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Original Article

Effects of magnesium sulfate and labetalol combined therapy on blood pressure and pregnancy outcomes in early-onset severe preeclampsia

Yuchun Zhu, Qiang Zhou

Department of Obstetrics, Weifang People's Hospital, No. 151 Guangwen Road, Weifang 261041, Shandong Province, P. R. China

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Abstract: Objective: To observe the efficacy of magnesium sulfate and labetalol combined therapy in early-onset severe preeclampsia. Methods: One hundred and twenty cases of pregnant women with early-onset severe preeclampsia admitted to our hospital from January 2010 to December 2014 were included in this study. The subjects were randomly divided into two groups: the study group and the control group. The study group was treated with magnesium sulfate and labetalol, while the control group was treated with magnesium sulfate and nifedipine. The two groups were compared in terms of changes in systolic pressure/diastolic blood pressure at 1 hr and 4 hrs after medical treatment, respectively; gestational age at delivery gestational age at delivery, modes of delivery and neonatal Apgar scores respectively; and the changes inurinary protein concentrations and the serum creatinine levels, the pregnancy outcomes of the two groups were also observed. Results: One hour after treatment, the systolic blood pressure in the study group decreased significantly compared with that of the control group, with a statistically significant difference ($P<0.05$); four hours after treatment, both the systolic and diastolic blood pressure of the two groups decreased significantly (the study group decreased more significantly), and the differences were statistically significant ($P<0.05$); the differences were statistically significant in gestational age at delivery gestational age at delivery and neonatal Apgar scores between the two groups ($P<0.05$). After treatment, urinary protein concentration and serum creatinine levels were significantly lower in the study group than in the control group ($P<0.05$) and the incidence of adverse pregnancy outcomes in the study group was also obviously lower than that of the control group ($P<0.05$). Conclusion: The labetalol and magnesium sulfate combined therapy was effective for lowering the blood pressure of patients with early-onset severe preeclampsia and can improve their pregnancy outcomes, so the regimen would be of significance in clinical practice.

Keywords: Labetalol, early-onset severe preeclampsia, efficacy

Introduction

Severe preeclampsia [1], a unique syndrome during pregnancy, tends to be one of the most common leading causes of neonatal and maternal deaths in the perinatal period. In particular, severe early-onset preeclampsia has a great impact on both pregnancies and neonates. Clinically, the disease is mainly associated with such conditions ashypertension, edema, proteinuria, and may even lead to convulsions, cerebrovascular accidents, coma, heart failure, disseminated intravascular coagulation (DIC) and placental abruption in some patients [2]. Therefore, spasmolysis and pressure reduction are the key methods to treat the disease. According to relevant literatures in China and western countries [3, 4] magnesium sulfate is often used as the first line drug for management of early-onset severe preeclampsia. When the patients are diagnosed with severe hypertension, magnesium sulfate should be immediately administered and stopped when their condition is under control. In addition, it is used as aprophylactic drug when the disease develops or obvious symptoms of eclampsia appear. However, this drug can neither considerably lower the blood pressure nor take effects rapidly so it is not effective. By contrast, labetalol, a kind of salicylamide derivative, can success-

fully lower blood pressure by competitively antagonizing against α and β-adrenergic receptors. To some extent, it can also play a role in anti-platelet coagulation by increasing prostacyclin levels and decreasing platelet consumption [5]. Besides, the agent can also promote fetal lung maturity, favorable to both maternal and fetal prognosis. A combined therapy of the two drugs can lower blood pressure quickly and minimize the toxicity due to an overdose of magnesium sulfate. The aim of this study was to show the effectiveness of a therapy by combining labetalol with magnesium sulfate to treat early-onset severe preeclampsia and observe the clinical efficacy, reported as follows.

Materials and methods

Subjects

One hundred and twenty cases of pregnant women with early-onset severe preeclampsia admitted to our hospital from January 2010 to December 2014 were recruited and randomly divided into the study group and the control group, 60 cases in each group. The inclusion criteria for this study were qualified to the diagnostic criteria for early-onset severe preeclampsia diagnosis in *The Obstetrics and Gynecology Guidelines* developed in 2004 by the American College of Obstetricians and Gynecologists (ACOG) [6, 7]; and they were: 1) 20-34 weeks of gestation, systolic blood pressure (SBP)≥160 mm Hg or diastolic blood pressure (DBP)≥110 mm Hg; urinary protein ≥2 g/24 h or qualitative test of urinary protein indicates as (++) or more; accompanied with epigastric discomfort, headache, visual disturbance, and other complications; 2) oliguria, serum creatinine levels >106 umol/L; 3) elevated liver enzyme, lactate dehydrogenase (LDH), serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels; 4) oligohydramnios, pulmonary edema and fetal growth restriction. Exclusion criteria included [8]: 1) patients with labetalol contraindications; 2) patients with other complications like diabetes and those with severely impaired hepatic and renal functions. The patients of the study group varied in age from 22 to 37 years (mean (27.5±1.7) years), and their gestational age ranged from 23 to 33 weeks (mean (31.6±1.5) weeks); while the patients of the control group varied in age from 25 to 38 years (mean (28.8±1.9) years); and their gestational age ranged from 24 to 35 weeks (mean (32.3±1.8) weeks). All the pregnant patients in the two groups were single ton and nulliparous. There were no significant differences in the general information between the two groups (P>0.05).

Methods

All the included patients in the study are advised to have a complete bed rest, low-salt diet and to keep away from sound or light. In addition, they were exposed to blood pressure reduction, sedation, oxygen intake and symptomatic treatment. The patients in the study group received intravenous labetalol (100 mg) plus 5% glucose injection (500 mL) with the infusion speed being adjusted to the blood pressure, followed by intravenous magnesium sulfate (5 g) plus 5% glucose injection (100 mL) at the infusion speed of 1-2 g/h within 30 minutes. On the other hand, patients in the control group received oral administration of nifedipine (10 mg) [9], with 8 hrs interval, followed by intravenous magnesium sulfate. The administration method was the same as that of the study group. Detailed records were taken (1 hr and 4 hrs after administration, respectively) concerning the changes in systolic and diastolic blood pressure, follow-ups of pregnancy outcomes and gestational age at delivery of the patients in the two groups.

Observation indicators

The patients were observed (1 h and 4 h after administration respectively) concerning the changes in systolic and diastolic blood pressure, gestational age at delivery, mode of delivery, neonatal Apgar [10] scores, urinary protein and serum creatinine levels [11] and the incidence of different pregnancy outcomes (including neonatal asphyxia, cervical laceration, postpartum hemorrhage, fetal distress and premature delivery [12]).

Statistical methods

The SPSS21.0 statistical software was adopted in the study. The measurement data were shown in the form of mean ± standard deviation ($\overline{x}\pm s$), and the t-test (also called Student's t-test) was performed for data analysis. The count data were expressed as percentage; the χ^2 test was performed to make parametric sta-

Table 1. Comparison of changes in the blood pressure before and after treatment between the two groups

Group	Cases	SBP	DBP	SBP	DBP
		1 h after treatment		4 h after treatment	
Study group	60	142.25±6.58	88.02±2.93	134.96±4.62[a]	83.85±2.01[a]
Control group	60	149.96±7.35	88.37±3.08	140.35±4.96[a]	87.58±2.83
T	—	-6.05	-0.64	-6.16	-8.23
P	—	0.000	0.262	0.000	0.000

Note: The differences were statistically significant for comparison of changes in the blood pressure at 1 hr and 4 hrs after administration ([a]P<0.05).

Table 2. Comparison in termination of pregnancy, modes of delivery and neonatal Apgar scores in the two group

Group	Cases	Time for pregnancy termination (d)	Delivery mode		Neonatal Apgar scores	
			Vaginal delivery	Cesarean section	4-7	>7
Study group	60	237.88±5.62	11	49	3	57
Control group	60	244.32±8.96	12	48	11	49
T/χ^2	—	-4.72	0.054		5.18	
P	—	0.000	0.082		0.023	

tistics; the Wilcoxon rank sum test (U test [13]) was performed to make nonparametric statistics. P<0.05 was considered statistically significant.

Results

Comparison of changes in blood pressure before and after administration

One hour after administration, systolic blood pressure (SBP) of the study group decreased significantly compared to the control group, and the differences were statistically significant (P<0.05). The diastolic blood pressure (DBP) of the study group changed insignificantly compared to that of the control group and the differences were not statistically significant (P>0.05). Four hours after administration, both systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the study group decreased significantly compared to those of the control group, and the differences were statistically significant (P<0.05). When compared within each group, SBP and DBP at 4 hrs after administration in each group significantly lowered compared to those in each group at 1 hr after administration and the differences were statistically significant (P<0.05), as shown in **Table 1**.

Comparison in gestational age at delivery, mode of delivery and neonatal Apgar scores

The gestational age at delivery in the study group was significantly shortened compared to the control group, and the differences were statistically significant (P<0.05); there were no statistically significant differences in ratios of vaginal delivery and cesarean section between the two groups; the number of neonates whose Apgar scores >7 in the study group was significantly larger than that of the control group, and the differences were statistically significant (P<0.01) as shown in **Table 2**.

Comparison of changes in urinary protein and serum creatinine levels

Urinary protein and serum creatinine levels of the patients in the two groups significantly decreased after administration (P<0.05), indicating that the two medication protocols could improve renal function [14] of the patients with early-onset severe preeclampsia, and their renal filtration function, renal blood flow (RBF) and blood pressure were also significantly improved, as shown in **Table 3**.

Comparison of the incidence of different pregnancy outcomes

The incidence of adverse pregnancy outcomes of the patients with regards to postpartum hemorrhage, neonatal asphyxia and premature delivery in the study group were significantly lower compared to those the control group (P<0.05), but there were no significant differences between the two groups in the incidence of cervical laceration and fetal distress (P>0.05), as shown in **Table 4**.

Discussion

Early-onset severe preeclampsia is a common disease treated in the Department of Obs-

Table 3. Comparison in urinary protein and serum creatinine levels ($\bar{x}\pm s$) of the patients

Group	Cases	Urinary protein (mg)		Serum creatinine (umol/L)	
		Before treatment	After treatment	Before treatment	After treatment
Study group	60	3269±77	2667±58[a]	110.2±13.31	78.85±7.93[a]
Control group	60	3263±81	3133±63[a]	109.3±11.45	96.68±8.85[a]
T	—	0.42	-42.15	0.40	-11.62
P	—	0.339	0.000	0.346	0.000

Note: The difference was statistically significant for comparison in urinary protein and serum creatinine levels before and after administration ([a]P<0.05).

Table 4. Comparison in the incidence of different pregnancy outcomes of the patients (n (%))

Group	Cases	Cervical laceration (%)	Postpartum hemorrhage (%)	Neonatal asphyxia (%)	Complication of fetal distress (%)	Premature delivery (%)
Study group	60	2 (3.33%)	2 (3.33%)	2 (3.33%)	2 (3.33%)	8 (13.33%)
Control group	60	4 (6.67%)	15 (25.0%)	13 (21.67%)	5 (8.33%)	17 (28.33%)
χ^2	—	-0.71	-11.58	-9.21	-1.36	-4.09
P	—	0.402	0.001	0.002	0.242	0.043

tetrics. The patients often present the following major physiological changes: generalized arteriole spasms reduce perfusion in all the organs and systems, even cause fetal and maternal deaths. The main mechanisms are as follows [15]: generalized arteriole spasms in preeclampsia can cause placental vascular spasms and lead to a significantly reduced placental blood perfusion, which results in fetal ischemia, hypoxia and fetal intrauterine growth restriction. As a result, postnatal preterm neonates may develop immature organs, particularly immaturity in the liver, lung and kidney and other vital organs while the pregnant women in the second trimester may develop severe proteinuria and hypertension, accompanied by such conditions as severe edema, hypoproteinemia, coagulation disorders and liver dysfunction, even symptoms of coma and convulsions. Therefore, early-onset severe preeclampsia has been considered as one of the main causes for neonatal and maternal morbidities and mortalities in the perinatal period [16].

Numerous studies suggest that [17, 18] the mechanism of action of labetalol is to inhibit sympathetic nerve activity by antagonizing against adrenergic receptors and to reduce catecholamine secretion by feedback, so as to lower blood pressure by dilating blood vessels without reducing placental blood flow. Thus labetalolis often clinically administered as a major agent for gestational hypertension. In this trial, the magnesium sulfate and labetalol combined protocol for the study group was significantly more effective in blood pressure reduction and anti-hypertension than the protocol of the control group (P<0.05), indicating labetalol has a clinically conspicuous antihypertensive effect in patients with severe preeclampsia and no significant antagonism was caused in interaction of the two drugs. The gestational age at delivery in the study group was significantly shortened compared with that of the control group (P<0.05) and the number of patients with neonatal Apgar score >7 points was significantly larger than that of the control group. Previous studies show that [19], the efficacy of labetalol on renal function was mainly manifested in inhibiting renin secretion, reducing peripheral vascular resistance and increasing renal plasma flow. In this trial, serum creatinine and urinary protein levels of the patients in the study group were significantly lower than those of the control group, indicating the magnesium sulfate and labetalol combined protocol can improve the patients' renal functions, thereby reducing the toxicity to the patients, and intravenous labetalol administration can lower blood pressure without adverse events like nausea, vomiting or palpitation [20].

However, there were some limits in this study. Firstly, the specificity of the drugs waits to be

further determined due to the inadequate sample size, so validating the long-term efficacy of the agents on patients would be dependent on future large-scale clinical trials. Secondly, the duration of study was too short, the experimental data were not convincing and the referential potential of the findings remains to be confirmed, so the time for sampling and follow-ups should be appropriately prolonged. Moreover, as no blank control group was designed, there was insufficient evidence supporting the favorable efficacy of labetalol and magnesium sulfate combined protocol on blood pressure reduction and pregnancy outcomes. Therefore, a blank control group with stroke-physiological saline solution should be designed in the future.

Disclosure of conflict of interest

None.

Address correspondence to: Qiang Zhou, Department of Obstetrics, Weifang People's Hospital, No. 151 Guangwen Road, Weifang 261041, Shandong Province, P. R. China. Tel: +86-536-8192009; Fax: +86-536-8192009; E-mail: qiangzhou20161012@163.com

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