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Original Article

Effects of magnesium sulphuricum combined with low molecular weight heparin sodium on the blood pressure, D-D and hs-CRP levels in patients with severe preeclampsia

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Abstract: Objective: This study aimed to analyze the effects of magnesium sulphuricum combined with low molecular weight heparin sodium on blood pressure, D-dimer (D-D) and high-sensitivity C-reactive protein (hs-CRP) in patients with severe preeclampsia. Methods: A total of 103 patients with severe preeclampsia were analyzed for their clinical data and divided into the control group (CG) for treatment with magnesium sulphuricum and the observation group (OG) for treatment with magnesium sulphuricum and low molecular weight heparin sodium. The 2 groups were compared for diastolic blood pressure (DBP), systolic blood pressure (SBP), 24 h urine protein (PRO), D-D and high-sensitivity C-reactive protein (hs-CRP), number of gestational weeks for pregnancy termination, average treatment duration and complications. Results: After treatment, the SBP, DBP, mean arterial blood pressure (MABP), D-D and hs-CRP levels were lower, the PRO was less, the gestational weeks for pregnancy termination and average treatment duration were shorter in the OG ($P<0.05$). The incidence of complications was 7.69% (4/52) in the OG and 27.45% (14/51) in the CG ($P<0.05$). Conclusion: The combination of magnesium sulphuricum and low molecular weight heparin sodium in patients with severe preeclampsia can effectively control blood pressure, improve D-D and hs-CRP levels, inhibit inflammatory reactions and reduce the incidence of complications.

Keywords: Severe preeclampsia, magnesium sulphuricum, low molecular weight heparin sodium, blood pressure control, D-D, hs-CRP

Introduction

Clinically, preeclampsia is a disorder that occurs 20 weeks after pregnancy and is characterized by high proteinuria and blood pressure, and symptoms such as epigastric discomfort, vomiting, nausea, blurred vision and headache [1]. Severe preeclampsia is an idiopathic disease, and also results from hypertension in pregnancy, which is easily causes adverse maternal and infant outcomes. In serious cases, it may even endanger the life and safety of the perinatal infant and mother [2, 3]. Therefore, a scientific and effective way to treat the disease in real time becomes necessary [4].

The clinical treatment of preeclampsia follows the principles of sedation, anti-hypertension, spasmolysis, diuresis and dilatation if necessary, and termination of pregnancy in time according to the case severity, gestational weeks and response to treatment. Once eclampsia occurs and the conditions are effectively controlled, the pregnancy may be terminated [5, 6]. Magnesium sulphuricum is the drug of choice to prevent the development of severe preeclampsia turning into eclampsia, by effective control of the convulsions associated with eclampsia, and spasmolysis [7]. However, the high concentration of magnesium ions in the blood will damage the functions of the liver, the kidneys, and the respiratory system, and even lead to sudden death in severe cases. Therefore, the long-term application of magnesium sulphuricum at a high doses is not suggested in the clinic practice [8]. Low molecular weight

heparin sodium has the ability to enhance fibrinolytic activity, resisting thrombus and blood coagulation, promote the improvement of placental circulation, protect the kidneys, subsiding swelling, diuresis and reduce blood pressure [9, 10].

To further enhance the treatment of severe preeclampsia, effective control of blood pressure and improvement of D-dimer (D-D) and high-sensitivity C-reactive protein (hs-CRP) levels, magnesium sulphuricum was combined with low molecular weight heparin sodium, in this study.

Materials and methods

Materials

A total of 103 patients with severe preeclampsia in our hospital were analyzed for their clinical materials, and divided into the control group (CG, n=51) for treatment with magnesium sulphuricum, and the observation group (OG, n=52) for treatment with magnesium sulphuricum and low molecular weight heparin sodium. (1) Inclusion criteria: patients who complied with the diagnostic criteria for preeclampsia specified in the *Obstetrics and Gynecology* (Edition 7) [11], and had typical signs and syndromes of preeclampsia but no contraindications to the drugs studied, and thoes who provided informed consent. The Study was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University. (2) Exclusion criteria: some patients were excluded as (1) they had diseases in the liver and kidneys or infection, coagulation disorders, premature rupture of membranes, acute bacterial endocarditis, or (2) they were treated with drugs which affected the coagulation function within 1 month prior to the study, or (3) they had organ damage, were prone to bleeding or a tendency of bleeding or contradictions to the drugs studied.

Methods

CG: patients were advised to lie in the bed and maintain a low-fat and low-salt diet, and were closely monitored for intake and output. At the same time, by intravenous drip they were given a mixture of 25 ml 25% magnesium sulphuricum (manufacturer: Nanchang Baiyun Pharmaceutical Co., Ltd., approval document No.: GYZZ H20093036, specification: 500 g) and 100 ml 5% glucose solution (manufacturer: Sichuan Kelun Pharmaceutical Co., Ltd., approval document No.: GYZZ H20113501, specification: 1000 ml:100 g) at a high rate within 30 min, and then with a mixture of 60 ml 25% magnesium sulphuricum and 500 ml 5% glucose solution at the rate between 1.5 and 2.0 g/h. The daily total dose was controlled between 20 and 25 g until termination of the pregnancy. During the treatment, patients were closely monitored for breathing and urinary production to continously monitor for any poisoning by magnesium sulphuricum.

OG: patients in the OG were given magnesium sulphuricum, the same way as the CG, and 5000 U low molecular weight heparin sodium (approval document No.: GYZZ J20090095, manufacturer: Aventis Pharmaceutical Co., Ltd., France, specification: 0.6 ml:6000AxaIU* 2 pieces/box) additionally once a day through hypodermic injection until the end of pregnancy.

Both groups were provided with sedation treatment as needed. A treatment course lasted 1 week.

Observation indices

(1) Blood pressure: diastolic blood pressure (DBP), systolic blood pressure (SBP) and mean arterial blood pressure (MABP) were measured in the 2 groups before and after treatment.

(2) 24 h urine protein (PRO): before and after treatment, 20 ml of morning urine was collected in both groups, and PRO was measured with a biochemistry analyzer produced by HIGHLIGHT, from the United States.

(3) D-D and hs-CRP: 5 ml blood was drawn from all patients in the morning under a fasting state before and after treatment. The blood was centrifuged at the speed of 3500 r/min for 15 min. The separated serum was stored in a -80°C freezer and tested by an enzymatic method for D-D, and by immunoturbidimetry for hs-CRP. All operations were conducted in strict accordance with the instructions of the kit [12, 13].

(4) The 2 groups were compared for gestational weeks of pregnancy and average treatment duration.

(5) Complications: complications included postpartum hemorrhage, heart failure and premature rupture of membranes, etc.

Table 1. Comparison between the OG and the CG for General Data [n (%)]/($\bar{x}$ ± s)

Materials	OG (n=52)	CG (n=51)	t/X^2	*P*
Age (y)	29.15±2.15	29.12±2.12	0.071	0.943
Gestational weeks (week) based on diagnosis upon hospitalization	33.15±2.18	33.11±2.13	0.094	0.925
Parity (times)	1.25±0.25	1.21±0.21	0.878	0.382
Type of the pregnant woman (n)				
Primipara	38 (73.08)	36 (70.59)	0.079	0.779
Multipara	14 (26.92)	15 (29.41)		
Symptom (cases)				
Proteinuria	25 (48.08)	23 (45.10)	0.015	0.968
Hypertension	10 (19.23)	8 (15.69)		
Convulsion	6 (11.54)	7 (13.73)		
Edema	11 (21.16)	13 (25.49)		

Statistical analysis

Statistical analysis was performed with SPSS 22.0. In case of numerical data expressed as Mean ± Standard Deviation, comparison studies were carried out through independent-samples *t* test for data which were normally distributed, and Mann-Whitney U test for data which were not normally distributed, paired test for pre-and-pro comparison in the group. In case of nominal data expressed as [n (%)], comparison studies were carried out through chi-squared test for intergroup comparison. For all statistical comparisons, significance was defined as P<0.05.

Results

Comparison between the OG and the CG for general data

Patients were aged between 24 and 36 years, with a mean value of (29.15±2.15), and were pregnant for 25 to 37 weeks with mean value of (33.15±2.18) weeks in the OG (n=52). Accordingly, in the CG (n=51), the age varied from 25 to 35 years with a mean value of (29.12±2.12), and the gestational weeks were between 24 and 38 with mean value of (33.11±2.13). In addition, the parity was 1-4 in the OG with mean value of (1.25±0.25), and 1-3 in the CG with mean value of (1.21±0.21) in the CG. Primiparas and multiparas were 38 (73.08%) and 14 (26.92%) in the OG; and 36 (70.59%) and 15 (29.41%) in the CG. There were 25 cases with proteinuria, 10 cases with hypertension, 6 cases with convulsion, and 11 cases with edema in the OG, and the corresponding numbers were respectively 23, 8, 7 and 13, in the CG. Between the OG and the CG, no statistical difference was observed in terms of general data such as average age, average gestational weeks, average parity, type of the pregnant women, and symptoms (P>0.05, **Table 1**).

Comparison between the OG and the CG for blood pressure

Before treatment, the SBP, DBP and MABP were (168.52±10.28) mmHg, (105.26±8.52) mmHg and (153.26±12.08) mmHg in the OG; while they were (168.58±10.22) mmHg, (105.32±8.49) mmHg and (153.28±12.05) mmHg in the CG (P>0.05). After treatment, the three indices changed to: (140.28±5.28) mmHg, (90.12±1.28) mmHg and (108.52±3.18) mmHg in the OG; and (157.58±6.29) mmHg, (108.63±3.12) mmHg and (125.26±3.85) mmHg in the CG (P<0.05, **Figures 1**-**3**).

Comparison between the OG and the CG for PRO

Before treatment, the 2 groups demonstrated no statistical difference in PRO (P>0.05). After treatment, PRO reduced in both groups and to a far lower level in the OG as compared with the CG (P<0.05, **Table 2**).

Comparison between the OG and the CG for D-D and hs-CRP

With no statistical difference before treatment (P>0.05), the D-D and hs-CRP reduced in both groups after treatment (P<0.05), and to a far lower level in the OG as compared with the CG (P<0.05) (**Table 3**).

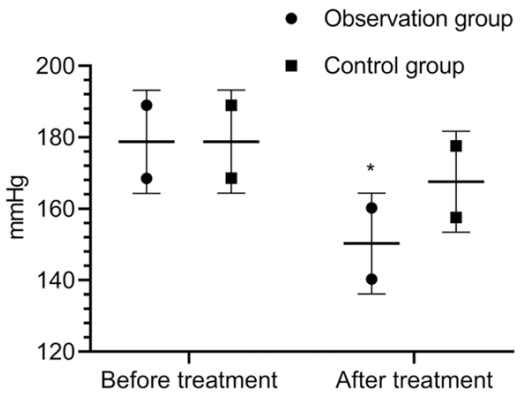

Figure 1. Comparison between the 2 groups for SBP before and after treatment. Before treatment, no statistical difference was found between the 2 groups for SBP (P>0.05); after treatment, the SBP was lower in the OG as compared to the CG (P<0.05). * indicates P<0.05 as compared with the CG.

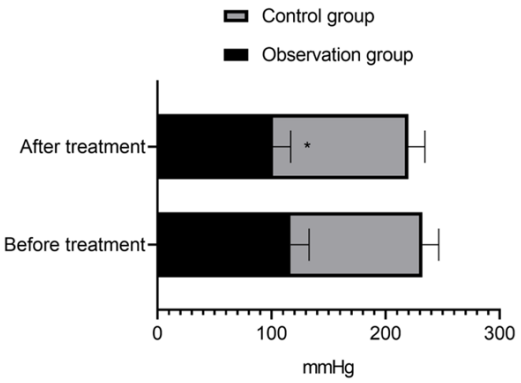

Figure 2. Comparison between the 2 groups for DBP before and after treatment. Statistical difference was not found between the 2 groups for DBP before treatment (P>0.05); after treatment, a lower level was observed in the OG (P<0.05). * indicates P<0.05 as compared with the CG.

Comparison between the OG and the CG for gestational weeks of pregnancy termination, and average treatment duration

Comparison showed that the gestational weeks of pregnancy and average treatment duration were shorter in the OG (P<0.05, **Table 4**).

Comparison between the OG and the CG for the incidence of complications

The number of patients with postpartum hemorrhage, heart failure and premature rupture of membranes were 1, 2 and 1 in the OG (4/52, 7.69%); and 3, 6 and 5 in the CG (14/51, 27.45%) (P<0.05, **Table 5**).

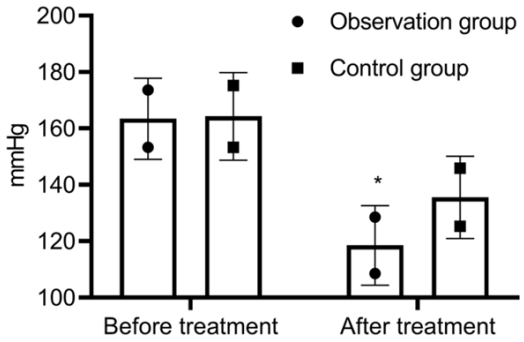

Figure 3. Comparison between the 2 groups for MABP before and after treatment. Without statistical difference in DBP before treatment (P>0.05), the OG yielded a lower MABP as compared with the CG (P<0.05). * indicates P<0.05 as compared with the CG.

Table 2. Comparison between the OG and the CG for PRO ($\bar{x}$ ± s, g)

Group	Before treatment	After treatment
CG (n=51)	4.48±0.52	1.98±0.46#
OG (n=52)	4.52±0.49	1.05±0.22#,*
t	0.402	13.129
P	0.689	0.000

Note: #indicates P<0.05 as compared with the conditions before treatment; *indicates P<0.05 as compared with the CG.

Discussion

Severe preeclampsia is a common obstetric disease with specific pathogenesis that has not been fully defined in clinical practice. It is generally believed to be associated with genetic factors, impaired vascular endothelial function, abnormal immune regulation and trophoblast invasion [14, 15]. The basic pathological changes of the disease include endothelial dysfunction and systemic arteriospasm, which can lead to the decrease of blood perfusion of target organs such as liver, kidneys, brain, and cardiovascular system, and other related complications [16]. At present, the disease is one of the important causes accounting for maternal and infant injuries in clinical practice. In view of its great harm, finding an effective treatment has always been the focus of obstetric research [17, 18].

Table 3. Comparison between the OG and the CG for D-D and hs-CRP Levels ($\bar{x}$ ± s, mg/L)

Group	D-D		hs-CRP	
	Before treatment	After treatment	Before treatment	After treatment
CG (n=51)	2.56±0.52	1.88±0.32#	3.12±0.62	2.18±0.48#
OG (n=52)	2.58±0.49	0.62±0.22#,*	3.18±0.59	1.03±0.12#,*
t	0.201	23.325	0.657	16.753
P	0.841	0.000	0.513	0.000

Note: #indicates P<0.05 as compared with the conditions before treatment; *indicates P<0.05 as compared with the CG.

Table 4. Comparison between the OG and the CG for Gestational Weeks of Pregnancy and Average Treatment Duration ($\bar{x}$ ± s)

Group	Gestational weeks of pregnancy (week)	Average treatment duration (d)
CG (n=51)	36.89±2.18	15.69±2.48
OG (n=52)	30.12±1.08*	8.32±1.02*
t	20.029	19.792
P	0.000	0.000

Note: *indicates P<0.05 as compared with the CG.

Table 5. Comparison between the 2 groups for complications

Group	Postpartum hemorrhage	Heart failure	Premature rupture of membranes	Incidence (%)
CG (n=51)	3	6	5	27.45
OG (n=52)	1	2	1	7.69*
X^2				6.970
P				0.008

Note: *indicates P<0.05 as compared with the CG.

Magnesium sulphuricum is the first choice drug with good antispasmodic effects for the treatment of preeclampsia [19]. The drug can relieve arteriolar spasm at multiple links, reduce heart load, promote blood circulation, improve blood supply of target organs, and achieve effective control of blood pressure levels [20, 21]. Regardless of its ideal clinical efficacy in the treatment of preeclampsia, the drug needs to be reasonably controlled for its dosage to avoid poisoning [22]. To further improve the clinical efficacy and effectively control the blood pressure level, this study combined the anticoagulant low molecular weight heparin sodium with magnesium sulphuricum. The results showed that compared with CG, the SBP, DBP and MABP were lower and PRO was less in the OG after treatment. Zhou et al. also found that SBP, DBP, and MABP of patients treated with the magnesium sulphuricum combined with low molecular weight heparin sodium were lower than those treated with the magnesium sulphuricum alone, and PRO was less than that treated with the magnesium sulphuricum alone, which was highly consistent with the results of this study [23], suggesting that the combination can effectively control the blood pressure and reduce PRO in patients with severe preeclampsia. Those effects may be attributed to the functions of low molecular weight heparin sodium such as enhancing fibrinolytic activity, resisting thrombus and coagulation [24]. Furthermore, the drug can also promote the improvement of placental circulation, largely supplement endogenous heparin, effectively protect the kidneys, and reduce the urine protein for the purposes of swelling subsidence, diuresis and blood pressure reduction [25]. Secondly, the results of this study also showed that compared with CG, the OG had shorter geographic weeks prior to termination and average treatment duration, and lower incidence of complications (P<0.05), which further proved the effectiveness of magnesium sulphuricum combined with low molecular weight heparin sodium in patients with severe preeclampsia. In such a process, the synergistic effect between the 2 drugs works to ensure high safety.

hs-CRP is an acute reactive protein rising significantly in human body durring infection or injury, and it plays an important role in the immune response [26]. The main function of hs-CRP is to enhance the phagocyte functions, activate complements, eliminate pathogenic microorganisms and repair damaged cells in tissues. Pregnancy is a process of allogeneic tissue implantation, during which, amniotic fluid and fetal excreta will somehow stimulate the body of the pregnant women, and then cause inflammatory reactions, especially in

patients with severe preeclampsia characterized by a higher level of hs-CRP [27]. D-D is a kind of cross-linked fibrin working effectively in the activation of plasmin and the formation of cross-linked fibrin. Its level in patients could reflect the prethrombotic state to some extent [28], and also the secondary fibrinolytic strength. In patients with severe preeclampsia, the activity of coagulation will increase abnormally, accompanied by diffuse intravascular coagulation, mostly in the microcirculation of uterus and placenta [29]. Because of the abnormal coagulation state in patients with severe preeclampsia, the repair and regeneration of endometrium will be accelerated during the coagulation period, resulting in abnormally elevated D-D, compromised normal placental functions, and impeded normal growth and development of the fetus, and even causing the fetal intrauterine hypoxia or death in serious cases. According to the results of this study, compared with the CG, the D-D and hs-CRP levels were far lower in patients of the OG ($P<0.05$), indicating that the combination of magnesium sulphuricum and low molecular weight heparin sodium could better improve the hypercoagulative state of blood and alleviate the inflammatory reactions in patients with severe preeclampsia than in the case of magnesium sulphuricum alone.

In conclusion, the combination of magnesium sulphuricum and low molecular weight heparin sodium could effectively control blood pressure, improve the D-D and hs-CRP levels, inhibit inflammatory reactions and reduce the incidence of complications in patients with severe preeclampsia.

However, this study included few subjects to obtain sufficiently representative results. Future studies will pay more attention to this aspect, be based on a longer duration and larger sample size.

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Disclosure of conflict of interest

None.

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