ORIGINAL ARTICLE

Magnesium sulfate has an antihypertensive effect on severe pregnancy induced hypertension

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Aim: The aim of this study was to assess the effect of magnesium sulfate as a potent antihypertensive agent in patients with severe pregnancy induced hypertension (PIH).

Methods: To assess the antihypertensive effect of magnesium sulfate, we retrospectively analyzed 27 women who were administered magnesium sulfate for seizure prophylaxis without any other antihypertensive agents. Average blood pressure was compared before and after administration.

Results: Blood pressure after administration ($155 \pm 9.5/96 \pm 8.4$ mmHg) was significantly lower than that before administration ($166 \pm 8.2/102 \pm 8.0$ mmHg) ($P < 0.01$). An antihypertensive effect was observed in 59.3% (16/27) of patients ("effective cases"). Among the effective cases, an adequate effect was observed in 14 patients and an excessive effect in two patients. The maximum antihypertensive effect was achieved just after initial loading and was maintained until delivery, as well as 2 h after loading in most effective cases. In patients aged ≥ 40 years, the proportion of effective cases (16.7%, 1/6) was significantly lower than that among patients aged < 40 years (71.4%, 15/21; $P = 0.016$). The proportion of effective cases among patients with early-onset PIH (16.7%, 1/6) was also significantly lower than that among patients with late-onset PIH (71.4%, 15/21; $P = 0.016$).

Conclusion: We demonstrated that magnesium sulfate has an antihypertensive effect in patients with severe PIH. However, this effect was not sufficient for controlling the blood pressure of patients aged ≥ 40 years or those with early-onset PIH.

Introduction

Preeclampsia arises as a complication in 2–5% of all pregnancies¹⁾ and remains one of the main causes of maternal and fetal death and morbidity.²⁾ The main reasons of maternal death are eclampsia and cerebral stroke due to the aggravation of pregnancy induced hypertension (PIH). Therefore, the prevention of eclampsia and the control of blood pressure (BP) are very important in the management of PIH. At Showa University Hospital, magnesium sulfate is administered to all patients with severe PIH.^{3–6)} Magnesium sulfate has been reported to decrease BP.⁷⁾ To adequately control BP in patients with severe PIH, effects of the combination of antihypertensive drugs and magnesium sulfate should

be carefully monitored, because these two agents may have a synergistic effect on BP. The aim of this study is to assess the effect of magnesium sulfate alone on BP in patients with severe PIH.

Methods

There were 53 patients with severe PIH who were treated at Showa University Hospital between July 2012 and September 2013. In 27 of these patients, magnesium sulfate was administered for seizure prophylaxis without any other antihypertensive agent. Magnesium sulfate was administered to all patients with PIH when BP increased to a severe or emergency level. The antihypertensive effect was retrospectively assessed in relation to

gestational age at the onset of PIH, type of PIH, and BP before or after administration.

According to our hospital's current protocol regarding the use of magnesium sulfate, 4 g of magnesium sulfate is administered as an initial loading dose and then administered at 1 g/h as a continuous dose. This is continued at least until delivery if BP does not increase to an emergency level. BP was measured at least five times, including 1 h before administration, just before administration, just after initial loading, and 1 h and 2 h after loading. Average BP was evaluated before and after administration. Differences in effectiveness according to patient characteristics, such as maternal age at delivery, body mass index (BMI), gestational age at onset of PIH, type of PIH (gestational hypertension [GH] or preeclampsia [PE]), timing of administration, and severity of BP, were also assessed. Initially, 4 g of magnesium sulfate was administered over the course of 30 min at the time of initial loading. However, because acute administration may lead to an excessive effect, the duration was later changed to 60 min. Therefore, the effects of differences in loading duration (i.e., 30 vs. 60 min.) were also assessed. BP levels of hypertension were classified as follows: emergency (systolic BP ≥ 180 or diastolic BP ≥ 120), severe ($180 > \text{systolic BP} \geq 160$ or $120 > \text{diastolic BP} \geq 110$), and mild ($160 > \text{systolic BP} \geq 140$ or $110 > \text{diastolic BP} \geq 90$). An adequate effect was defined as a controlled BP in the mild level range or a decrease in BP by 10%–20%. An excessive effect was defined as a BP that dropped below the mild level or by over 20%. Pearson's chi-square test and the two-sample *t*-test were used for statistical analyses. $P < 0.05$ was considered statistically significant. This study was approved by the institutional ethics committee of Showa University Hospital.

Results

Patient characteristics are shown in Table 1. The average gestational age at administration of magnesium sulfate was 36.1 ± 3.9 weeks and the average birth weight was $2,380 \pm 837$ g. The proportion of primipara was 81%. The average serum magnesium concentration in nine patients for whom measurements were taken was 4.1 ± 0.4 mg/dl, and this concentration was maintained for 2–12 h after loading. Study participants included nine patients with preeclampsia and 18 with gestational hypertension. There were six patients (22%) with early-onset PIH and 21 with late-onset PIH. Average BP after administration of magnesium sulfate ($155 \pm 9.5/96 \pm 8.4$ mmHg) was significantly lower than that before administration ($166 \pm 8.2/102 \pm 8.0$ mmHg) ($P < 0.01$, Table 2). Changes in BP after administration of magnesium sulfate are shown in Figures 1A and 1B. An antihypertensive effect

Table 1. Patient characteristics ($n = 27$)

Characteristic	Average or % of cases
Age (years)	35.5 ± 4.7
Maternal body weight (kg)	64.9 ± 10.0
Primipara	81.4% ($n = 22$)
Single pregnancy	85.2% ($n = 23$)
Serum magnesium concentration (mg/dl)	4.1 ± 0.4
Early-onset PIH	22.2% ($n = 6$)
Preeclampsia	33.3% ($n = 9$)
Gestational hypertension	66.7% ($n = 18$)
Gestational age at administration (weeks)	36.1 ± 3.9
Bleeding amount at delivery (ml)	978 ± 628
Birth weight (g)	$2,380 \pm 837$

Data are expressed as mean $\pm$ SD.

PIH, pregnancy induced hypertension.

Table 2. Changes in BP before and after magnesium sulfate administration ($n = 27$)

	Before	After	<i>P</i> -value
Systolic BP (mmHg)	166.2 ± 8.2	155.1 ± 9.5	$P < 0.01$
Diastolic BP (mmHg)	101.7 ± 8.0	96.4 ± 8.4	$P < 0.01$

Data are expressed as mean $\pm$ SD.

BP, blood pressure.

was observed in 16 of 27 patients (59.3%). Maximum antihypertensive effects were achieved just after initial loading and these effects were maintained until delivery, as well as 2 h after loading in 93% (14/15) of effective cases (i.e., patients in whom an antihypertensive effect was observed). Effective cases included 14 patients with an adequate effect (51.9% of total cases) and two with an excessive effect (7.4% of total cases) (Figure 2). Although an antihypertensive effect was observed in only one of six patients aged ≥ 40 years (16.7%), an effect was observed in nine of 15 patients aged < 40 years (71.4%). The effective ratio in patients aged ≥ 40 years was significantly higher than that among younger patients ($P = 0.016$). Although an antihypertensive effect was observed in only one of six patients with early-onset PIH (16.7%), an effect was observed in nine of 15 patients with late-onset PIH (71.4%). In patients with late-onset PIH, the effective ratio was significantly higher than that in patients with early-onset PIH ($P = 0.016$). However, no other factor appeared to influence the antihypertensive effect of magnesium sulfate. There was no significant difference in the antihypertensive effect between preeclampsia and gestational hypertension, by timing of administration (i.e., before and after labor), by BMI, or by the duration of initial loading. Furthermore, there was no difference in effect between patients with emergency and non-emergency BP levels (Table 3).

Figure 1A. Changes in systolic blood pressure before and after the administration of magnesium sulfate.

Figure 1B. Changes in diastolic blood pressure before and after the administration of magnesium sulfate.

We assessed blood pressure at five points (1 h before administration, at administration, just after loading, 1 h after loading, and 2 h after loading). Some data in the ineffective cases were omitted due to the administration of other antihypertensive agents or cesarean section.

Table 3. Influence of patient characteristics on the antihypertensive effect of magnesium sulfate

	Category	Effective	Ineffective	P-value
Age, years	≥ 40	1	5	<i>P</i> = 0.016
	< 40	15	6	
BMI	≥ 30	2	1	n.s.
	< 30	14	10	
Onset	Early-onset	1	5	<i>P</i> = 0.016
	Late-onset	15	6	
Type of PIH	PE	5	4	n.s.
	GH	11	7	
Administration timing	Before labor	7	6	n.s.
	After labor	9	5	
Duration of initial administration	30 min	6	5	n.s.
	60 min	10	6	
Hypertension level	Emergency	1	1	n.s.
	Non-emergency	15	10	

PIH, pregnancy induced hypertension; PE, preeclampsia; GH, gestational hypertension; n.s., not significant.

Figure 2. Antihypertensive effect of magnesium sulfate. **Figure 3.** Current treatment protocol for patients with severe pregnancy induced hypertension at Showa University Hospital.

Discussion

Adequate control of BP in patients with PIH is challenging, especially during delivery. An excessive antihypertensive effect on BP often leads to a non-reassuring fetal status. Therefore, determining the most effective dose of antihypertensive agents to control BP in PIH is important. Magnesium sulfate is generally accepted as the best prophylactic agent for eclampsia.^{3–5} In other circumstances, magnesium sulfate does not have a sufficient effect as an antihypertensive agent.^{3,8,9} Because magnesium sulfate is not accepted as a sufficient prophylactic antihypertensive agent for cerebral stroke, calcium blockers or hydralazine are typically used in that context. However, magnesium sulfate has an effect on vascular smooth muscle relaxation.^{10,11} In clinical practice, we often experience a decrease in BP after administering magnesium sulfate. In the present study, we studied the antihypertensive effect of magnesium sulfate in patients with PIH.

Systolic and diastolic BPs after administration of magnesium sulfate were significantly lower than those before administration (Figure 1A, 1B). In most effective cases, BP decreased to the mild level range for at least 2 h after administration. Cotton et al. previously reported that magnesium sulfate has a transient hypotensive effect on mean arterial pressure when infused as a bolus.⁷ However, the effect was not observed with continuous infusion. In contrast, in the present study, BP decreased to mild levels with continuous infusion. The maximum antihypertensive effect was achieved just after initial loading and was maintained until delivery, as well as 2 h after loading in most effective cases. This suggests that magnesium sulfate has a definite antihypertensive effect. We might be able to judge the antihypertension effect just

after initial loading.

In a previous study, Belfort et al. reported that 380 of 831 (45.7%) patients with severe preeclampsia decreased their BPs by loading 4–6 g of magnesium sulfate.⁴⁾ In the present study, we observed an adequate antihypertensive effect in 59.3% of patients (16/27) and the proportion of effective cases was somewhat higher in the present study compared to the previous report. Since only two patients (7.4%) demonstrated an excessive hypotensive effect, we consider magnesium sulfate to be a relatively safe antihypertensive agent. In effective cases, it was not necessary to administer other antihypertensive drugs. In other words, iatrogenic hypotension may have been caused by the simultaneous administration of both magnesium sulfate and other antihypertensive drugs in these effective cases.

In patients aged ≥ 40 years and in those with early-onset type PIH, magnesium sulfate was not as effective relative to when administered to patients aged < 40 years and in those with late-onset PIH. We speculate that this may have been due to vessels being too damaged to react to magnesium sulfate in the older patients, or the more severe phenotype of early-onset PIH. These results indicate that other antihypertensive agents might be needed in such cases.

We developed a treatment protocol for controlling BP in patients with severe PIH at our hospital (Figure 3). If BP is not at the emergency level, but is severe, 4 g of magnesium sulfate should be administered as the initial loading dose. After initial loading, if the BP level is still above the severe level, other antihypertensive agents are considered under the continuous administration of magnesium sulfate (1 g/h). This process may prevent iatrogenic hypotension due to the additional use of antihypertensive agents.

In conclusion, our findings suggest that magnesium sulfate has an antihypertensive effect. Magnesium sulfate was sufficiently effective as an antihypertensive agent in more than half of the patients with severe PIH, although an excessive hypotensive effect was occasionally observed. We also found that the antihypertensive effect of magnesium sulfate is not sufficient for controlling

hypertension in some patients, in particular, those aged ≥ 40 years and those with early-onset PIH.

Conflict of interest

None.

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