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Original Article

Efficacy of aspirin combined with labetalol on gestational hypertension and effect on serum PAPP-A, APN and HMGB1

Feiyue Zhang[1], Bide Duan[1], Yanming Liu[2], Cuicui Wang[1]

[1]*Obstetrics Department, Zibo Central Hospital, Zibo 255000, Shandong, China;* [2]*Rehabilitation Medicine Department, Zibo Central Hospital, Zibo 255000, Shandong, China*

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Abstract: Objective: To determine the clinical efficacy of aspirin combined with labetalol on gestational hypertension (GH) and its influence on serum pregnancy associated plasma protein-A (PAPP-A), adiponectin (APN), and high mobility group box-1 (HMGB1). Methods: A total of 146 patients with GH admitted to the Zibo Central Hospital between April 2018 and January 2020 were analyzed retrospectively. The control group (Con group, n=71) was treated by labetalol monotherapy, and on this basis, the research group (Res group, n=75) was additionally given aspirin. The following criteria of the 2 groups were evaluated: total effectiveness rate, incidence of adverse reactions, blood pressure-associated indices, coagulation function-associated indices, changes in serum PAPP-A, APN, and HMGB1 levels, adverse maternal and infant outcomes, and neonatal Apgar score. Results: After therapy, the Res group showed a notably higher total effective rate than the Con group, with no remarkable difference in the incidence of adverse reactions. Additionally, compared to the Con group, the Res group showed notably lower systolic blood pressure (SBP) and diastolic blood pressure (DBP), greatly improved coagulation function, significantly lower levels of serum PAPP-A and HMGB1, and significantly higher level of serum APN. Moreover, the incidence of adverse maternal and infant outcomes in the Res group was much lower than that in the Con group after therapy, and the one- and five-min Apgar scores of neonates in the Res group were both notably higher than those in the Con group after delivery. Conclusion: For patients with GH, aspirin combined with labetalol can effectively control blood pressure, improve coagulation function and clinical efficacy, lower serum PAPP-A and HMGB1, and increase serum APN, and ameliorate maternal and infant outcome.

Keywords: Gestational hypertension, aspirin, labetalol, clinical efficacy

Introduction

Gestational hypertension (GH) is a condition of high blood pressure (BP) during pregnancy and is a common complication in the obstetrics department [1]. With primary clinical symptoms of proteinuria, edema, and multiple organ damage, it can give rise to serious complications such as coma, convulsion, and even maternal or infant death in severe cases [2]. GH is a common disease peculiar to women during pregnancy, with an incidence of approximate 5%-10% in China [3]. The adverse maternal and infant outcomes caused by this disease mainly include postpartum hemorrhage, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, fetal abortion, fetal growth restriction, fetal distress, fetal malformation, and neonatal asphyxia, which are primary causes of maternal and perinatal death [3]. Currently, the clinical pathogenesis of GH is still under investigation. However, many studies have revealed its association with excessive oxidative stress, genetic factors, systemic vascular endothelial cell damage, nutrient deficiency, immune imbalance in the maternal-fetal interface, and insulin resistance [4, 5]. Pregnant women with GH experience a series of changes such as coagulation function abnormality, increased inflammatory factors including high mobility group box-1 (HMGB1), and adiponectin (APN) that decreases with the severity of the disease [6-8]. Associated plasma protein-A (PAPP-A) is synthesized and secreted by syncytiotrophoblasts

and placental X cells in the body. It can enter the fetal and maternal blood circulation and plays an essential role in the immune and metabolic systems, and its level will increase in patients with GH [9, 10]. At present, GH is mainly treated by drugs and surgery. The principle of drug therapy is mainly to lower BP, improve microcirculation, relieve spasms, and expand capacity. Surgical therapy, as the only effective treatment for GH, is mainly to terminate pregnancy [11, 12]. Therefore, finding a safe and effective drug treatment scheme is of great value for clinical practice [13].

Labetalol is widely used in treatment of GH. With a strong effect on dilating the vascular function of patients, it can accelerate the recovery of systemic arteriolar vasospasm and thus lower the heart load, improve coronary circulation and reduce myocardial oxygen consumption. It also has a significant and lasting effect on lowering the BP, and the lowered BP is not likely to rebound after drug withdrawal [14, 15]. Aspirin is able to suppress the activity of cyclooxygenase and interfere with the conversion of arachidonic acid into TXA2, so it can reduce the production of TXA2 in platelets, inhibit platelet aggregation and thrombosis, and reduce vascular resistance, thereby lowering BP and relieving proteinuria and organ damage [16, 17]. But the effectiveness of one single drug is often limited. Therefore, in recent years, studies have been constantly exploring the efficacy of the combined application of two or even more drugs, with encouraging results [18]. Nevertheless, there are few studies on the combination therapy of aspirin and labetalol in the treatment of GH [19].

This study applied aspirin combined with labetalol to patients with GH, to determine its efficacy in this disease and its influence on serum PAPP-A, APN, and HMGB1.

Materials and methods

General materials

A total of 146 patients with GH admitted to the Zibo Central Hospital during April 2018 and January 2020 were enrolled. These patients were assigned to the control group (Con Group) or the research group (Res group). The Con group (n=71) was treated by labetalol monotherapy, while the Res group (n=75) was given aspirin additionally. The Res group was composed of patients between 23 and 35 years old (average: 29.78±2.53), while the Con group was composed of patients between 24 and 36 years old (average: 29.35±2.41). This study was approved by the Ethics Committee of Zibo Central Hospital. The study subjects and their families were informed of this study and signed an informed consent.

Inclusion and exclusion criteria

Inclusion criteria: Patients meeting the diagnostic criteria of GH [20]; Patients with singleton pregnancy.

Exclusion criteria: Patients allergic to the study medication; Patients with severe primary heart, liver, kidney, or other organ diseases, primary hypertension or coagulation dysfunction; Patients with cognitive impairment, central nervous system diseases or severe peripheral nerve diseases. Patients with incomplete clinical data.

Treatment methods

All patients were given routine antenatal care guidance after admission, covering diet, exercise, and health education.

In the Con group, each patient was treated with 50 mg labetalol hydrochloride injection (Desano Pharmaceutical Co., Ltd., Jiangsu, CN, SFDA Approval No.: H32026121) + 500 ml 5% glucose injection through intravenous drip, once a day, on the basis of routine antenatal care guidance. During the medication, vital signs including respiration, BP, and heart rate of each patient were closely monitored. When the BP of the patient dropped to 140/90 mmHg, she was asked to orally take labetalol tablets (Kaili Pharmaceutical Co., Ltd., Zhengzhou, CN, SFDA Approval No.: H41024906) at 100 mg/time, three times/d instead.

For the Res group, each patient was administrated additionally with low-dose aspirin (Cisen Pharmaceutical Co., Ltd., Jining, CN, SFDA Approval No.: H20113013) at 50 mg/time, twice a day, on the basis of therapy for the Con group. The two groups were treated continuously until 1 day before delivery.

Outcome measures

Primary outcome measures: (1) The total effectiveness rate: Efficacy evaluation criteria were

as follows. Markedly effective: The signs were improved, symptoms were alleviated or disappeared, and BP dropped to a normal level; effective: The signs, symptoms and BP were ameliorated; ineffective: The signs and symptoms did not change or deteriorated, and BP did not drop to a normal level. Total effective treatment rate (%) = (Number of markedly effectively treated patients + that of effectively treated patients)/total number of patients × 100%. (2) Coagulation function-associated indices: Fasting venous blood (5 mL) was drawn from all patients before therapy and after 7 days of treatment, and the plasma prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB), and D-dimer (D-D) were detected using an automatic coagulometer (Sysmex Corporation, Japan, SysmexCA7000). (3) Levels of serum PAPP-A, APN, and HMGB1: Fasting venous blood (5 mL) was collected from all the patients before and after 7 days of treatment, and PAPP-A, APN, and HMGB1 in the blood were measured by ELISA under strict instructions of human APN ELISA kit (Shanghai Fuyu Biotechnology Co., Ltd., Shanghai, China, FY-04029H2), and human PAPP-A and HMGB1 ELISA kits (Shanghai Jingkang Bioengineering Co., Ltd., Shanghai, China, JK-(a)-1797 and JK-(a)-0198).

Secondary outcome measures: (1) Incidence of adverse reactions: Adverse reactions, including palpitation, hypotension, gastrointestinal bleeding, nausea and vomiting, dizziness, and fatigue, were recorded in both groups. (2) BP-associated indices: The systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the two groups were measured by a multifunctional ECG monitor (Shenzhen Keman Medical Equipment Co., Ltd., Shenzhen, China, STAR8000E) before treatment and after 7 days of treatment. Each measurement was carried out repeatedly in a quiet state three times, and results were averaged. (3) The Apgar score: After delivery, the one- and five-min Apgar scores of neonates were evaluated based on the Apgar score criteria [21]. Normal: 8-10 points; mild asphyxia: 4-7 points; severe asphyxia: 0-3 points. (4) Adverse maternal and infant outcomes: We recorded the adverse maternal and infant outcomes including cesarean section, postpartum hemorrhage, placental abruption, fetal intrauterine distress, and neonatal asphyxia in the two groups during delivery.

Statistical analysis

Data in this study were statistically processed by SPSS24.0 (IBM Corp, Armonk, NY, the States), and visualized into corresponding figures using GraphPad Prism 7. Enumerated data, presented by [n (%)], was compared by the chi-square test between groups. Measured data were expressed by (x±sd); The t-test of independent samples was used for inter-group comparison, and the paired T-test was used for intra-group comparison before and after treatment. $P<0.05$ indicates a significant difference.

Results

General materials

The two groups were not significantly different in clinical baseline data such as age, gestational week, body mass index (BMI), place of residence, education background, smoking history, drinking history, diabetes history, and hypertension history (all $P>0.05$, **Table 1**).

Total effectiveness rate of therapy

After therapy, the total effectiveness rate in the Res group was higher than that in the Con group (96.00% *vs.* 80.28%, $P<0.05$, **Table 2**).

Incidence of adverse reactions

After therapy, the incidence of adverse reactions was not significantly different between the Res group and the Con group (6.66% *vs.* 15.49%, $P<0.05$, **Table 3**).

BP-associated indices

Before therapy, the two groups were not significantly different in SBP and DBP (both $P>0.05$), while after 7 days of treatment, the DBP and SBP of both groups decreased greatly and the levels of them in the Res group were notably lower (both $P<0.05$, **Figure 1**).

Coagulation function-associated indices

Before therapy, no notable difference was found between the two groups in PT, APTT, Fib and D-D (all $P>0.05$), while after 7 days of therapy, both groups showed notable increases in PT, APTT, and TT, and notable decreases in Fib and D-D. The changes in the above indices

Table 1. General data in the two groups [n (%)] (x±sd)

Item	Research group (n=75)	Control group (n=71)	t/χ^2 value	*P*-value
Age (Y)	29.78±2.53	29.35±2.41	1.050	0.295
Gestational week (weeks)	33.85±2.47	34.02±2.33	0.427	0.669
BMI (kg/m^2)	24.18±3.54	24.28±3.32	0.175	0.860
Place of residence			0.021	0.882
Urban area	40 (53.33)	37 (52.11)		
Rural area	35 (46.67)	34 (47.89)		
Education background			0.201	0.653
≥ senior high school	30 (40.00)	31 (43.66)		
<senior high school	45 (60.00)	40 (56.34)		
Smoking history			0.271	0.602
Yes	23 (30.67)	19 (26.76)		
No	52 (69.33)	52 (73.24)		
Drinking history			0.432	0.510
Yes	26 (34.67)	21 (29.58)		
No	49 (65.33)	50 (70.42)		
Diabetes mellitus history			0.232	0.629
Yes	15 (20.00)	12 (16.90)		
No	60 (80.00)	59 (83.10)		
Hypertension history			0.050	0.822
Yes	17 (22.67)	15 (21.13)		
No	58 (77.33)	56 (78.87)		

were more significant in the Res group compared to the Con group (all P<0.05, **Figure 2**).

Apgar score

After delivery, the one- and five-min Apgar scores in the Res group were much higher than those in the Con group (P<0.05, **Figure 3**).

Levels of serum PAPP-A, APN and HMGB1

Before therapy, the two groups were not significantly different in the levels of serum PAPP-A, APN, and HMGB1 (all P>0.05), while after 7 days of therapy, both groups presented notable decreases in serum PAPP-A and HMGB1 and an increase in APN. The changes in the above values in the Res group were significantly greater than those in the Con group (all P<0.05, **Figure 4**).

Adverse maternal and infant outcomes

After therapy, the Res group showed much lower incidence of adverse maternal and infant outcomes than the Con group (8.00% *vs.* 28.17%, P<0.05, **Table 4**).

Discussion

GH is common among pregnant and puerperal women, with a complex pathogenesis that may be related to obesity, multiple pregnancies, and advanced maternal age [22]. Its primary pathologic feature is systemic arteriolar spasm, which causes narrowing of the uterine cavity and increased BP, finally leading to proteinuria and edema; Moreover, various organs of the patient's will be damaged due to ischemia and hypoxia, which seriously threatens the safety of mother and baby [23-25]. Therefore, it is crucial to find a safe and effective clinical therapy for GH.

In the study by Zhang et al. [26], the combination of magnesium sulfate, phentolamine, and nifedipine was found to effectively improve the hemodynamic indexes, 24-hour urinary protein, clinical efficacy and maternal and infant outcomes of patients with hypertensive disorder complicating pregnancy, and reduce adverse reactions. In the study by Easterling et al. [27], both labetalol and nifedipine demonstrated a strong ability of controlling the BP of patients and can be used as the first choice for treatment. Similar to the result obtained by Zhang et al., our study found that the Res group had a notably higher total effective rate than the Con group, suggesting a stronger effect of aspirin combined with labetalol in controlling BP and improving clinical efficacy. Our study also compared the incidence of adverse reactions between the two groups after therapy, and found no notable difference between them. This suggests that aspirin combined with labetalol is safe and effective because it will not increase the incidence of adverse drug reactions. The SBP and DBP of patients are strong indicators for clinical efficacy. In our study, the Res group showed a more notable decrease in BP than the Con group, indicating that aspirin combined with labetalol could better lower BP, which was in line with the result obtained by Easterling et al. [27]. The study by Webster et al. [14] revealed

Table 2. Comparison of total effectiveness rate between the two groups after therapy [n (%)]

Group	Effectively treated patients	Markedly effectively treated patients	Ineffectively treated patients	Total incidence
Research group (n=75)	47 (62.67)	25 (33.33)	3 (4.00)	72 (96.00)
Control group (n=71)	28 (39.44)	29 (40.84)	14 (19.72)	57 (80.28)
χ^2	-	-	-	8.759
P	-	-	-	0.003

Table 3. Comparison of incidence of adverse reactions between the two groups after therapy [n (%)]

Group	Palpitation	Hypotension	Gastrointestinal bleeding	Nausea and vomiting	Dizziness and hypodynamia	Total incidence
Research group (n=75)	1 (1.33)	0 (0.00)	1 (1.33)	2 (2.67)	1 (1.33)	5 (6.66)
Control group (n=71)	2 (2.82)	2 (2.82)	1 (1.41)	3 (4.23)	3 (4.23)	11 (15.49)
χ^2	-	-	-	-	-	2.912
P	-	-	-	-	-	0.087

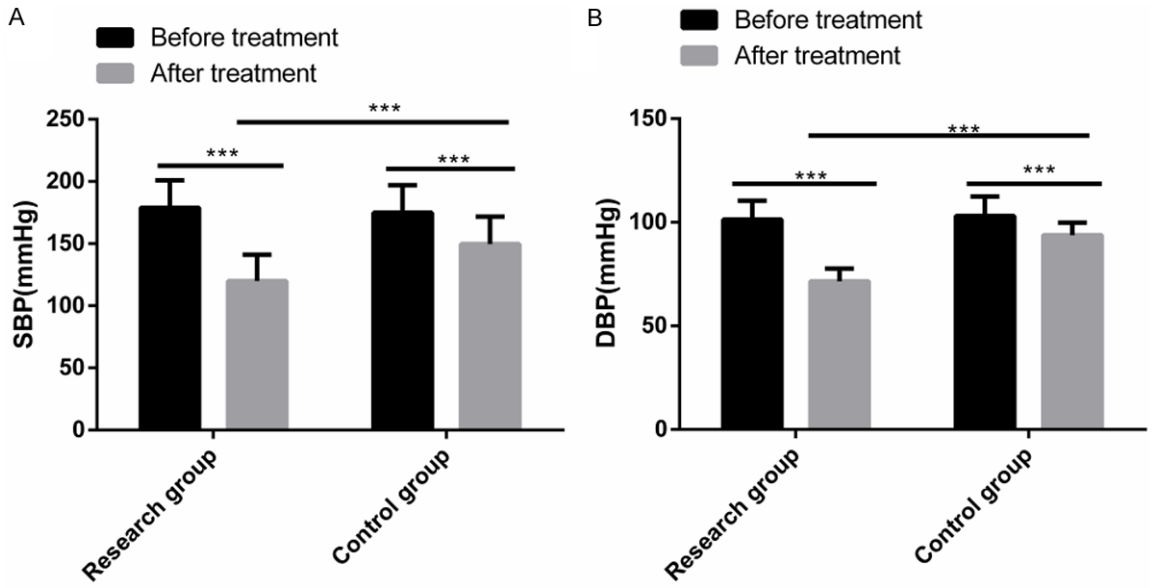

Figure 1. Comparison of BP-associated indices between the two groups. After 7 days of treatment, the SBP (A) and DBP (B) of both groups decreased, and their levels in the research group were lower than those of the Control group. Note: ***P<0.001.

that both labetalol and nifedipine can effectively control patients' BP, but the efficacy was more potent when they were used as a combination, which was similar to our research results. In addition, the present study revealed notably higher PT, APTT, and TT levels and lower Fib and D-D levels in the Res group than those of the Con group, suggesting that aspirin combined with labetalol could relieve the hypercoagulable state more effectively. It may be explained by the fact that aspirin can effectively inhibit platelet aggregation and thrombosis, thus improving the hypercoagulable state of the body and avoiding re-increase of BP. Similar to the results of our study, the study by Theilen et al. [28] revealed that low-dose aspirin could greatly reduce patients' platelet level and relieve the hypercoagulable state. Moreover, compared with the Con group, our Res group presented notably lower PAPP-A and HMGB1 levels and a notably higher APN level, indicating a stronger effect of aspirin combined with labetalol in controlling the inflammatory reaction and maintaining the stability of BP.

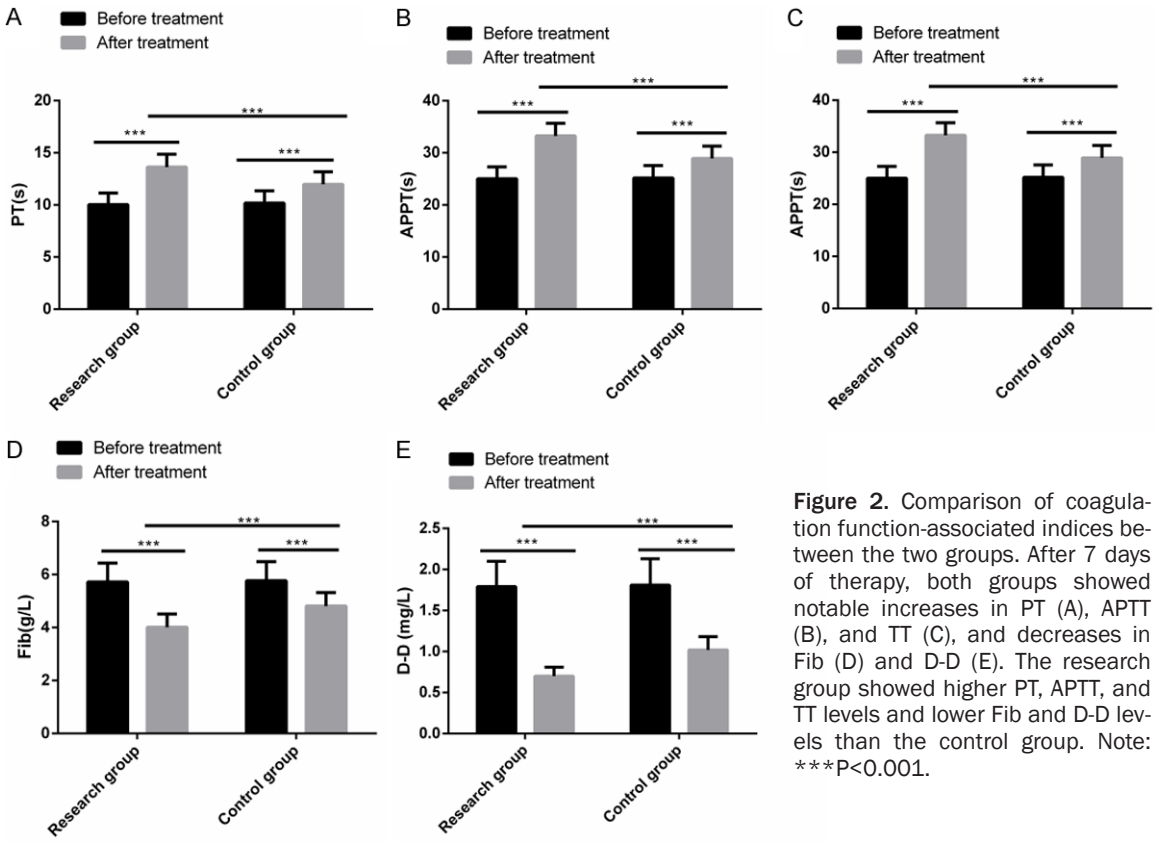

Figure 2. Comparison of coagulation function-associated indices between the two groups. After 7 days of therapy, both groups showed notable increases in PT (A), APTT (B), and TT (C), and decreases in Fib (D) and D-D (E). The research group showed higher PT, APTT, and TT levels and lower Fib and D-D levels than the control group. Note: ***P<0.001.

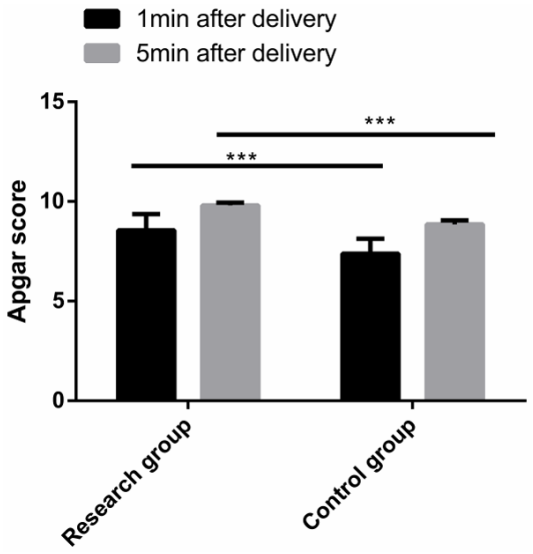

Figure 3. Comparison of Apgar scores. The research group had higher one and five-min Apgar scores than the control group after delivery. Note: ***P<0.001.

According to the study by Zhang et al. [29], patients with GH had notably higher levels of PAPP-A and HMGB1 than healthy individuals. Labetalol can effectively block α and β receptors and dilate peripheral blood vessels to produce a hypotensive effect. Aspirin has the effect of anticoagulation and can improve local blood supply. By inhibiting cyclooxygenase and reducing arachidonic acid, it can inhibit platelet aggregation and thrombutane production, which to some extent, reduces the sensitivity of blood vessels to active substances, thus promoting blood vessel dilation and producing an antihypertensive effect [30, 31]. The study by Magee et al. [32] revealed a role for labetalol in improving maternal and infant outcomes. Furthermore, in our study, the Res group had notably higher one- and five-min Apgar scores than the Con group after delivery, with a lower incidence of adverse maternal and infant outcomes. These results indicate that aspirin can effectively control the BP andreduce the disease's damage to the mother and infant, which is similar to the results obtained by Magee.

To sum up, in patients with GH, aspirin combined with labetalol can render more benefits as a safe and effective scheme, because it can more significantly contribute to optimal BP, better coagulation function, lower serum PAPP-A

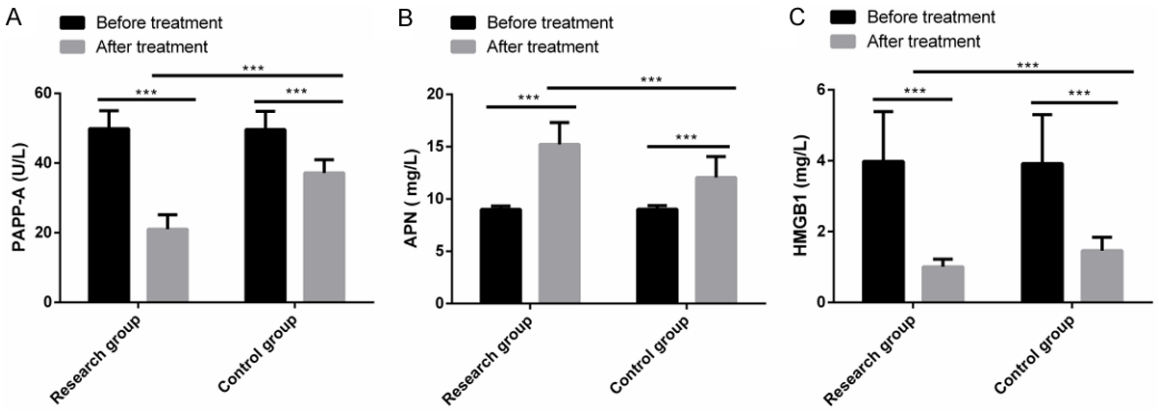

Figure 4. Comparison of serum PAPP-A, APN, and HMGB1 levels between the two groups. After 7 days of therapy, both groups presented notable decreases in serum PAPP-A and HMGB1 and an increase in APN. The research group showed lower levels of serum PAPP-A and HMGB1 and a higher levels of APN than the control group. Note: ***P<0.001.

Table 4. Comparison of incidence of adverse maternal and infant outcomes between the two groups after therapy [n (%)]

Group	Cesarean delivery	Postpartum hemorrhage	Placental abruption	Fetal intrauterine distress	Neonatal asphyxia	Total incidence
Research group (n=75)	3 (4.00)	2 (2.67)	0 (0.00)	0 (0.00)	1 (1.33)	6 (8.00)
Control group (n=71)	7 (9.86)	4 (5.63)	3 (4.23)	2 (2.82)	4 (5.63)	20 (28.17)
X^2	-	-	-	-	-	10.140
P	-	-	-	-	-	0.001

and HMGB1, and higher serum APN, thus delivering higher clinical efficacy and ameliorating adverse maternal and infant outcomes. Although this study has achieved encouraging results, it still has some limitations. For example, longer-term follow-up would better show the long-term efficacy of treatment. We also plan to conduct animal experiments to further probe its possible mechanism of action.

Disclosure of conflict of interest

None.

Address correspondence to: Cuicui Wang, Obstetrics Department, Zibo Central Hospital, No. 54 on Gongqingtuan West Road, Zibo 255000, Shandong, China. Tel: +86-186781877702; E-mail: Wangcuicui77@163.com

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