

## Original Article

# Effects of magnesium sulfate combined with compound Danshen injection on pregnancy outcome, vascular endothelia function, liver and kidney function in patients with EOSPE

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**Abstract:** Objective: This study was designed to analyze the effects of magnesium sulfate combined with compound Danshen injection on pregnancy outcome, vascular endothelial function, liver and kidney function of patients with early onset severe preeclampsia (EOSPE). Methods: 91 patients with EOSPE admitted to our hospital were retrospectively analyzed for clinical data, and divided into two groups based on the treatment methods, including the control group (CG, n=45) for treatment with magnesium sulfate, and the observation group (OG, n=46) for treatment with magnesium sulfate combined with compound Danshen injection. The two groups were compared for diastolic blood pressure (DBP), systolic blood pressure (SBP), 24 h urine protein (PRO), indicators for liver and kidney functions, including serum creatinine (SCr), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and indicators for vascular endothelial function, including endothelin-1 (ET-1) and nitric oxide (NO), as well as the pregnancy outcome and adverse reactions. Results: Compared with the CG, the OG achieved lower SBP, DBP, PRO, SCr, BUN, AST, ALT, and ET-1, and higher NO level after treatment ( $P<0.05$ ). After treatment, the vaginal delivery (VD) and cesarean section (C-S) rates, incidences of postpartum hemorrhage, uterine inertia and fetal distress were 65.22% (30/46), 34.78% (16/46), 2.17% (1/46), 4.35% (2/46) and 4.35% (2/46) in the OG, 40.00% (18/45), 60.00% (27/45), 20.00% (9/45), 17.78% (8/45) and 15.56% (7/45) in the CG ( $P<0.05$ ). The incidence of adverse reactions was 13.33% in the CG and 15.22% in the OG. There was no significant difference in the incidence of adverse reactions between the two groups ( $P>0.05$ ). Conclusion: The combination of magnesium sulfate and compound Danshen injection could improve pregnancy outcome, liver and kidney functions, and vascular endothelial function in the treatment of EOSPE.

**Keywords:** Early onset, severe, preeclampsia, magnesium sulfate, compound Danshen injection, pregnancy outcome, vascular endothelial function, liver and kidney functions

## Introduction

Clinically, preeclampsia is a common gestational disease, which refers to the occurrence of elevated proteinuria, blood pressure and other conditions after 20 weeks of gestation, accompanied by varying degrees of epigastric discomfort, vomiting, nausea, dizziness and headache [1, 2].

The specific pathogenesis of preeclampsia has not been fully clarified so far, and a higher inci-

dence is observed in pregnant women and primiparas with vascular diseases and hypertension [3, 4]. Patients with EOSPE are usually in a hypercoagulable state with lower extremities swelling, increased proteinuria, and elevated blood pressure, etc., which will seriously affect the mother and infant [5, 6]. Magnesium sulfate is a commonly used drug in the clinical treatment of severe preeclampsia, which can effectively prevent maternal convulsions and protect the fetus, but long-term medication can easily cause magnesium ion poisoning [7, 8]. In

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recent years, with the deepening of research, traditional Chinese medicine (TCM) has demonstrated its obvious advantages in the pre-stage treatment of early onset severe preeclampsia (EOSPE) [9]. Compound Danshen injection is a TCM preparation and widely applied in clinic to pacify the patients for peaceful sleep because of its functions of lowering blood lipid and blood pressure [10].

Therefore, in order to improve the liver and kidney function and vascular endothelial function, and reduce the incidence of adverse pregnancy events in patients with EOSPE, magnesium sulfate and compound Danshen injection were combined in this study to achieve a better clinical efficacy.

### Materials and methods

#### Materials

91 patients with EOSPE admitted to our hospital were retrospectively analyzed for clinical data, and divided into two groups based on the treatment methods, including 45 patients aged 25-46 years in the control group (CG) for treatment with magnesium sulfate, and 46 patients aged 26-45 years in the observation group (OG) for treatment with magnesium sulfate and compound Danshen injection. (1) Inclusion criteria: patients who conformed to the diagnosis criteria of severe preeclampsia formulated by the Group of Hypertensive Disorders in Pregnancy, Chinese Medical Association Gynecology and Obstetrics Branch in 2015 [11], and reported no drug contradictions and history of preeclampsia were included. Informed consents were obtained from all patients before participating in the study. This study was approved by the Ethics Committee of Hebei University of Chinese Medicine. (2) Exclusion criteria: some patients were excluded as they had diseases in the blood system, hypertension, malignant tumors or severe liver and kidney dysfunctions or due to their allergic constitution.

#### Methods

CG: after hospitalization, patients were supplemented with proteins, reminded to take food low in salt and fat, and given routine treatments including sedation and reduction of blood pressure as appropriate. In the meantime, they were administrated with magnesium sulfate by

adding 5 g of 25% magnesium sulfate injection (approval document No.: GYZZ H41023035, manufacturer: Anyang Jiuzhou Pharmaceuticals Co., Ltd., specification: 10 ml: 2.5 g) into 100 ml of 5% glucose injection (approval document No.: GYZZ H53020343, manufacturer: Dali Pharmaceuticals Co., Ltd., specification: 100 ml: 5 g) for intravenous drip of 5-10 min for the first administration. Consequently, 10 g of 25% magnesium sulfate injection was mixed with 500 ml of 5% glucose injection for intravenous drip at the rate of 1-2 g/h. Daily dose was controlled at 30 g, and the treatment lasted for 2 weeks.

OG: on the basis of treatments provided to patients in the CG, compound Danshen injection was added. The specific process was mixing 16 ml of compound Danshen injection (approval document No.: GYZZ Z32020678, manufacturer: Bikang Pharmaceuticals Jiangsu Co., Ltd., specification: 2 ml/piece) into 250 ml of 5% glucose injection for intravenous drip once a day. The treatment lasted for 2 weeks.

#### Observation indicators

Blood pressure and 24 h urine protein (PRO): before treatment, at 24 h, 1 week, and 2 weeks after treatment, all patients were measured for diastolic blood pressure (DBP) and systolic blood pressure (SBP) with an electronic sphygmomanometer (produced by Guangzhou Baiyunshan Chenliji Pharmaceuticals Factory), and their urine was collected for PRO measurement with allophanamide.

Liver and kidney functions: before and after treatment, 3 ml of blood was drawn from the veins of all patients in the morning in a fasting state, and then centrifuged at 3000 r/min for 10 min to isolate the serum. All indicators of liver and kidney functions, including serum creatinine (SCr), blood urea nitrogen (BUN), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were assayed by an automatic biochemical analyzer (produced by Shenzhen Kubeier Biotechnology Co., Ltd.) [12].

Vascular endothelial function: before and after treatment, 3 ml of blood was drawn from the veins of all patients in the morning in a fasting state, and centrifuged at 3000 r/min for 10 min to isolate the serum. Endothelin-1 (ET-1) was

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**Table 1.** Comparison of the general data between the OG and the CG [n (%)]/( $\bar{x} \pm sd$ )

General Data		OG (n=46)	CG (n=45)	t/X <sup>2</sup>	P
Type of the Pregnant (n)	Primipara	36 (78.26)	33 (73.33)	0.301	0.583
	Multipara	10 (21.74)	12 (26.67)		
Age (y)		32.15±1.05	32.19±1.02	0.184	0.854
Gestational week (week)		30.28±1.48	30.22±1.43	0.197	0.845
Course of disease (month)		3.15±0.25	3.19±0.22	0.809	0.420

**Table 2.** Comparison of SBP and DBP before and after treatment between the OG and the CG ( $\bar{x} \pm sd$ , mmHg)

Group	SBP				DBP			
	Before treatment	24 h after treatment	1 week after treatment	2 week after treatment	Before treatment	24 h after treatment	1 week after treatment	2 week after treatment
OG (n=46)	167.85±8.05	132.63±2.12 <sup>*,*</sup>	112.05±2.28 <sup>*,*</sup>	109.96±1.28 <sup>*,*</sup>	105.63±4.52	89.96±3.25 <sup>*,*</sup>	72.15±2.12 <sup>*,*</sup>	70.15±1.22 <sup>*,*</sup>
CG (n=45)	167.88±8.02	145.89±3.26 <sup>*,*</sup>	132.26±7.15 <sup>*</sup>	129.56±1.25 <sup>*,*</sup>	105.69±4.49	96.23±3.58 <sup>*,*</sup>	88.98±3.98 <sup>*</sup>	85.12±3.25 <sup>*,*</sup>
t	0.018	15.528	18.248	19.632	0.064	10.236	25.253	15.632
P	0.986	0.000	0.000	0.000	0.949	0.000	0.000	0.000

Note: \*indicates  $P < 0.05$  as compared with the conditions before treatment; <sup>\*</sup>indicates  $P < 0.05$  as compared with the CG.

assayed by ELISA, and nitric oxide (NO) with nitrate reductase [13].

Pregnancy outcome: the two groups were compared for delivery mode, postpartum hemorrhage, uterine inertia and fetal distress, etc.

Adverse reactions: adverse reactions were compared between the two groups.

### Statistical analysis

Statistical analysis was performed with SPSS-22.0. In case of numerical data expressed as mean  $\pm$  standard deviation, independent-samples *t* test was used for normal distribution data, Mann-Whitney U test was used for non-normal distribution data, and paired test was used for pre-and-pro comparison in the group. In case of nominal data expressed as [n (%)],  $\chi^2$  test was adopted for intergroup comparison. For all statistical comparisons,  $P < 0.05$  was considered as significant difference.

### Results

#### Comparison of the general data between the OG and the CG

Patients aged between 26 and 45 with mean value of 32.15±1.05 years, and were pregnant for 28 to 33 weeks with mean value of 30.28±1.48 weeks in the OG. Accordingly, in

the CG, the age varied from 25 to 46 with mean value of 32.19±1.02 years, and the gestational weeks were between 27 and 32 weeks with mean value of 30.22±1.43 weeks. In addition, the course of disease and mean value were 2-5 (3.15±0.25) months in the OG, 2-6 (3.19±0.22) months in the CG. Primiparas and multiparas were 36 (78.26%) and 10 (21.74%) in the OG, 33 (73.33%) and 12 (26.67%) in the CG. Between the OG and the CG, no statistical difference was observed in terms of general materials such as age, course of disease, gestational weeks and type of the pregnant ( $P > 0.05$ , **Table 1**).

#### Comparison of blood pressure before and after treatment between the OG and the CG

Before treatment, the two groups demonstrated no statistical difference in SBP and DBP ( $P > 0.05$ ); at 24 h, 1 week, and 2 weeks after treatment, the SBP and DBP reduced in both groups ( $P < 0.05$ ), and the reduction was more significant in the OG ( $P < 0.05$ ) (**Table 2**).

#### Comparison of PRO before and after treatment between the OG and the CG

Without statistical difference before treatment ( $P > 0.05$ ), both groups attained decreases in PRO after treatment ( $P < 0.05$ ), which was more significant in the OG ( $P < 0.05$ , **Table 3**).

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**Table 3.** Comparison of PRO before and after treatment between the OG and the CG ( $\bar{x} \pm \text{sd}$ , g/24 h)

Group	Before treatment	After treatment
OG (n=46)	4.19±0.05	1.12±0.02 <sup>#,*</sup>
CG (n=45)	4.22±0.03	2.15±0.18 <sup>#</sup>
t	3.461	38.572
P	0.001	0.000

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

### *Comparison of indicators of liver and kidney functions before and after treatment between the OG and the CG*

While no statistical difference was observed between the two groups for indicators of liver and kidney functions before treatment ( $P > 0.05$ ), after treatment, both groups reported reductions in SCr, BUN, AST and ALT ( $P < 0.05$ ), which were more prominent in the OG ( $P < 0.05$ ) (Table 4).

### *Comparison of indicators of vascular endothelia function before and after treatment between the OG and the CG*

The NO and ET-1 were  $54.28 \pm 2.42 \mu\text{mol/L}$  and  $136.58 \pm 2.18 \text{ ng/L}$  in the OG,  $54.22 \pm 2.38 \mu\text{mol/L}$  and  $136.53 \pm 2.15 \text{ ng/L}$  in the CG before treatment ( $P > 0.05$ ); after treatment, the NO and ET-1 changed to  $72.28 \pm 3.28 \mu\text{mol/L}$  and  $92.15 \pm 1.22 \text{ ng/L}$  in the OG,  $60.12 \pm 3.15 \mu\text{mol/L}$  and  $118.85 \pm 2.63 \text{ ng/L}$  in the CG ( $P < 0.05$ , Figures 1 and 2).

### *Comparison of pregnancy outcome between the OG and the CG*

The VD rate, C-S rate, incidences of postpartum hemorrhage, uterine inertia and fetal distress were 65.22% (30/46), 34.78% (16/46), 2.17% (1/46), 4.35% (2/46) and 4.35% (2/46) in the OG, 40.00% (18/45), 60.00% (27/45), 20.00% (9/45), 17.78% (8/45), and 15.56% (7/45) in the CG ( $P < 0.05$ , Figures 3 and 4).

### *Comparison of adverse reactions between the OG and the CG*

In the CG, there were 2 cases with rapid blood pressure decline, 3 cases with transient hypotension, and 1 case with mild palpitation, with

the incidence of adverse reactions of 13.33%. In the OG, there were 3 cases with rapid blood pressure decline, 2 cases with transient hypotension, and 2 cases with mild palpitation, with the incidence of adverse reactions of 15.22%. There was no significant difference in the incidence of adverse reactions between the two groups ( $P > 0.05$ ) (Table 5).

## Discussion

Clinically, EOSPE is a severe obstetrical complication with high mortality of the newborn and serious threats to the mother and the infant [14, 15]. The disease attacks patients in the early stage far before maturity, progresses rapidly, and maintains relationship with a high incidence of complications [16] and complicated pathogeneses, including injury to the endothelial cell functions, increased placental toxic substances, and abnormal placenta, etc. In general cases, patients will suffer from severe swelling, elevated platelet level, injury to liver and kidney functions, increased proteinuria and hypertension to various extents, and in worst cases, it will directly threaten the life of the mother and infant [17, 18].

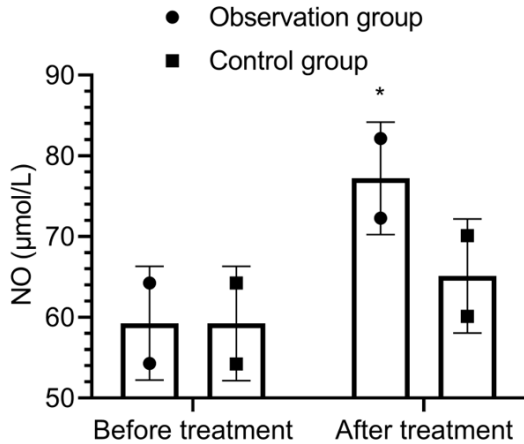
Modern treatment of EOSPE is the termination of pregnancy. However, from the perspective of patients, in case of early pregnancy based on short gestational weeks, the fetus may be underdeveloped in terms of physical functions, which leads to compromised capacity to adapt to and survive in the external world. Blinded extension of gestational weeks will obviously elevate the incidence of pregnancy complications, which would danger the pregnancy in serious cases [11, 19]. Therefore, the key to treat the disease lies in the balance between the extension of gestational weeks, and the development of fetus [20]. Magnesium sulfate is a common drug developed against EOSPE by promoting the relaxation of skeletal muscles, and suppressing the central nervous system [21]. Although its application effect has been widely recognized in clinic, in the case of high blood concentration, the pregnant woman is prone to diarrhea, abdominal pain, vomiting, nausea, dizziness and other symptoms, which seriously threatens the life of fetuses and pregnant women [22]. Therefore, the drug is clinically combined with other drugs to enhance the clinical efficacy and reduce the incidence of drug-related adverse reactions [23].

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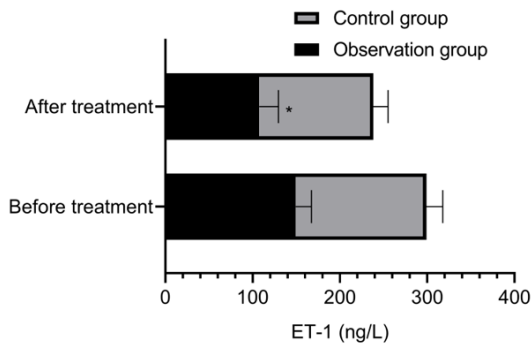
**Table 4.** Comparison of indicators of liver and kidney functions before and after treatment between the OG and the CG ( $\bar{x} \pm sd$ )

Group	SCr ( $\mu\text{mol/L}$ )		BUN (mmol/L)		AST (U/L)		ALT (U/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
OG (n=46)	322.56 $\pm$ 3.05	222.12 $\pm$ 2.28 <sup>#,*</sup>	6.28 $\pm$ 0.58	3.21 $\pm$ 0.22 <sup>#,*</sup>	45.96 $\pm$ 2.48	25.12 $\pm$ 2.15 <sup>#,*</sup>	34.58 $\pm$ 3.25	20.12 $\pm$ 1.08 <sup>#,*</sup>
CG (n=45)	322.59 $\pm$ 3.02	278.96 $\pm$ 2.88 <sup>#</sup>	6.32 $\pm$ 0.53	4.28 $\pm$ 0.38 <sup>#</sup>	45.99 $\pm$ 2.42	33.28 $\pm$ 3.89 <sup>#</sup>	34.62 $\pm$ 3.22	28.98 $\pm$ 2.28 <sup>#</sup>
t	0.031	87.768	0.343	16.483	0.058	12.420	0.059	23.772
P	0.975	0.000	0.732	0.000	0.954	0.000	0.953	0.000

Note: <sup>#</sup>indicates  $P < 0.05$  as compared with the conditions before treatment; <sup>\*</sup>implies  $P < 0.05$  as compared with the CG.

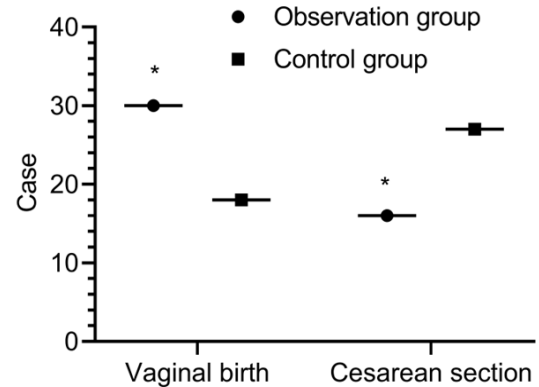


**Figure 1.** Comparison of NO before and after treatment between the OG and the CG. Before treatment, no statistical difference was found between the two groups for NO ( $P > 0.05$ ); after treatment, the NO in the OG was higher as compared with that of the CG ( $P < 0.05$ ). \* means  $P < 0.05$  as compared with the CG.

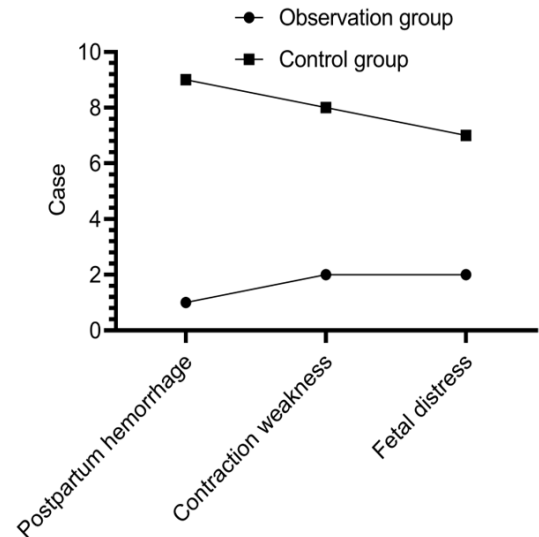


**Figure 2.** Comparison of ET-1 before and after treatment between the OG and the CG. Before treatment, no statistical difference was found between the 2 groups for ET-1 ( $P > 0.05$ ); after treatment, the ET-1 in the OG was lower as compared with that of the CG ( $P < 0.05$ ). \* indicates  $P < 0.05$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

In this study, SBP, DBP, PRO, SCr, BUN, AST, ALT and ET-1 were lower and the NO was higher in the OG as compared with the CG ( $P < 0.05$ ). Besides, the higher VD rate of 65.22% (30/46),



**Figure 3.** Comparison of delivery mode between the OG and the CG. The rates of VD and C-S were 65.22% (30/46) and 34.78% (16/46) in the OG, 40.00% (18/45) and 60.00% (27/45) in the CG ( $P < 0.05$ ). \* indicates  $P < 0.05$  as compared with the CG.



**Figure 4.** Comparison of the incidences of postpartum hemorrhage, uterine inertia and fetal distress between the OG and the CG. The incidences of postpartum hemorrhage, uterine inertia and fetal distress were 2.17% (1/46), 4.35% (2/46) and 4.35% (2/46) in the OG, 20.00% (9/45), 17.78% (8/45) and 15.56% (7/45) in the CG ( $P < 0.05$ ). \* indicates  $P < 0.05$  as compared with the CG.

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**Table 5.** Comparison of adverse reactions between the OG and the CG

Group	Rapid blood pressure decline	Transient hypotension	Mild palpitation	Total incidence
CG (n=45)	2 (4.44)	3 (6.67)	1 (2.22)	6 (13.33)
OG (n=46)	3 (6.52)	2 (4.35)	2 (4.35)	7 (15.22)
$\chi^2$				0.066
<i>P</i>				0.797

and lower incidences of postpartum hemorrhage, uterine inertia and fetal distress in the OG ( $P < 0.05$ ) also indicate that the combination of magnesium sulfate and compound Danshen injection could improve the pregnancy outcome, liver and kidney functions and vascular endothelial function in patients with EOSPE. The reasons shall be explained from the perspective of TCM, in which, severe preeclampsia is recorded as a disease with deficiency in origin and excess in superficiality. It develops when the body is weak and blood is transmitted to the fetus, leading to insufficient essence and blood, and unbalance between the *Yin* and the *Yang*. Therefore, clinical treatment of the disease shall strictly follow the principles of “activating blood circulation to dissipate blood stasis”, “invigorating the spleen to remove dampness”, and “replenishing qi and nourishing *Yin*” [24]. As a TCM preparation, the compound Danshen injection is mainly made of *Lignum acronychiae* and *Radix Salviae Miltiorrhizae*. *Lignum acronychiae* is essentially moderate with the functions of dissipating blood stasis, stopping bleeding, smoothening Qi and relieving pains, while *Radix Salviae Miltiorrhizae* contains tanshinone, which is capable of calming the mind to relieve pain, promoting blood circulation to remove blood stasis, and regulating meridians. Modern medical studies have revealed that the compound Danshen injection could inhibit the aggregation and synthesis of platelets, improve the abnormal coagulation functions, and dilate the microcirculation to achieve better cellular metabolism [25]. Besides, under the effect of the injection, the glomerular basement membrane could recover its permeability, thereby reducing proteinuria.

In conclusion, the combination of magnesium sulfate and compound Danshen injection could improve pregnancy outcome, liver and kidney functions, and vascular endothelial function in the treatment of EOSPE.

However, this study included fewer objects that its results were less representative. In the

future, studies based on larger sample size are required.

### Disclosure of conflict of interest

None.

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