandong Province, China; ²Department of Obstetrics, Liaocheng City Dong Changlefu Maternity and Infant Healthy Institute, Liaocheng, Shandong Province, China; ³Department of Pharmacy, Tiantai Hospital of Hangzhou Medical College, Taizhou, Zhejiang Province, China

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Abstract: Objective: To investigate the effect of metformin combined with insulin aspart on blood glucose levels and maternal and neonatal outcomes in women with gestational diabetes mellitus (GDM) accompanied by chronic hypertension (CH). Methods: A prospective study was conducted on 112 women with GDM and CH. The patients were divided into the control group and the observation group according to a random number table method, with 56 patients in each group. The control group received injections of insulin aspart based on blood pressure control, and the observation group received injections of insulin aspart combined with oral metformin based on blood pressure control. Besides, blood glucose levels, maternal pregnancy outcomes and neonatal complications before and after intervention were compared between the two groups. Results: Before intervention, there was no significant difference in blood glucose and blood pressure levels between the two groups (P > 0.05). After intervention, the observation group showed significantly decreased fasting blood glucose, 2-h postprandial plasma glucose and glycosylated hemoglobin levels than the control group (P < 0.05); the blood pressure in the observation group was significantly lower as compared with that before intervention (P < 0.05). Additionally, the incidences of adverse pregnancy outcomes (e.g., premature rupture of membranes) and neonatal jaundice and macrosomia were significantly lower in the observation group than in the control group after intervention (both P < 0.05). Conclusion: Metformin combined with insulin aspart for treating GDM and CH can effectively control blood glucose and blood pressure levels and reduce the risk of adverse perinatal and neonatal outcomes, which exerts positive effect in clinical treatment.

Keywords: Metformin, insulin aspart, gestational diabetes mellitus, hypertension

Introduction

Gestational diabetes mellitus (GDM) is a metabolic disorder commonly occurring in pregnant women with a high incidence during pregnancy. In recent years, the number of GDM patients has been increasing worldwide. Before 2010, cohort study data from the United Kingdom and Ireland showed that the incidence of GDM was only 1-3% [1]. While after 2010, relevant data revealed that the incidence of GDM increased to 9-26% globally with an average of about 18%, and the incidence of GDM in China ranged from 9.3 to 18.9% [2-4]. Pregnant women with GDM have an increased likelihood of concurrent preeclampsia, preterm birth, and their newborns are more prone to develop hypoglycemia, macrosomia, hyperbilirubinemia, etc. [5, 6].

Data show that GDM affects the health of one-seventh of live-birth infants worldwide [7]. Hypoglycemic agents such as insulin, metformin and glibenclamide are often used to control blood glucose in clinical practice, but the effect of monotherapy is limited. Hence, the combination of drugs is a common choice for treating GDM [8, 9]. In recent years, the number of preg-
Metformin combined with insulin aspart for treating GDM

Pregnant women with GDM and chronic hypertension (CH) has increased dramatically, which is related to the increased average gestational age and BMI in women [10]. To our knowledge, our study is the first to report the effect of metformin combined with insulin aspart on blood glucose levels and maternal and neonatal outcomes in pregnant women with GDM and CH.

Materials and methods

Data collection

We selected 112 pregnant women receiving treatment for GDM accompanied by CH in our hospital from July 2017 to July 2020. This study was approved by the Ethics Committee of our hospital.

Women were included if they fulfilled the diagnostic criteria of GDM, i.e., pregnant women show any degree of glucose intolerance during pregnancy, with no history of diabetes [11-13]; met the diagnostic criteria of CH in pregnancy, i.e., women had a history of hypertension before pregnancy, or had hypertension after 4 months of pregnancy and over 3 months after delivery [10, 14]; were graded according to the WHO classification as 140 mmHg \(\leq\) systolic blood pressure < 160 mmHg and 90 mmHg \(\leq\) diastolic blood pressure < 160 mmHg (grade 1), 160 mmHg \(\leq\) systolic blood pressure < 180 mmHg and 100 mmHg \(\leq\) diastolic blood pressure < 110 mmHg (grade 2), and systolic blood pressure \(\geq\) 180 mmHg, diastolic blood pressure \(\geq\) 110 mmHg (grade 3), [15]. All patients and their families were fully informed about the treatment and voluntarily signed the informed consent.

Women with abnormal liver and kidney function, or nervous, respiratory and cardiovascular diseases were excluded. Women who were not suitable for the clinical drug research were also excluded.

Group and treatment methods

All women were divided into the control group (n=56) and the observation group (n=56) according to a random number table method. The control group received subcutaneous injections of insulin aspart combined with oral metformin (Sino-American Shanghai Squibb Pharmaceuticals Ltd., China) based on antihypertensive treatment. The indicators were observed, and treatment was continued until delivery.

Outcome measures

Indicators for pregnant women: Blood glucose determination of pregnant women before drug intervention and delivery: Determination of fasting blood glucose (FBG): Before blood collection, the patients needed to fast for 12 h. Then blood samples were collected with sterile tubes, centrifuged at 3000 rpm for 20 min at 4°C to separate the upper serum, and a Roche c702 automatic biochemical analyzer was used for measurement. Determination of 2 h post-prandial plasma glucose (2hPG): Blood samples were collected two hours after breakfast, and the determination method and instrument were the same as above. Determination of glycosylated hemoglobin (HbA1c): Blood samples were collected with the same methods for determining FBG, and then measured by automatic glycosylated hemoglobin detector Premier Hb9210.

Blood pressure classification: Blood pressure levels were measured using Omron HEM-7071 electronic sphygmomanometer and graded according to the WHO Classification (see above for details).

Adverse pregnancy outcomes: Premature rupture of membranes and puerperal infection of patients in both groups were recorded. Incidence of adverse pregnancy outcomes = number of adverse outcome cases in each group/total number of cases in each group.

Indicators for neonates

Neonatal jaundice: The jaundice occurred within 24 hours after birth with a serum bilirubin level above 205 μmol/L [16].

Macrosomia: The newborns whose birthweight was more than 4 kg within 1 h after birth were diagnosed with macrosomia [17].

Respiratory distress: The newborns who had progressive dyspnea after birth with signs confirmed by X-ray (e.g., air bronchogram and
patchy shadow) were diagnosed with respiratory distress [18]. Incidence of adverse neonatal outcomes = number of adverse outcome cases in each group/total number of cases in each group.

**Statistical analysis**

Data analyses were performed with the SPSS 23.0 software package. The measurement data in accordance with a normal distribution were expressed as mean ± standard deviation (X ± sd). Independent sample t-test was applied for the comparison between the two groups. Chi-square test (χ² test) was used for comparison between the two groups, enumeration data was expressed as the percentage or case/percentage (n, %). Moreover, the ranked data were compared using rank-sum test. P < 0.05 was considered statistically significant.

**Results**

**General data**

The patients in the control group were aged 24-39 years, with a mean age of 30.6 years and an average BMI of 23.85 kg/m². While in the observation group, the patients were aged 27-40 years with a mean age of 31.1 years and an average BMI of 23.81 kg/m². There was no significant difference in the age and BMI between the two groups (P > 0.05), suggesting the two groups were comparable. See **Table 1**.

**Comparison of FBG, 2hPG and HbA1c levels before and after intervention**

Before the use of a two-drug combination, no significant difference was found in the levels of FBG, 2hPG and HbA1c between the two groups (P > 0.05). After intervention, the observation group showed significantly decreased levels of FBG, 2hPG and HbA1c than the control group (P < 0.05). See **Table 2** and **Figure 1**.

**Comparison of incidence of related diseases in neonates**

The incidences of neonatal jaundice and macrosomia were higher in the control group than in the observation group (P < 0.05). Moreover, there was no difference in the incidence of neonatal respiratory distress between the two groups (P > 0.05). See **Table 5**.

**Discussion**

GDM refers to any degree of glucose intolerance with first onset or recognition during pregnancy [19]. GDM increases the risk of adverse pregnancy outcomes, and hyperglycemia can affect infant health by crossing the placenta, which enhances the occurrence of diseases such as macrosomia and neonatal jaundice [20]. For most women with GDM, blood glucose levels cannot be effectively controlled by dietary balance or exercise, so they often rely on drug therapy for blood glucose control so as to reduce adverse pregnancy outcomes [21]. Clinically, insulin is a commonly used hypoglycemic agent for treating GDM but it is reported
Metformin combined with insulin aspart for treating GDM

Table 2. Comparison of FBG, 2hPG and HbA1c levels before and after intervention

<table>
<thead>
<tr>
<th>Group</th>
<th>Control group (n=56)</th>
<th>Observation group (n=56)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBG mmol/L</td>
<td>8.63±1.37</td>
<td>8.72±1.57</td>
<td>-0.318</td>
<td>0.751</td>
</tr>
<tr>
<td>2hPG mmol/L</td>
<td>11.47±1.05</td>
<td>11.57±1.56</td>
<td>-0.412</td>
<td>0.681</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.61±0.93</td>
<td>8.62±1.38</td>
<td>-0.076</td>
<td>0.940</td>
</tr>
<tr>
<td>After intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBG mmol/L</td>
<td>6.57±0.93</td>
<td>5.93±0.96**</td>
<td>3.578</td>
<td>0.001</td>
</tr>
<tr>
<td>2hPG mmol/L</td>
<td>8.82±1.05</td>
<td>7.92±1.56**</td>
<td>3.569</td>
<td>0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.58±0.99</td>
<td>6.11±1.06</td>
<td>2.423</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Note: Compared with the control group after intervention, *P < 0.05, **P < 0.01.
FBG: fasting blood glucose; 2hPG: 2-h postprandial plasma glucose; HbA1c: glycosylated hemoglobin.

As an insulin analogue, insulin aspart is superior to human insulin in lowering postprandial blood glucose levels [26]. There is no evidence proving that insulin aspart has teratogenic effects on newborns [6]. Moreover, a study indicated that insulin aspart could reduce drug dose without increasing the incidence of adverse neonatal outcomes [27]. Hence, insulin aspart is often used as the first choice of hypoglycemic drugs for the treatment of GDM in clinical practice. In recent years, the increased prevalence of GDM is closely related to the lack of exercise and obesity in pregnant women, while metformin has a favorable effect on obesity-induced diabetes [28]. Its combination with insulin can not only increase insulin sensitivity but also reduce the dose of insulin, thereby reducing the risk of hypoglycemia in patients [29]. Our study demonstrated that the effect of insulin aspart combined with metformin on GDM patients with CH was better than that of insulin aspart alone, which was consistent with the findings of Wen and Guo et al. [30, 31].

Meanwhile, in line with the study reported by Liu et al. the use of a two-drug combination can reduce the incidence of adverse maternal and neonatal outcomes such as premature rupture of membranes, neonatal jaundice, and macrosomia in GDM patients with CH [32]. The patients receiving combined drug use showed lower incidences of puerperal infection and neonatal respiratory distress after intervention.
Metformin combined with insulin aspart for treating GDM

Table 3. Comparison of blood pressure classification before and after intervention (n, %)

<table>
<thead>
<tr>
<th>Group</th>
<th>Before intervention (n, %)</th>
<th>After intervention (n, %)</th>
<th>z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td>-0.868</td>
<td>0.385</td>
</tr>
<tr>
<td>Grade 1</td>
<td>17 (30.36)</td>
<td>19 (33.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>24 (42.86)</td>
<td>27 (48.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>15 (26.79)</td>
<td>10 (17.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation group</td>
<td></td>
<td></td>
<td>-2.209</td>
<td>0.027</td>
</tr>
<tr>
<td>Grade 1</td>
<td>16 (28.57)</td>
<td>23 (41.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>26 (46.43)</td>
<td>29 (51.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>14 (25.00)</td>
<td>4 (7.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>z</td>
<td>-0.006</td>
<td>-1.304</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.995</td>
<td>0.192</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Comparison of adverse pregnancy outcome (n, %)

<table>
<thead>
<tr>
<th>Group</th>
<th>Control group (n, %)</th>
<th>Observation group (n, %)</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature rupture of membranes</td>
<td>13 (23.21)</td>
<td>5 (8.93)</td>
<td>4.236</td>
<td>0.040</td>
</tr>
<tr>
<td>Puerperal infection</td>
<td>9 (16.07)</td>
<td>3 (5.36)</td>
<td>2.333</td>
<td>0.127</td>
</tr>
</tbody>
</table>

Table 5. Comparison of incidence of related diseases in neonates (n, %)

<table>
<thead>
<tr>
<th>Group</th>
<th>Jaundice (n, %)</th>
<th>Macrosomia (n, %)</th>
<th>Respiratory distress (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (n, %)</td>
<td>15 (26.79)</td>
<td>13 (23.21)</td>
<td>8 (14.29)</td>
</tr>
<tr>
<td>Observation group (n, %)</td>
<td>6 (10.71)</td>
<td>5 (8.93)</td>
<td>3 (5.36)</td>
</tr>
<tr>
<td>χ²</td>
<td>4.747</td>
<td>4.236</td>
<td>1.613</td>
</tr>
<tr>
<td>P</td>
<td>0.029</td>
<td>0.040</td>
<td>0.204</td>
</tr>
</tbody>
</table>

than the patients undergoing monotherapy. But there was no significant statistically difference, which may be due to the sample size. In the future, we will further investigate the topic with larger sample sizes. A previous study has confirmed that insulin aspart combined with metformin can reduce the incidence of hypertension disorders in pregnant women [33]. However, there is no study reporting the effect of the combination therapy on the blood pressure level in GDM patients with CH. Our study found that the use of a two-drug combination can reduce the incidence of grade 3 hypertension and promote the transition from severe to mild-to-moderate hypertension. Research has revealed that metformin plays a role in reducing blood pressure in hypertensive rats by inhibiting inflammation and oxidative stress to protect the structural and functional integrity of the aorta [34]. Furthermore, a previous review concluded the possible mechanism of metformin in preventing hypertensive disorders of pregnancy [35]. Generally, metformin prevented and treated hypertension by inhibiting inflammation and oxidative stress and protecting vascular endothelium and trophoblast cells. Also, a meta-analysis of 15 clinical studies revealed that metformin exerted a positive effect on the prevention of hypertension during pregnancy compared with other placebos [36].

This study is the first to elaborate on the clinical effect of insulin aspart combined with metformin in women with GDM and CH. The results indicate that the combined use of drugs can not only has a good hypoglycemic effect, but also has a value in lowering blood pressure, with certain clinical significance. However, this study still has some limitations in the group design. If a group of metformin treatment by itself is set up, the effect of the use of a two-drug combination will be more obvious. At the same time, this study lacks further exploration for the mechanism of the combination of drug use. In the future, we will further investigate the effect of the use of a two-drug combination on serum inflammatory factors and the body’s oxidative stress level in women with GDM and CH.

In conclusion, the clinical efficacy of insulin aspart combined with metformin is confirmed to effectively ameliorate blood glucose, blood pressure and adverse maternal and neonatal outcomes in women with GDM and CH.
Metformin combined with insulin aspart for treating GDM

Disclosure of conflict of interest
None.

Address correspondence to: Qun Lin, Department of Pharmacy, Tiantai Hospital of Hangzhou Medical College, No. 1 Kangning Middle Road, Shifeng Street, Tiantai County, Taizhou 317200, Zhejiang Province, China. Tel: +86-0576-81302021; E-mail: linqun1q2w@163.com

References


Metformin combined with insulin aspart for treating GDM


