EFFECT OF MAGNESIUM SULFATE COMBINED WITH MISOPROSTOL ON POSTPARTUM HEMORRHAGE AND HS-CRP, ANG-II, PGE2 IN PATIENTS WITH PREGNANCY-INDUCED HYPERTENSION SYNDROME

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ABSTRACT

Objective: *To study the effect of magnesium sulfate combined with misoprostol on postpartum hemorrhage and hs-CRP, Ang-II, PGE2 in PIH patients.*

Methods: *A total of 159 PIH patients in our hospital from February 2018 to March 2019 were selected as research objects, and were enrolled into two groups according to different treatment methods. Among them, those treated by magnesium sulfate combined with misoprostol were taken as an intervention group (IG) (88 cases) and those treated by magnesium sulfate combined with oxytocin were regarded as a control group (CG) (71 cases). The clinical indexes (blood pressure, heart rate, respiration) and postpartum hemorrhage (time of the third stage of labor, effective control time of hemorrhage, amount of hemorrhage 2 h and 12 h after delivery) of patients in the two groups after treatment were observed. The efficacy of patients in both groups after treatment and the adverse reactions during treatment were recorded. Enzyme-linked immunosorbent assay (ELISA) was used to detect the levels of hs-CRP, Ang-II and PGE2 before and after treatment. The predictive value of hs-CRP, Ang-II and PGE2 on the efficacy of patients was also analyzed.*

Results: *Blood pressure, heart rate and respiration got better after treatment in the IG than those in the CG, and postpartum hemorrhage improved better after treatment in the IG than that in the CG. After treatment, the total effective rate in the IG was obviously higher than that in the CG, the incidence of adverse reactions in the IG was significantly lower than that in the CG, and hs-CRP, Ang-II and PGE2 in the IG were dramatically lower than those in the CG. The predicted AUC of serum hs-CRP for ineffective treatment was 0.809, that of Ang-II for ineffective treatment was 0.810, and that of PGE2 for ineffective treatment was 0.896.*

Conclusion: *Magnesium sulfate combined with misoprostol on PIH can improve the blood pressure of patients, reduce the risk of postpartum hemorrhage, and improve the expression of hs-CRP, Ang-II and PGE2 in serum.*

Keywords: *Magnesium sulfate combined with misoprostol, pregnancy-induced hypertension syndrome, postpartum hemorrhage, hs-CRP, Ang-II, PGE2.*

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Introduction

Pregnancy-induced hypertension syndrome (PIH) is a common disease of pregnant women during pregnancy, most of which occurs 20 weeks after pregnancy[1]. Studies have shown that 20% of maternal deaths in obstetrics and gynecology are related to PIH. Mild pregnant women will suffer proteinuria and edema, while severe cases often suffer from blurred vision and headache[2]. PIH is also a common risk factor for postpartum hemorrhage[3]. Postpartum hemorrhage is one of the main causes of maternal death[4], which refers to the occurrence of hemostasis disorder within 24 h after delivery, and uterine atony is another cause[5]. Without timely treatment, it will lead to hypovolemic shock, while severe hemorrhage will bring about death, which seriously affects the postpartum recovery of patients[6]. Therefore, it's particularly important to adopt effective methods to stop bleeding after delivery.

Clinically, the increase of local blood pressure will further aggravate the amount of postpartum hemorrhage, and relieving vasospasm is a vital measure for treatment and prevention[7-8]. Magnesium sulfate is an anticonvulsant, which can inhibit the neuromuscular and blood vessels of PIH patients by

central inhibition, and indirectly reduce their blood pressure by dilating blood vessels[9]. Some studies have shown that it can act on vascular smooth muscle to dilate peripheral blood vessels, and has a strong antihypertensive effect. It can also reduce blood pressure and relieve cardiac and cerebral insufficiency of pregnant women[10]. Misoprostol is an analog of prostaglandin E1, which can be used for oral, rectal and vaginal administration of parturients. It undergoes de-esterification reaction in the liver to become Misoprostol acid, which causes changes in the physical and chemical structure of cervical collagen, thus leading to softening and maturation of the cervix and facilitating cervical dilatation[11].

Clinical studies show that pregnant women with hypertension during pregnancy show marked differences in inflammatory process and cardiovascular risk biomarkers[12]. For example, hs-CRP and Ang-II increased significantly in the serum of PIH patients, which showed that hs-CRP could be used as a predictive marker of disease severity in them[13-14]. PGE2 is a crucial cell growth and regulation factor. Studies show that when the body is affected to different degrees, the synthesis and secretion of PGE2 will be significantly reduced, resulting in the increased reactivity of vascular walls to pressurized substances, thus increasing the pressure of peripheral blood vessels and causing the increase of blood pressure of patients[15, 16].

At present, there is little clinical research on the combined treatment of magnesium sulfate and misoprostol for PIH patients. This study aims to improve the reference basis for PIH patients by observing the effect of the combined treatment of magnesium sulfate and misoprostol on efficacy, postpartum hemorrhage and expression of hs-CRP, Ang-II and PGE2.

Materials and methods

General information

A total of 159 PIH patients for diagnosis of pregnancy in our hospital from February 2018 to March 2019 were selected as research objects. Among them, those treated by magnesium sulfate combined with misoprostol was taken as an intervention group (IG) (88 cases) and those treated by magnesium sulfate combined with oxytocin were regarded as a control group (CG) (71 cases).

Inclusion criteria:

• In line with the diagnostic criteria for PIH[17], all parturients were singleton pregnancy, gestational weeks >24 weeks, amniotic fluid was normal, prostaglandin inhibitors had not been used recently, there was no taboo on the drugs used in this study, and fetal development was normal;

• Patients and their families understood and signed a certificate of consent regarding the process and purpose of this study, and it has been approved by the Medical Ethics Committee of our hospital.

Exclusion criteria were as follows:

• Patients with bronchial asthma, patients who could not cooperate due to mental diseases;

• Patients who withdrew from the experiment midway;

• Patients with serious medical diseases;

• Patients with multiple pregnancies;

• Patients who had not signed informed consent;

• Patients who had not been interviewed.

Treatment methods

Patients in the CG were given 10 ml+ concentration magnesium sulfate injection during delivery, which was put into 10% concentration 100 ml glucose injection and given intravenous drip. All of them needed to finish the drip within 30 min, and the drip could be completed according to their condition of the standard of 1-2 g/h until they delivered successfully. They were given oxytocin immediately after successful delivery (Jinsui Biotechnology Co., Ltd., Shanghai, China, 50-56-6). The application method was to add 20 IU of oxytocin into 500 mL of sodium chloride injection with a concentration of 0.9%, administer it intravenously, and massage the patient's uterus to promote uterine contraction and hemostasis.

All those in the IG were additionally treated with misoprostol (New Hualian Pharmaceutical Co., Ltd., Shanghai, China, H20094136) on the basis of the treatment in the CG. It was 200 μg of oral medication after the patient successfully delivered. At the same time, 200 μg of misoprostol was inserted into the rectum, followed by uterine massage.

Outcome measures

Blood pressure and other clinical indicators

After treatment, blood pressure (systolic pressure, diastolic pressure), heart rate and respiration of patients in the two groups were observed and recorded.

Clinical symptoms

After treatment, we observed and recorded the time of the third stage of labor, the effective control time of hemorrhage, and the amount of hemorrhage 2 h and 12 h after delivery in both groups.

Postpartum hemorrhage efficacy

• Markedly effective:

After treatment, the clinical symptoms (blood pressure, heart rate) and other indicators of all patients had been effectively improved, the uterine contraction of patients had been enhanced, and the amount of hemorrhage had been greatly reduced;

• Effective:

The clinical symptoms (blood pressure, heart rate) and uterine contraction of all patients after treatment had been significantly improved, and the amount of postpartum hemorrhage had been effectively controlled;

• Ineffective:

After treatment, the patient did not achieve the above effect, the bleeding volume was not controlled, and he was transferred to other therapies for treatment. The total effective rate = (markedly effective number +effective number)/total number ×100%.

Adverse reactions

The adverse reactions of patients in the two groups after medication were recorded, mainly including vomiting, nausea, shiver, vertigo, limb weakness and fever.

Detection of hs-CRP, Ang-II and PGE2 levels

5 mL of venous blood was drawn from patients in the two groups before and after treatment, respectively. It was centrifuged 10 min at 1500Xg, 4°C, and placed in a low temperature refrigerator at -70°C for later use. The concentrations of high sensitivity C-reactive protein (hs-CRP), angiotensin II (Ang-II) and prostaglandin E2 (PGE2) were assessed via enzyme-linked immunosorbent assay (ELISA) (18), in accordance with the instructions of hs-CRP (Elabscience Biotechnology Co.,Ltd., Beijing, China), Ang-II (Winter Song Boye Biotechnology Co. Ltd., Beijing, China) and PGE2 (Fine Biotechnology Co., Ltd., Wuhan, China).

Statistical methods

SPSS version 21.0 statistical software (EASYBIO, China) was used for analysis. The counting data within groups were expressed by the number of cases/percentage [n(%)]. The comparison of those data between groups adopted chi-square test, and when the theoretical frequency in the chi-square test was less than 5, the continuity correction chi-square test was adopted. The measurement data were expressed by mean±SD; the comparison of those data between groups adopted independent-samples t test, and the comparison of those data within groups successively adopted paired t test. The ROC curve was used to evaluate the efficacy of serum hs-CRP, Ang-II and PGE2 in the diagnosis of patients after treatment. The experimental pictures were drawn via GraphPad Prism 6 software. $P<0.05$ was considered to be statistically different.

Results

Baseline data of patients in the two groups

There was no marked difference in BMI, age, gestational weeks, abdominal circumference, total cholesterol, educational background, diabetes history, drinking history, smoking history, place of residence, economic level and other general data between the IG and the CG before re-pregnancy ($P>0.05$) (Table 1).

Factor	Intervention group (IG) (n=88)	Control group (CG) (n=71)	χ^2/t	P
BMI before pregnancy (kg/m^2)			0.026	0.871
< 23	41 (46.59)	34 (47.89)		
≥ 23	47 (53.41)	37 (52.11)		
Age (years)			0.384	0.535
< 35	49 (55.68)	43 (60.56)		
≥ 35	39 (44.32)	28 (39.44)		
Gestational age (week)			1.154	0.250
	24.46±1.67	24.75±1.45		
Abdominal circumference (cm)			0.969	0.334
	100.35±6.62	101.35±6.27		
Total cholesterol (mmol/L)			1.255	0.211
	5.76±1.53	6.05±1.34		
Education			2.512	0.113
Below high school	36 (40.91)	38 (53.52)		
Above high school	52 (59.09)	33 (46.48)		
History of diabetes			2.857	0.091
No	61 (69.32)	40 (56.34)		
Yes	27 (30.68)	31 (43.66)		
History of drinking			1.603	0.205
No	63 (71.59)	57 (80.28)		
Yes	25 (28.41)	14 (19.72)		
History of smoking			0.001	0.977
No	68 (77.27)	55 (77.46)		
Yes	20 (22.73)	16 (22.54)		
Place of residence			0.341	0.559
Countryside	43 (48.86)	38 (53.52)		
Cities and towns	45 (51.14)	33 (46.48)		
Economic level			1.166	0.558
Difficult	23 (26.14)	22 (30.99)		
well-to-do	36 (40.91)	31 (43.66)		
Rich	29 (32.95)	18 (25.35)		

Table 1: Baseline data of patients in the two groups [n(%), mean±SD].

Comparison of clinical indexes such as blood pressure after treatment of patients between both groups

After treatment, systolic pressure, diastolic pressure, heart rate and respiration in the IG got better than those in the CG ($P < 0.05$) (Table 2).

Group	n	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Heart rate (times /min)	Breathing (times /min)
Intervention group (IG)	88	119.47±10.45	86.34±7.73	75.87±5.34	23.24±4.12
Control group (CG)	71	127.54±10.35	97.76±7.92	74.12±5.21	24.68±4.10
t	-	4.862	9.160	2.077	2.196
P	-	<0.001	<0.001	0.039	0.029

Table 2: Comparison of blood pressure of patients in both groups after treatment (mean±SD).

Comparison of clinical symptoms of patients between both groups

Observing the clinical symptoms of patients in the two groups, we found that the time of the third stage of labor and the effective bleeding control time of the patients in the IG after treatment were both less than those in the CG ($P<0.05$), and the amount of bleeding 2 h and 12 h after delivery was also significantly less than that in the CG ($P<0.05$) (Table 3).

Group	n	Time of the third stage of labor (min)	Effective bleeding control time (min)	Postpartum 2 h hemorrhage (mL)	12 h postpartum hemorrhage (mL)
Intervention group (IG)	88	7.83±1.25	4.37±0.82	202.24±11.25	321.35±15.35
Control group (CG)	71	12.39±2.71	7.56±0.91	257.76±12.65	416.65±15.87
t	-		23.220	29.260	38.330
P	-	<0.001	<0.001	<0.001	<0.001

Table 3: Comparison of clinical symptoms between patients in the two groups (mean±SD).

Comparison of clinical efficacy of patients between the two groups after treatment

After treatment, 63 cases (71.59%), 23 cases (26.14%), 2 cases (2.27%) were ineffective in the IG, with a total effective rate of 97.73%. Besides, 28 cases (39.44%), 40.85%, 14 cases (19.72%) were ineffective in the CG, with a total effective rate of 80.28%. The total effective rate of the IG was higher than that of the CG ($P<0.05$) (Table 4).

Group	n	Markedly effective	Effective	Ineffective	Total efficiency
Intervention group (IG)	88	63 (71.59)	23 (26.14)	2 (2.27)	86 (97.73)
Control group (CG)	71	28 (39.44)	29 (40.85)	14 (19.72)	57 (80.28)
χ^2	-	-	-	-	13.211
P	-	-	-	-	0.001

Table 4: Comparison of clinical efficacy of patients in the two groups after treatment [n(%)].

Comparison of adverse reactions of patients between the two groups during treatment

During the treatment, the probability of vomiting, nausea, shiver, vertigo, limb weakness and fever in the IG was dramatically lower than that in the CG ($P<0.05$) (Table 5).

Group	n	Vomiting and nausea	Shiver	Vertigo	Limb weakness	Fever	Total incidence
Intervention group (IG)	88	2 (2.27)	1 (1.14)	0 (0.00)	1 (1.14)	1 (1.14)	5 (5.68)
Control group (CG)	71	3 (4.23)	2 (2.82)	1 (1.41)	2 (2.82)	1 (1.41)	9 (12.68)
χ^2	-	0.492	0.599	1.247	0.438	0.023	2.394
P	-	0.483	0.438	0.264	0.599	0.878	0.122

Table 5: Comparison of adverse reactions of patients between the two groups during treatment [n(%)].

Comparison of hs-CRP expression levels between patients in the two groups before and after treatment

There was no remarkable difference in the hs-CRP expression level between patients in the two groups before treatment ($P>0.05$); hs-CRP was improved after treatment. The hs-CRP expression level in the IG was significantly lower than that in the CG ($P<0.05$) (Figure 1).

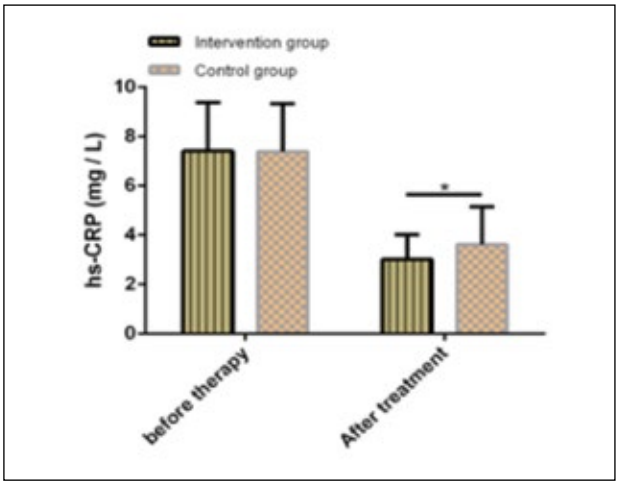

Figure 1: Comparison of hs-CRP expression level between patients in the two groups before and after treatment.There was no difference in the hs-CRP expression between the two groups before treatment; its expression in the IG was dramatically lower than that in the CG after treatment.

Note: compared with before treatment, $^{*}<0.05$; compared with CG after treatment, $^{\#}<0.05$.

Comparison of Ang-II expression levels of patients before and after treatment

There was no marked difference in the Ang-II expression level between patients in the two groups before treatment ($P>0.05$); Ang-II was improved af-

ter treatment. The Ang-II expression level in the IG was significantly lower than that in the CG (P<0.05) (Figure 2).

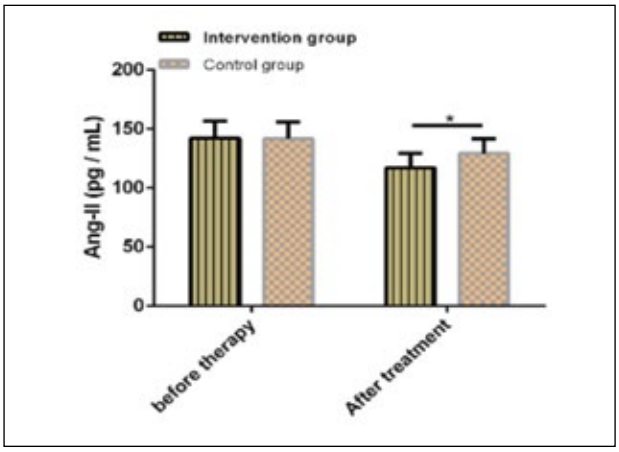

Figure 2: Comparison of Ang-II expression level between patients in the two groups before and after treatment. There was no difference in Ang-II expression between both groups before treatment; its expression in the IG was significantly lower than that in the CG after treatment.
*Note: compared with before treatment, *<0.05; compared with CG after treatment, #<0.05.*

Comparison of PGE2 expression levels before and after treatment between patients in the two groups

There was no remarkable difference in the PGE2 expression level between patients in the two groups before treatment (P>0.05); PGE2 was improved after treatment. The PGE2 expression level in the IG was significantly higher than that in the CG (P<0.05) (Figure 3).

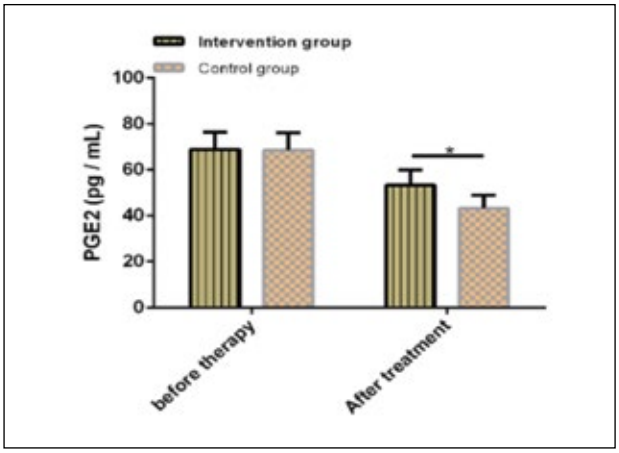

Figure 3: Comparison of PGE2 expression level between patients in the two groups before and after treatment. There was no difference in PGE2 expression between patients in the two groups before treatment; its expression in the IG was significantly higher than that in the CG after treatment.
*Note: compared with before treatment, *<0.05; compared with CG after treatment, #<0.05.*

Predictive value of serum hs-CRP, Ang-II, PGE2 on efficacy

According to the different therapeutic effects of the patients, we divided those with PIH into an effective group (143 cases) and an ineffective group (16 cases). After examination, it was found that the serum hs-CRP, Ang-II, PGE2, hs-CRP, Ang-II and PGE2 in the effective group were (3.06±1.05), (118.53±12.19), (53.34±6.35), (4.79±1.57), (134.62±12.85) and (41.62±6.54) respectively.

The difference was statistically significant (P<0.05). We further found that the predicted AUC of hs-CRP for ineffective treatment was 0.809, the predicted AUC of Ang-II for ineffective treatment was 0.810, and the predicted AUC of PGE2 for ineffective treatment was 0.896 through ROC analysis. The results showed that hs-CRP, Ang-II and PGE2 all had good predictive value (Figure 4).

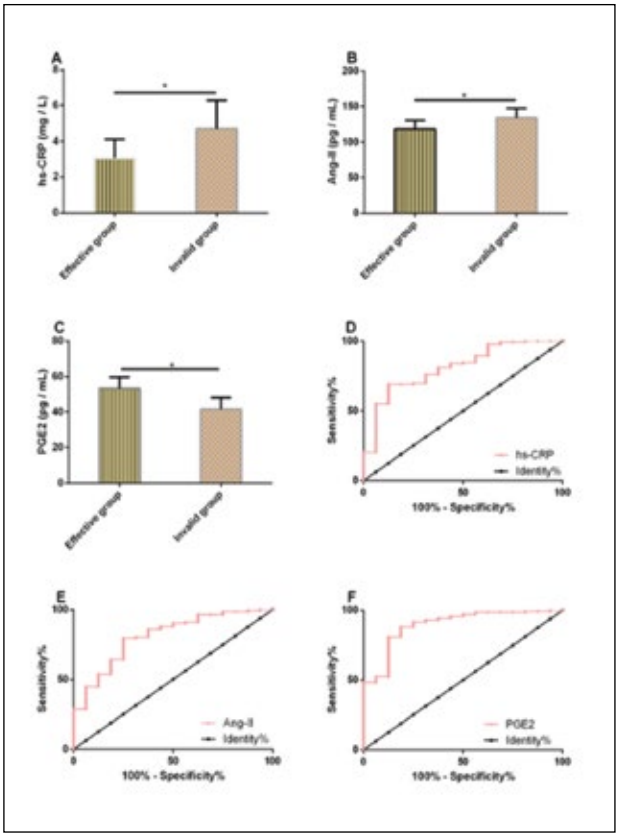

Figure 4: Predictive value of serum hs-CRP, Ang-II, PGE2 on efficacy. (A) The hs-CRP expression in serum of the effective group was significantly lower than that of the ineffective group. (B) The Ang-II expression in serum of the effective group was significantly lower than that of the ineffective group. (C) The PGE2 expression in serum of the effective group was significantly higher than that of the ineffective group. (D) predictive value of serum hs-CRP for efficacy (E) predictive value of serum Ang-II for efficacy. (F) predictive value of serum PGE2 for efficacy
*Note: *P<0.05.*

Discussion

Hypertension is one of the most common diseases in pregnancy, which can lead to decimus complicated pregnancy.

Gestational hypertension can bring about increased proteinuria, renal insufficiency, severe headache, etc. of pregnant women, and is also tied to adverse reactions (premature delivery, maternal and infant mortality, neonatal death, etc.)[19]. PIH, as a common complication of pregnant women during pregnancy, is one of the vital causes of maternal death caused by postpartum hemorrhage, and active prevention is quite significant. Clinical studies show that the key factors to prevent postpartum hemorrhage during uterine contraction are enhanced[20-21].

In this study, we used magnesium sulfate combined with misoprostol to treat PIH patients. Magnesium sulfate is widely used clinically as uterine contraction inhibitor. It may be mentioned that it is used to prevent premature contraction and inhibit the occurrence of preterm labor in parturients. It also has anti-inflammatory properties[22]. It is also shown that it can reduce blood pressure and urine protein in hypertensive rats during pregnancy[23]. The local blood pressure of PIH patients began to increase due to spasm of small veins, which eventually led to postpartum hemorrhage[24].

This study combined misoprostol for treatment. Misoprostol is a prostaglandin E1 analog with strong uterine contraction, which is mostly used to prevent postpartum hemorrhage clinically[25]. The results of this study showed that systolic pressure, diastolic pressure, heart rate and respiration of the patients in the IG after treatment got better than those in the CG, and the time of the third stage of labor, the effective control time of hemorrhage, and the amount of hemorrhage 2 h and 12 h after delivery in the IG were also significantly lower than those in the CG. This showed that magnesium sulfate combined with misoprostol could effectively reduce the blood pressure and postpartum hemorrhage of patients. Misoprostol could dilate blood vessels and promote contraction of uterine smooth muscle, while the combined application with magnesium sulfate could synergistically control maternal blood pressure, promote postpartum uterine contraction and reduce the possibility of postpartum hemorrhage. The total effective rate of patients in the IG after treatment was significantly higher than that in the CG, indicating that magnesium sulfate combined with misoprostol had a high efficacy. PIH was prone to local blood pressure increase, which led to postpartum hemorrhage, while misoprostol could dilate spasm peripheral blood vessels, and reduce blood pressure and the risk of postpartum hemorrhage. Observing the adverse reactions of patients in the two groups during the treatment process, we found that they had adverse reactions such as vomiting, nausea, shiver, vertigo, limb weakness, fever, etc., but they were all within the clinically controllable range, proving that the combination of the two drugs had higher safety.

Hs-CRP is a non-specific inflammatory marker, which is one of the strongest predictors and risk factors of cardiovascular diseases, and indicates that it is significantly increased in the serum of PIH patients[26]. Wang L and others confirmed that the increase of serum hs-CRP level might be related to vascular endothelial cell injury in PIH patients, and it could be used as an auxiliary index to diagnose and determine the severity of pregnancy-induced hypertension[27]. Ang-II could promote hypertension due to systemic arteriole contraction and aldosterone secretion in adrenal cortex. Research manifested that increased sensitivity of blood vessels to Ang-II was a marker of human hypertension[28].

Other studies have shown that the content of PGE2 in the serum of PIH patients decreases, while the content of PGE2 can be significantly increased after drug treatment, which indicates that the change of PGE2 in the serum reflects the hypertension risk of pregnant women to some extent[29]. The results of this study showed that the expression levels of hs-CRP and Ang-II in the IG were significantly lower than those in the CG, while the PGE2 expression level was higher than that in the CG. This indicated that after magnesium sulfate combined with misoprostol treatment, the combination of the two groups could play a synergistic role in controlling blood pressure, so that the hypertension of patients could be effectively controlled. This also indicated that hs-CRP, Ang-II and PGE2 had potential value for early diagnosis of PIH. Research results on efficacy prediction manifested that the expression levels of s-CRP and Ang-II in serum of patients in the effective group were significantly lower than those in the ineffective group, while the PGE2 expression level was higher than that in the ineffective group. The predicted AUC of hs-CRP for ineffective treatment was 0.809, that of Ang-II for ineffective treatment was 0.810, and that of PGE2 for ineffective treatment was 0.896, which indicated that hs-CRP, Ang-II and PGE2 had higher predictive value for the efficacy of PIH patients.

Conclusion

Although this study confirmed that magnesium sulfate combined with misoprostol on PIH could improve patients' blood pressure, reduce the risk of postpartum hemorrhage, and improve the expression of hs-CRP, Ang-II and PGE2 in serum.

However, there is still room for improvement in this study. For example, we can supplement the basic experiments of the therapeutic mechanism of the two therapeutic methods, explore the risk factors that affect the efficacy of patients from the molecular level, increase the sample size of patients, and improve the accuracy and universality of the research results. In the future, we will gradually improve the research from the above perspective.

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