Heparina de bajo peso molecular combinada con progesterona de baja dosis en el tratamiento del aborto amenazado

Low Molecular Weight Heparin Combined with Low Dose Progesterone in the Treatment of Threatened Abortion

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Resumen
La heparina de bajo peso molecular tiene un efecto antitrombótico obvio y duradero, y la actividad antitrombótica es más fuerte que la actividad anticoagulante, por lo que el riesgo relativo de hemorragia es menor. En este artículo, se estudió el efecto de la heparina sódica de bajo peso molecular y la progesterona en dosis bajas sobre la amenaza de aborto. Los pacientes en el grupo experimental fueron tratados con heparina de bajo peso molecular y progesterona en dosis bajas. El tiempo de alivio de los síntomas clínicos y las reacciones adversas se compararon entre los dos grupos. Resultados comparados con el grupo control, la incidencia de reacciones adversas en el grupo experimental fue 4% menor que en el grupo control (23%), y la diferencia entre los dos grupos fue estadísticamente significativa; en comparación con el grupo control, el tiempo de alivio de los síntomas clínicos en el grupo experimental fue más corto que en el grupo control (P <0.05) La combinación de heparina sódica de bajo peso molecular y dosis bajas de progesterona en el tratamiento del aborto amenazado tiene efecto clínico, que puede mejorar de manera integral los síntomas clínicos de los pacientes. Los síntomas clínicos de los pacientes son relativamente cortos en tiempo de remisión, y la incidencia de reacciones adversas es relativamente pequeña, y la seguridad de la medicación clínica es relativamente baja, lo que es digno de aplicación clínica.

Palabras clave: heparina sódica de bajo peso molecular; Reacciones adversas; Amenaza de aborto; Progesterona

Abstract
Low molecular weight heparin has obvious and lasting antithrombotic effect, and antithrombotic activity is stronger than anticoagulant activity, so the relative risk of bleeding is smaller. In this paper, the effect of low molecular weight heparin sodium and low dose progesterone on threatened abortion was studied. The patients in the experimental group were treated with low-molecular-weight heparin and low-dose progesterone. The clinical symptom relief time and adverse reactions were compared between the two groups. Results compared with the control group, the incidence of adverse reactions in the experimental group was 4% lower than that in the control group (23%), and the difference between the two groups was statistically significant; compared with the control group, the relief time of clinical symptoms in the experimental group was shorter than that in the control group (P<0.05) . The combination of low molecular weight heparin sodium and low dose progesterone in the treatment of threatened abortion has significant clinical effect, which can comprehensively improve the clinical symptoms of patients. The clinical symptoms of patients are relatively short in remission time, and the incidence of adverse reactions is relatively small, and the clinical medication safety is relatively low, which is worthy of clinical application.

Key words: low molecular weight heparin sodium; Adverse reactions; Threatened abortion; Progesterone

1. Introduction

Low molecular weight heparin is a kind of low molecular weight aminodextran sulfate with an average molecular weight of 4000-6000 daltons. The short chain heparin preparation made by various depolymerization and grouping methods can be divided into different commercial preparations according to the different molecular weight, end structure and compound binding salts Low molecular weight heparin has obvious and lasting antithrombotic effect, and antithrombotic activity is stronger than anticoagulant activity, so the relative risk of bleeding is smaller, and its side effects such as thrombocytopenia and osteoporosis are less, the half-life
of plasma is long, and the efficacy is lasting, so there is no need to monitor the blood coagulation index and platelet\cite{1}. The safety is better, neither can pass through the placenta nor pass through the placenta like unfractionated heparin. Secreted in milk, it is safe to use in pregnancy and lactation, and has no teratogenic effect on fetus, so it is widely used in clinical.

In the process of pregnancy, a certain proportion of women will have the symptoms of abortion, and the causes of abortion are various, such as endocrine, genetic, environmental, anatomical, etc., but in addition to the above reasons, there are still many reasons for abortion. Some studies have shown that about 24.8% of recurrent abortions with unknown causes have varying degrees of hypercoagulability and anticardiolipin antibodies\cite{2-3}. Therefore, in the Chinese expert consensus on the prevention and treatment of spontaneous abortion by low molecular weight heparin (2018), low molecular weight heparin is considered to have a good effect on spontaneous abortion caused by antiphospholipid syndrome (APS), thrombophilia (PTS), autoimmune diseases (AID). Therefore, low molecular weight heparin is widely used in the field of Obstetrics and gynecology. Progesterone is the first choice in clinical treatment, but patients are prone to a variety of adverse reactions after conventional dose treatment\cite{4}. With the continuous clinical research in recent years, low-molecular-weight heparin sodium is used to treat threatened abortion, and remarkable clinical effects have been achieved. In this study, 80 patients with threatened abortion admitted in our hospital from December 2017 to December 2018 were selected, and low-molecular-weight heparin sodium combined with low-dose progesterone were used. The therapeutic effect was analyzed.

2. Materials and methods

2.1 Clinical data
From December 2017 to December 2018, 80 patients with threatened abortion were selected, all of whom voluntarily participated in the study and signed relevant informed documents. The 80 patients were divided into experimental group and control group, 40 cases each. The average age of the control group was (27.23 ± 1.18), the experimental group was (22-34), and the average age was (27.21 ± 1.17). The basic clinical data of the experimental group and the control group were input into SPSS 21.0 software, and there was no significant difference in the analysis and comparison of the results, which was comparable.

2.2 Diagnostic criteria
All of them met the diagnostic criteria of threatened abortion in clinical obstetrics and Gynecology, and all of them were accompanied with symptoms such as low abdomen, cervix not opened, bleeding and pain.

2.3 Inclusion and exclusion criteria
Exclusion criteria: (1) Patients with reproductive organ tumors; (2) Patients with endocrine system diseases; (3) Patients with ectopic pregnancy and pregnancy hypertension; (4) Patients with mental diseases. Inclusion criteria: (1)Patients without other diseases; (2) Patients with sound cognitive function; (3) Patients with clinical diagnosis criteria.

2.4 Method
2.4.1 Treatment
The fasting progesterone values of the two groups were measured, and the results were treated with different doses of progesterone injection (Guangzhou Baiyunshan Mingxing Pharmaceutical Co., Ltd., gyzh44020229). When the progesterone value of the patients is less than 10 ng / ml, the patients in the control group are given 20 mg / D progesterone intramuscular injection treatment, and the patients in the experimental group are given 10 mg / D progesterone; if the progesterone value of the patients is 10-20 ng / ml, the patients in the control group are given 10 mg / D progesterone intramuscular injection treatment, and the patients in the experimental group are given 5 mg / D treatment. On the basis of progesterone treatment, the patients in the experimental group were given 4 250 IU / 0.4 ml low-molecular-weight heparin sodium (alfaville ± Mann pharmaceutical company, imported drug registration certificate No. h20090246) by subcutaneous injection once a day, and the treatment time of the two groups was one week after the stop of bleeding symptoms.

2.4.2 Observation indicators
The clinical symptom relief time and adverse reactions were compared between the two groups.

2.4.3 Evaluation criteria of efficacy
Clinical symptoms include lumbago, abdominal pain, hemostasis and so on, and the time of remission is comprehensively recorded; adverse reactions include breast swelling and pain, headache, vomiting, pruritus and so on.
2.5 Statistical methods

The data of this study were all processed by SPSS 21.0 statistical software, the measurement data were represented by \( \bar{x} \pm S \) and the comparison between groups was t-test; the number of cases of counting data (n) was represented by \( x^2 \) test, and the difference was statistically significant (\( P < 0.05 \)).

3. Results

3.1 Comparison of clinical symptom relief time between the two groups

The relief time of lumbago acid, hemostasis and abdominal pain in the experimental group was shorter than that in the control group, and the difference between the two groups was statistically significant (\( P < 0.05 \)), as shown in Table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>Waist acid relief time (d)</th>
<th>Abdominal pain relief time (d)</th>
<th>Hemostasis relief time (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test group</td>
<td>2.48±0.37</td>
<td>2.19±0.41</td>
<td>2.02±0.29</td>
</tr>
<tr>
<td>Control group</td>
<td>3.34±0.61</td>
<td>3.14±0.59</td>
<td>3.12±0.53</td>
</tr>
<tr>
<td>t</td>
<td>7.623 7</td>
<td>9.859 1</td>
<td>11.513 3</td>
</tr>
<tr>
<td>P</td>
<td>0.000 0</td>
<td>0.000 0</td>
<td>0.000 0</td>
</tr>
</tbody>
</table>

3.2 Comparison of the changes of high sensitive C-reactive protein, fibrinogen, D-dimer and platelet levels between the two groups before and after treatment

After treatment, the levels of hypersensitive C-reactive protein, fibrinogen, D-dimer and platelet in the observation group and the control group were significantly lower than those before treatment (t-values in the observation group were -28.667, -13.732, -9.262; t-values in the control group were -15.416, -6.157, -20.160, -7.091), with statistical significance (pg0.001), as shown in Table 2. Based on the levels of hypersensitive C-reactive protein, fibrinogen, D-dimer and platelets before treatment in the two groups, it can be seen that the decrease degree of each index in the observation group after treatment is significantly higher than that in the control group (T values are 12.621, 10.828, 4.653 and 2.099, respectively, \( P < 0.05 \)), as shown in Table 3.

<table>
<thead>
<tr>
<th>Group</th>
<th>Period</th>
<th>Hypersensitive C-reactive protein (ng/ml)</th>
<th>Fibrinogen (g/L)</th>
<th>D- two dimer (μg/L)</th>
<th>Platelet (×10^9/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test group</td>
<td>Before treatment</td>
<td>92.19±11.29</td>
<td>1.85±0.21</td>
<td>4.27±0.29</td>
<td>253.19±34.09</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>51.45±11.18</td>
<td>1.54±0.14</td>
<td>3.13±0.21</td>
<td>213.59±33.51</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>94.69±12.59</td>
<td>1.94±0.15</td>
<td>4.39±0.41</td>
<td>261.09±36.21</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>70.39±11.39</td>
<td>1.84±0.09</td>
<td>3.45±0.29</td>
<td>229.19±32.19</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

3.3 Comparison of adverse reactions between the two groups

The total incidence of the experimental group was 5% lower than that of the control group (25%). The difference between the groups was statistically significant (\( P < 0.05 \)), as shown in Table 4.
Luteal dysfunction in early pregnancy is one of the important inducements of threatened abortion. Luteal dysfunction in patients leads to the decrease of hormone synthesis and progesterone secretion in luteal cells, which leads to vaginal bleeding and other adverse reactions[8]. Progesterone is used to make up for the symptoms of threatened abortion caused by luteal dysfunction in patients, so as to enable the patients to be able to Enough to keep growing. Chromosomal abnormality, maternal systemic disease, endocrine abnormality, immune function abnormality and other factors are also the key pathogenic factors of threatened abortion[9-10]. Among them, antiphospholipid antibody is one of the main factors to promote coagulation and activate platelets, which leads to platelet aggregation and thrombosis in patients. Therefore, it is considered that anticoagulation therapy can effectively improve the risk of threatened abortion Good at adverse reactions. Progesterone is a commonly used drug in the treatment of threatened abortion, which is widely used in clinic. As a commonly used anticoagulant, low-molecular-weight heparin sodium can inhibit the formation of placental membrane thrombosis by inhibiting the fibrinogen conversion process of patients[11].

For this kind of symptom, giving artificial progesterone can make up for the low progesterone caused by luteal dysfunction, improve the clinical symptoms of patients, and avoid threatened abortion. At present, progesterone is the first choice in clinical treatment, which is widely used[12-14]. However, long-term use of progesterone can easily lead to a variety of adverse reactions in patients with high risk of drug use. Low molecular weight heparin sodium can effectively inhibit the conversion of fibrinogen to fibrin, thus effectively block the agglutination and thrombosis of fibrin in placental basement membrane[15]. This drug belongs to a kind of drug Anticoagulants play an important role in improving the uterine blood circulation of patients. Li Hui et al. Showed that according to the clinical progesterone level of the patients, the corresponding low dose progesterone treatment was given, the clinical treatment effect and drug safety were high. Combined with low molecular weight heparin sodium, the clinical symptom relief time of the patients could be shortened comprehensively, and the incidence of adverse reactions was as low as 4%[16-18]. It can be seen that low-molecular-weight heparin sodium and low-dose progesterone in the treatment of threatened abortion have significant effect on improving the clinical symptoms of patients, can comprehensively shorten the time of symptom improvement and promote the recovery of patients, which is also consistent with the results of this study. The results showed that the incidence of adverse reactions in the experimental group was 5%, which was significantly lower than that in the control group. However, due to the small number of cases selected in this study, the therapeutic effect and research results need to be further confirmed.

This study found that the clinical treatment effect of the observation group was significantly better than that of the control group, and the time of low back acid, vaginal bleeding, abdominal pain and the total treatment time of the observation group were also significantly less than that of the control group, indicating that progesterone combined with low molecular weight heparin sodium can significantly improve the treatment effect of patients and shorten the duration of symptoms, which is similar to other conclusions[19]. The results are consistent. Some researches have pointed out that the bleeding symptoms in the clinical symptoms of threatened abortion are related to the damage of placental chorion, and the hypercoagulable state of placental blood and inflammatory reaction are the main inducements of the bleeding caused by the damage of chorion. Low molecular weight heparin sodium, as a common anticoagulant, can alleviate the hypercoagulable state of patients' blood, and then reduce the symptoms of vaginal bleeding, while progesterone can reduce the level of inflammatory factors in patients, and then inhibit the bleeding symptoms caused by the damage of chorionic vessels[20]. This study found that the difference of HS CPR, fibrinogen, D-dimer and platelet levels in the observation group was significantly higher than that in the control group, which also showed that low molecular weight heparin combined with progesterone could improve the local hypercoagulable state of patients and

### Table 4. Adverse reactions in two groups [n (%)]

<table>
<thead>
<tr>
<th>Group</th>
<th>Breast swelling and pain</th>
<th>Nausea</th>
<th>Headache</th>
<th>Skin Itch</th>
<th>Total incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental group (n=40)</td>
<td>1 (2.50)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>1 (2.50)</td>
<td>2 (5.00)</td>
</tr>
<tr>
<td>Control group (n=40)</td>
<td>2 (5.00)</td>
<td>2 (5.00)</td>
<td>3 (7.50)</td>
<td>3 (7.50)</td>
<td>10 (25.00)</td>
</tr>
</tbody>
</table>

| X²                          | 6.274                    |
| P                           | 0.012                    |

### 4. Discussion

#### 4.1 Analysis of experimental results

One of the most common diseases in early pregnancy is threatened abortion, which has a high incidence in pregnant women. The pathogenesis of the disease is complex, and it has an important correlation with the fetus itself and the mother itself[5]. The poor luteal function of the patients in the early pregnancy is the main factor leading to the occurrence of the disease. The decrease of luteal cell hormone synthesis and progesterone secretion has an important effect on embryo implantation in cervix. The clinical symptoms are mostly waist swelling and pain and vaginal bleeding[6-7].

Luteal dysfunction in early pregnancy is one of the important inducements of threatened abortion. Luteal dysfunction in patients leads to the decrease of hormone synthesis and progesterone secretion in luteal cells, which leads to vaginal bleeding and waist pain and other adverse reactions[8]. In clinic, progesterone is used to make up for the symptoms of threatened abortion caused by luteal dysfunction in patients, so as to enable the patients to be able to Enough to keep growing. Chromosomal abnormality, maternal systemic disease, endocrine abnormality, immune function abnormality and other factors are also the key pathogenic factors of threatened abortion[9-10]. Among them, antiphospholipid antibody is one of the main factors to promote coagulation and activate platelets, which leads to platelet aggregation and thrombosis in patients. Therefore, it is considered that anticoagulation therapy can effectively improve the risk of threatened abortion Good at adverse reactions. Progesterone is a commonly used drug in the treatment of threatened abortion, which is widely used in clinic. As a commonly used anticoagulant, low-molecular-weight heparin sodium can inhibit the formation of placental basement membrane thrombosis by inhibiting the fibrinogen conversion process of patients[11].

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increase the placental blood supply. Therefore, the combination of the two drugs can effectively inhibit the damage of chorionic vessels and improve the effect of threatened abortion.

4.2 The influence of psychological behavior intervention on the psychological state and the success rate of pregnancy protection of patients with threatened abortion

The psychological behavior intervention can improve the psychological state of the patients with threatened abortion, alleviate and eliminate the anxiety and depression to a large extent. Analysis of the reasons: psychological and behavioral intervention focuses on the cultivation of a good way of thinking for patients, so that they can actively participate in the process of fetal care, which is helpful to reduce the psychological pressure of patients. It is of great significance to guide the patients to solve the problems and difficulties encountered in the process of fetal care and improve their self-efficacy.

Psychological and behavioral intervention can improve the success rate of the threatened abortion. It has been found that the psychological state of pregnant women is closely related to the immune system of the body. If the patients are always in the stress state of anxiety, tension and depression, it will destroy the immune balance mechanism of the body, and then lead to endocrine disorders and aggravate the patients' condition. Psychological and behavioral intervention can keep patients' happy mood, better maintain patients' immune balance and avoid aggravating the disease. Generally, the process of fetal protection is tedious and the period is long. Patients need to take progesterone strictly according to the dosage for a long time, so it is easy to produce boredom or resistance in the midway of fetal protection. Psychological and behavioral intervention can improve the compliance of patients with fetal protection treatment, so that the drugs can play a better role in fetal protection. And psychological and behavioral intervention can make pregnant women maintain an optimistic emotional state for a long time, which is conducive to avoid the increase of blood pressure and heart rate caused by emotional tension, which may aggravate the symptoms of vaginal bleeding.

4.3 Safety analysis of low molecular weight heparin

At present, studies show that the tendency of thrombosis is related to spontaneous abortion, which can lead to adverse pregnancy outcomes. Low molecular weight heparin can inhibit the transformation of fibrinogen, avoid its deposition in placental vascular basement membrane, reduce blood viscosity and vascular resistance, promote blood circulation, and regulate the microenvironment of uterus. Therefore, in the field of Obstetrics and Gynecology, low molecular weight heparin is widely used in the prevention and treatment of spontaneous abortion. Many studies have confirmed that low molecular weight heparin has a clear therapeutic effect on recurrent abortion. It is believed that low molecular weight heparin can significantly reduce early and late abortion, significantly increase the live birth rate, significantly improve the pregnancy outcome, and the incidence of adverse reactions is very low, and the use process is safe. However, in the consensus of Chinese experts on the prevention and treatment of spontaneous abortion with low molecular weight heparin (2018 version), China's comprehensive After the internal and external data, due to the lack of large samples of research evidence, there is no clear recommendation of low molecular weight heparin routine treatment for recurrent abortion. In the "consensus on immunological diagnosis and treatment of recurrent abortion", it is also clear that it is used for immune recurrent abortion. In contrast, there are fewer studies on threatened abortion, and the conclusions are not clear enough. Most patients use low molecular weight heparin because of threatened abortion or early pregnancy. It is clearly confirmed that prethrombotic state and high resistance of uterine artery account for a few. It can be seen that there are obvious improper use cases. However, it is difficult to obtain the number of spontaneous abortion in the prescription, so it is not clear whether the patient has two or more spontaneous abortion history, which is one of the focuses that the author should continue to pay attention to later. About 10% of the patients also use low-molecular-weight heparin because of assisted reproductive technology, because some studies have shown that the application of low-dose low-molecular-weight heparin combined with traditional birth control treatment is conducive to improving the success rate of second pregnancy, baby holding rate and reducing the incidence of pregnancy complications.

In the prescription of low molecular weight heparin, more than half of the patients used 4100iu. It has been shown that the optimal dose of low molecular weight heparin can promote the secretion of hCG and the development of embryo. However, there is no report on the optimal low molecular weight heparin dosage for promoting embryo development. In addition, the adverse reactions of low molecular weight heparin will increase with the increase of dosage, so it is necessary to weigh the advantages and disadvantages. Therefore, from the perspective of safety and effectiveness, most of the prescriptions with middle dose are selected. Among the epidemiological factors of recurrent abortion, the age of pregnant women is the high-risk factor leading to spontaneous abortion. Generally, with the increase of age, the risk of abortion and the probability of multiple birth history increase. The probability of using low-molecular-weight heparin treatment should be higher than that of low-age group, but contrary to the speculation. In patients with low molecular weight heparin, more than half of them were under 30 years old, and more under 35 years old. There are still arguments about the course of treatment. It is said that the use of low molecular weight heparin can maintain the whole pregnancy period. It is...
also said that the treatment course should be different depending on the lost pregnancy period. However, it is difficult for outpatients to track the situation of follow-up in the later period, so the course of treatment used by patients cannot be determined vertically. In the frequency of use, only a few patients were twice a day or once a day, which was more consistent with the frequency of preventive dosage.

5. Conclusion

In conclusion, low-molecular-weight heparin combined with low-dose progesterone has better drug safety and effectiveness in the treatment of threatened abortion. Due to the small number of cases included in the study and the short observation time, the conclusion of this study needs to be further verified by multi center and large sample clinical practice.

References