Effects of compound Danshen injection combined with magnesium sulfate on serum MPO and hs-CRP in patients with severe preeclampsia

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Abstract. Effects of compound Danshen injection combined with magnesium sulfate on serum myeloperoxidase (MPO) and hypersensitive C-reactive protein (hs-CRP) in patients with severe preeclampsia (PE) were investigated. Five hundred patients with severe PE were randomly divided into early-onset observation, early-onset control, late-onset observation and late-onset control groups. Control group was treated with magnesium sulfate, while patients in observation group were treated with magnesium sulfate combined with compound Danshen injection. Serum levels of MPO and hs-CRP were measured by enzyme-linked immunosorbent assay (ELISA) and turbidimetric assay. The effects of compound Danshen injection combined with magnesium sulfate on the above indexes were observed. Serum levels of MPO and hs-CRP significantly decreased in early-onset observation, late-onset observation, early-onset control and late-onset control groups after treatment ($p<0.05$). After treatment, levels of MPO and hs-CRP were significantly lower in early-onset observation group than in early-onset control group ($p<0.05$), and levels of MPO and hs-CRP were also significantly lower in late-onset observation group than in late-onset control group ($p<0.05$). Total effective rate of early-onset observation group and late-onset observation group were higher than that of early-onset control group and late-onset control group. Compound Danshen injection combined with magnesium sulfate achieved better treatment outcomes in the treatment of severe PE than magnesium sulfate alone. The combined treatment can effectively reduce the serum levels of MPO and hs-CRP.

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Introduction

As a pregnancy-specific disease, preeclampsia (PE) seriously affects the health of pregnant women and the fetus. Severe PE may even bring damage to organs (1,2). At present, the pathogenesis of PE is still unclear, and most scholars believe that PE is caused by systemic vascular endothelial injury after placental pathophysiological changes (3,4). The pathogenesis of PE is also very complex, and may be associated with placental ischemia, genetic predisposition, immune adaptation and oxidative stress response (5,6). Hypersensitive C-reactive protein (hs-CRP) is an acute inflammatory protein that is synthesized by hepatocytes. As a hemoglobinase, myeloperoxidase (MPO) is a specific marker of myeloid cells. Rosa *et al* (7,8) found that MPO level was increased in patients with diabetes, hypertension and other metabolic diseases, suggesting that MPO is involved in the development of PE. Previous studies also showed that hs-CRP was an independent risk factor for cardiovascular disease (9). With Salvia, Panax, and borneol as major ingredients, compound Danshen injection has been widely used in the treatment of heart diseases such as angina (10). With the protective effects on blood vessel dilation, nerve and glia, magnesium sulfate can be used in the standard treatment of PE (11). In this study, serum levels of hs-CRP and MPO in 500 patients with severe PE were detected, and the effects of compound Danshen injection combined with magnesium sulfate on levels of serum MPO and hs-CRP in patients with severe PE were investigated.

Patients and methods

Selection of patients. A total of 500 patients with severe PE were selected in The Second People's Hospital of Liaocheng (Liaocheng, China) from October 2015 to May 2017. The patients included 250 with early-onset severe PE and 250 patients with late-onset severe PE. The 250 cases of early-onset PE were randomly divided into 125 cases of early-onset observation group and 125 cases of early-onset control group. Similarly, 250 cases of late-onset PE were also randomly divided into 125 cases of late-onset obser-

Table I. Comparison of general information between groups.

Items	Early-onset observation group	Early-onset control group	Late-onset observation group	Late-onset control group	t-value	P-value
Cases	125	125	125	125		
Age (years)	27.5±2.6	26.9±3.1	29.5±2.4	28.7±2.7	0.79	0.59
Gestational age	31.7±1.6	30.8±1.5	37.2±2.1	37.9±1.7	11.79	0.002
Pre-pregnancy BMI (KG/M^2)	19.5±1.6	18.6±2.1	18.3±1.4	19.3±1.8	0.88	0.49
Pregnancy BMI (KG/M^2)	25.3±1.4	24.7±1.2	25.1±1.7	24.8±1.6	0.86	0.51
Blood pressure (mmHg)						
Systolic	160.2±5.5	159.7±4.9	161.2±5.7	160.8±5.3	0.66	0.67
Diastolic	99.8±3.5	98.2±3.2	97.9±3.1	99.2±2.9	0.34	1.36
MAP (mmHg)	119.2±2.3	118.7±2.1	119.4±2.7	118.9±2.6	0.59	0.81
White blood cell count (x10^9/l)	10.3±2.4	10.7±2.6	8.4±2.1	8.1±2.7	9.56	0.019

Table II. Comparison of serum levels of MPO and hs-CRP before and after treatment.

Groups (n=125)	Time-points	hs-CRP (mg/l)	MPO (ng/l)
Early-onset observation	Before treatment	3.43±1.51	14.79±4.24
	After treatment	1.22±0.43$^{a\Delta}$	10.75±1.31$^{a\Delta}$
Late-onset observation	Before treatment	3.21±1.48	14.02±3.79
	After treatment	1.04±0.52$^{a\Delta\Delta}$	10.22±1.02$^{a\Delta\Delta}$
Early-onset control	Before treatment	3.64±1.69	16.53±4.72
	After treatment	1.78±0.84^{a}	14.28±1.53^{a}
Late-onset control	Before treatment	3.56±1.81	15.38±3.98
	After treatment	1.82±0.56^{a}	13.37±1.45^{a}

^{a}Compared with the pre-treatment level within the same group ($p<0.05$); $^{\Delta}$compared with early-onset control group ($p<0.05$); $^{\Delta\Delta}$compared with late-onset control group ($p<0.05$).

vation group and 125 cases of late-onset control group. The patients met the diagnostic criteria of PE described in 'Obstetrics and Gynecology'. Inclusion criteria: Blood pressure continually increased after the 20th week of pregnancy: Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg; serum creatinine ≥1.2 mg/dl; platelet <100,000/ml (<100x10^9/l); proteinuria ≥2.0 g/24 h, or proteinuria using random urine samples (++). The onset gestational weeks <34 weeks was treated as early onset, and the onset gestational weeks ≥34 weeks was treated as late onset. Exclusion criteria: Patients with diabetes, kidney, infectious and blood system diseases; patients without complete clinical data; patients with a recent medication history; patients with a history of smoking and drinking and other health damaging habits; patients gave up treatment. The patients signed informed consent, and this study was approved by the Ethics Committee of The Second People's Hospital of Liaocheng.

Treatment. Patients in early-onset and late-onset control group were subjected to intravenous injection (30 min) of 5 g magnesium sulfate (SFDA approval no. 201208; Tianjin Kingyork Group Co., Ltd., Tianjin, China) in 20 ml 5% glucose, then the patients were treated with intravenous injection (30 min) of 15 g magnesium sulfate in 500 ml 5% glucose with a speed of 1-2 g/h, and 25-30 g magnesium sulfate was used every day for 10 days. Besides treatment with magnesium sulfate, patients in early-onset and late-onset observation group were also intravenously injected with compound Danshen injection (production batch no. 140514, 10-20 ml in 250 ml 5% glucose; Tasly Pharmaceuticals, Inc., Tianjin, China), once per day for 10 days. Sedative and intracranial pressure drugs were also used to assist the treatment.

Detection methods and evaluation. Serum levels of hs-CRP and MPO before and 10 days after treatment were detected. Fasting venous blood samples were collected to prepare serum samples. Serum samples were stored in a fridge (-4˚C) before use. Serum levels of hs-CRP were measured by the turbidimetric method, using BN Prospec automatic protein analyzer (Siemens AG, Munich, Germany). Serum levels of MPO was determined by enzyme-linked immunosorbent assay (ELISA) using the kit provided by R&D Systems, Inc. (Minneapolis, MN, USA). Efficacy evaluation criteria: Cure: Patients with proteinuria, blood pressure and other signs all returned to normal. Improved: Patients with improved proteinuria, blood pressure and other signs, and the symptoms are relieved. Invalid: No change in symptoms.

Statistical analysis. The data were processed using SPSS 22.0 statistical software (IBM Corp., Armonk, NY, USA). Data were first subjected to normal distribution test. Measurement data with normal distribution were expressed by, and t-test was used for comparison between two groups. Comparison of levels before and after treatment were performed by paired t-test. Measurement data with non-normal distribution were expressed by the median values, and comparisons between groups was performed by Wilcoxon test. ANOVA was used for comparison among multiple groups and the post hoc test was Least Significant Difference test. Ratios were compared by χ^2 test. $P<0.05$ was considered to indicate a statistically significant difference.

Table III. Comparison of clinical efficacy (n, %).

Groups	Cases	Cure	Improvement	Invalid	Total effective rate (%)
Early-onset observation	125	54 (43.2)	64 (51.2)	7 (5.60)	94.4[a]
Early-onset control	125	28 (22.4)	71 (56.8)	26 (20.8)	79.2
Late-onset observation	125	49 (39.2)	63 (50.4)	13 (10.4)	89.6[b]
Late-onset control	125	24 (19.2)	73 (58.4)	28 (22.4)	77.6

[a]Compared with early-onset control group ($p<0.05$); [b]compared with late-onset control group ($p<0.05$).

Results

Comparison of general information. Significant higher gestational age and white blood cell count were found in late-onset group than in early-onset group ($p<0.05$). No significant differences in age, pre-pregnancy BMI, pregnancy BMI and blood pressure were found between late-onset group and early-onset group ($p>0.05$) (Table I).

Comparison of serum levels of MPO and hs-CRP before and after treatment. After treatment, significantly lower levels of MPO and hs-CRP were found in early-onset observation group than in early-onset control group ($p<0.05$). Similarly, significantly lower levels of MPO and hs-CRP were found in late-onset observation group than in late-onset control group ($p<0.05$) (Table II).

Comparison of clinical efficacy. Total effective rate was significantly higher in early-onset observation group and late-onset observation group than in early-onset control group and late-onset control group ($p<0.05$) (Table III).

Discussion

PE is a pregnancy-specific disease, and the incidence rate is ~5% (12). PE can increase the risk of hypertension and other cardiovascular and cerebrovascular diseases, and the recurrence rate is high (13,14). Magnesium sulfate is widely used in the treatment of PE. Magnesium sulfate can reduce intracranial pressure and bring sedation effects. Magnesium sulfate can also produce non-competitive antagonism to reduce Ca^{2+} concentration (15). Compound Danshen injection can improve the metabolic dysfunction caused by cell ischemia (16). Mizutani *et al* showed that the combination of magnesium sulfate and compound Danshen injection can effectively improve renal function and blood coagulation in patients with PE (17). In this study, effects of compound Danshen injection combined with magnesium sulfate on serum levels of MPO and hs-CRP in patients with severe PE were explored.

In this study, strict inclusion and exclusion criteria were used to select patients. So, the credibility of the results of the study was ensured. In addition, based on our knowledge, expression of MPO in severe PE has not been previously reported.

hs-CRP is a sensitive indicator of inflammation in the body's inflammatory response, and the mechanism of its function is closely related to inflammatory injury and vascular endothelial dysfunction (18). After vascular endothelial damage, the substances used to relax blood vessels will be reduced, so blood pressure will be increased (19). Ndoni e*t al* (20) showed that hs-CRP was involved in the development of PE. Interaction between hydrogen peroxide and chloride ions can produce hypochlorite (HClO) to form MPO-H_2O_2-halogen system, and under the conditions of local defense response, MPO catalytic reaction can generate excessive oxidants to cause oxidative stress injury (21-23). In this study, serum MPO and hs-CRP levels were relatively high in patients with severe PE before treatment. After treatment with magnesium sulfate and compound Danshen injection, serum levels of MPO and HS-CRP decreased in all 4 groups. The decrease was more significant in early-onset and late-onset observation groups than in early-onset and late-onset control group, which was consistent with the study reported by Salonen *et al* (24), indicating that compound Danshen injection combined with magnesium sulfate can effectively reduce the level of MPO and HS-CRP in patients. Clinical effective rate and cure rate of early-onset observation group and late-onset observation group were higher than those of early-onset control group and late-onset control group. While improvement rate and invalid rate of early-onset observation group and late-onset observation group were lower than those of early-onset control group and late-onset control group, which further supported the conclusion that compound Danshen injection combined with magnesium sulfate can achieve better treatment outcomes than magnesium sulfate, which is consistent with the study reported by Alsuwaida *et al* (25).

This study is still limited by the small sample size, which may affect the results. More studies are needed to elucidate the pathogenesis of PE. Individualized comprehensive treatment of PE is needed to reduce the incidence of PE in China.

In conclusion, compound Danshen injection combined with magnesium sulfate can effectively reduce serum levels of MPO and hs-CRP, and improve patient's condition. The combined treatment can achieve better efficacy than magnesium sulfate alone.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

KY wrote this manuscript and helped with treatment of patients. KY and GD analyzed and interpreted serum levels

of hs-CRP and MPO. JL contributed significantly to statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The Second People's Hospital of Liaocheng (Liaocheng, China). Patients who participated in this research, signed the informed consent and had complete clinical data. Signed informed consents were obtained from the patients or guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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