Published in final edited form as:

Hypertens Pregnancy. 2008 ; 27(1): 17–27. doi:10.1080/10641950701825721.

Prostacyclin and Thromboxane Levels in Women with Severe Preeclampsia Undergoing Magnesium Sulfate Therapy During Antepartum and Postpartum Periods

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Abstract

Objective—To study effects of magnesium sulfate (MgSO_4) on prostacyclin (PGI_2) and thromboxane A_2 (TXA_2) levels in women with severe preeclampsia during antepartum and postpartum periods.

Methods—Women with severe preeclampsia were randomized into two groups. Patients in Group A were continuously infused with MgSO_4 for 24 hours postpartum. In Group B, MgSO_4 administration was discontinued when urinary output was of ≥ 100 ml/hr for 2 consecutive hours. Patient demographic data were collected. Venous blood was drawn at time of MgSO_4 administration and 24 hours after delivery. Plasma levels of 6-keto- $\text{PGF}1\alpha$ and TXB_2 , stable metabolites of PGI_2 and TXA_2 , were measured by enzyme-linked immunosorbent assay (ELISA). Data are presented as mean $\pm$ SE, and analyzed by paired *t*-test.

Results—A total of 50 patients were recruited, with 27 in Group A and 23 in Group B. There were no statistical differences for demographic data between the two groups with regards to maternal age; gestational age; systolic and diastolic blood pressures at admission, 12 hours postpartum, and 24 hours postpartum; and mode of delivery. Platelet counts were all within the normal range at the time of enrollment. MgSO_4 was administered for an average of 10 hours postpartum in Group B. Maternal blood pressures returned to normal or close to normal levels in both groups at 24 hours postpartum. 6-keto $\text{PGF}1\alpha$ levels were significantly decreased 24 hours after delivery compared with the levels at enrollment in both groups, (Group A: 98 ± 13 vs. 180 ± 28 pg/mL; Group B: 142 ± 17 vs. 194 ± 31 pg/mL, $p < 0.05$, respectively). However, there was no difference detected between the two groups. TXB_2 levels were not different between group A and Group B at the time of enrollment, 38 ± 9 vs. 33 ± 8 pg/mL, and 24 hours postpartum, 26 ± 5 vs. 25 ± 3 pg/mL, respectively.

Conclusions—Administration of MgSO_4 does not affect prostacyclin and thromboxane levels in the maternal circulation in women with preeclampsia during antepartum and postpartum periods.

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We speculate that a higher level of prostacyclin before delivery may reflect compensatory effects of this vasodilator to offset increased maternal blood pressure during pregnancy.

Keywords

Magnesium sulfate; Preeclampsia; Prostacyclin; Thromboxane

INTRODUCTION

Increased systemic vasoconstriction resulting in maternal hypertension is one of the major underlying pathophysiological events in women with preeclampsia, a multi-system disorder during human pregnancy. Globally this pregnancy disorder accounts for approximately 50,000 maternal deaths annually. For several decades, magnesium sulfate has been used clinically as an anticonvulsant to prevent and treat the seizures of eclampsia. The prophylactic usage of magnesium sulfate is recommended antepartum, during labor, and for at least 24 hours postpartum to prevent seizures in all women with severe cases (1). The beneficial effects of this agent include a reduction of vasoconstriction and, thus, lowering maternal blood pressure. This ultimately decreases maternal mortality without affecting fetal outcomes. The favorable clinical outcomes of magnesium sulfate have been confirmed by the MAGPIE trial (2), which demonstrated that magnesium sulfate halves the risk of eclampsia, and reduces the risk for maternal death without harmful effects to both the mother and the baby in the short term. The nimodipine study, which compared of magnesium with nimodipine in patients with eclampsia, has also shown magnesium sulfate to be more effective than nimodipine in preventing seizures in severe preeclampsia (3).

Although the exact mechanism by which magnesium is preventing-seizures by inducing vasodilation in preeclampsia is not known, *in vitro* studies have shown that magnesium can induce vasodilatation mediated by endothelial-derived relaxing factor in porcine coronary arteries (4) and increase vasodilator prostacyclin (PGI_2) production by cultured umbilical cord endothelial cells (5). Inhibition of platelet activity and platelet aggregation is probably another important function for this agent (6). Platelets are the source of the vasoconstrictor thromboxane (TXA_2) in the maternal circulation. Platelet activation and abnormal coagulation have been demonstrated in women with preeclampsia (7). It is known that thromboxane levels, measured by its stable metabolite TXB_2 , are elevated in the maternal circulation of women with preeclampsia, compared with nonpreeclampsia women. This increase, along with decreased vasodilator PGI_2 , measured by its stable metabolite 6-keto $\text{PGF}1\alpha$, may play a major role in the increased vasoconstriction in this pregnancy disorder (8–11).

It has been proposed that magnesium administration may stimulate PGI_2 production and thus contribute to vasodilatation in women with preeclampsia. However, measurement of renal excretion of PGI_2 metabolites in preeclampsia with magnesium sulfate infusion failed to support this notion (12). There have been few documented efforts to determine effects of magnesium sulfate on maternal TXA_2 and PGI_2 levels in women with severe preeclampsia. Hence, the objectives of this study were (1) to determine whether magnesium sulfate affects maternal PGI_2 and TXA_2 levels antepartum and/or postpartum in women with severe preeclampsia, and (2) to determine the linkage of platelet counts with TXA_2 levels in women with preeclampsia before and after magnesium sulfate therapy. This study was carried out in women with severe preeclampsia and used two different durations of postpartum magnesium sulfate therapy, i.e., administration of magnesium sulfate for 24 hours postpartum or discontinuation of magnesium sulfate based on individual urinary output recordings.

MATERIALS AND METHODS

Patient Information

The patient population included women who delivered in the Labor and Delivery Unit at Louisiana State University Health Sciences Center at Shreveport from January to December, 2003, with documented severe preeclampsia. All were recruited in a randomized study defined as "A prospective randomized trial of fixed versus non-fixed intervals of postpartum magnesium sulfate." This study was approved by the Institutional Review Board (IRB) for Human Research at LSUHSC-Sh. Preeclampsia was defined as a maternal blood pressure of 140/90 mm Hg or higher with proteinuria (>1 + dipstick or >300 mg/24 hours) on two separate readings after 20 weeks of gestation. Preeclampsia was considered severe if one or more of the following criteria was present: maternal blood pressure $\geq 160/110$ mm Hg on two separate readings at least six hours apart; proteinuria >3 + or >5 gr/24 hours after 20 weeks of gestation; oliguria of less than 500 mL in 24 hours; intrauterine growth restriction, presence of persistent headache, visual disturbances; epigastric pain; thrombocytopenia, impaired liver function; pulmonary edema or evidence of intrauterine growth restriction. A total of 50 women were recruited in this study and were randomized into two groups. In Group A, patients were continuously administered MgSO_4 for 24 hours postpartum. The loading dose of 4 grams of MgSO_4 was given intravenously to patients over a period of 20 minutes. The loading dose was followed by a maintenance infusion of 2g/hour for 24 hours. In Group B, the loading dose of MgSO_4 was the same as Group A before delivery, but MgSO_4 administration was discontinued when urinary output was $\geq 100\text{mL/hour}$ for 2 consecutive hours postpartum. If the patient had worsening clinical symptoms after MgSO_4 therapy discontinuation, such as uncontrolled blood pressure, a significant decrease in urinary output, abnormal liver functions, or seizure, MgSO_4 therapy would be reinstituted intravenously until the patients signs and symptoms were stabilized. Venous blood was drawn at admission or before administration of magnesium sulfate and 24 hours postpartum. There were 27 patients in the Group A and 23 patients in the Group B. Patient demographic characteristics are presented in Table 1.

Measurement of Prostacyclin and Thromboxane

Plasma levels of PGI_2 and TXA_2 were measured by their stable metabolites of 6-keto- $\text{PGF1}\alpha$ and TXB_2 by enzyme-linked immunosorbent assay (ELISA). Both 6-keto- $\text{PGF1}\alpha$ and TXB_2 ELISA kits were purchased from Oxford Biomedical Research, Ins. (Oxford, Michigan, USA). Plasma samples for measurements of 6-keto- $\text{PGF1}\alpha$ and TXB_2 were extracted by C18 Sep-Pak column (Waters Corporation) following the standard manufacture instruction before assay. Briefly, 0.2 mL of methanol was added to 1.0 mL of plasma sample and mixed well. Then the mixture was applied into a C18 Sep-Pak column with flow rate to 1.0 mL per minute. The C18 Sep-Pak column was preconditioned with 2.0 mL of 100% methanol and 2.0 mL of double distilled H_2O . After the mixture passed the column, the column was washed with 2.0 mL of 15% methanol followed by 2.0 mL of petroleum ether. The 6-keto- $\text{PGF1}\alpha$ and TXB_2 sample was eluted by 2.0 mL of methyl formate, which was evaporated by a stream of nitrogen gas. The residue was diluted with 1.0 mL of extraction buffer provided by the ELISA kit.

The assay was performed in a 96-well ELISA plate. The ELISA kit included ELISA buffer, washing buffer, extraction buffer, substrate, standard enzyme conjugate and an antibody-coated plate. The standard curve for levels of TXB_2 has a range of 4 to 400 pg/mL. The standard curve for levels of 6-keto- $\text{PGF1}\alpha$ has a range of 20 to 200 pg/mL. An aliquot of 50 μL per sample was assayed in duplicate for both 6-keto- $\text{PGF1}\alpha$ and TXB_2 ELISA assays.

Statistical Analysis

Demographic data are presented as mean $\pm$ S.D. Data for 6-keto-PGF1 α and TXB₂ are presented as mean $\pm$ SE, and were analyzed by paired t-test or student t-test by a computer software StatView (SAS Institute, Inc. Cary, North Carolina, USA). Statistical significance was defined as $p < 0.05$.

RESULTS

A total of 50 women with severe preeclampsia were enrolled in this study, with 27 patients in Group A and 23 patients in Group B. The demographic data are shown in Table 1. There are no statistical differences for maternal age; gestational age; maternal blood pressure at admission, 12 hours postpartum, and 24 hours postpartum between Group A and Group B. The length of MgSO₄ infusion and maternal magnesium concentrations during MgSO₄ infusion are shown in Table 2. The average length of MgSO₄ infusion before delivery was 18 ± 19 hours in Group A and 16 ± 12 hours in Group B. The length of MgSO₄ infusion was 10 hours postpartum for Group B. This is significantly shorter than 24 hours in Group A, $p < 0.001$. Consistently, magnesium concentration in the maternal circulation was also significantly lower in Group B than that in Group A at 24 hours postpartum, $p < 0.001$. There were no statistical differences for the mean platelet count between the two groups at admission, 12 hours postpartum, and 24 hours postpartum (Table 2). No patients in Group B had worsening of clinical symptoms after MgSO₄ was discontinued.

Maternal plasma levels of prostacyclin and thromboxane as measured by their stable metabolites of 6-keto-PGF1 α and TXB₂ are shown in Fig. 1 and Fig. 2. The mean concentration for 6-keto-PGF1 α was significantly decreased 24 hours postpartum compared with the antepartum levels in both Group A and Group B (Group A: 98 ± 13 vs. 180 ± 28 pg/mL, $p < 0.05$; Group B: 142 ± 17 vs. 194 ± 31 pg/mL), $p < 0.05$. However, there was no statistical difference for 6-keto-PGF1 α levels between the groups (Figure 1A). Figure 1B shows the changes of 6-keto-PGF1 α levels in each individual patient at enrollment and 24 hours postpartum. Fig. 2 shows plasma TXB₂ concentrations at enrollment and 24 hours postpartum in Group A and Group B. No significant changes were observed for TXB₂ concentrations at enrollment and 24 hours postpartum between Group A: 38 ± 9 vs. 33 ± 8 pg/mL and Group B: 26 ± 5 vs. 25 ± 3 pg/mL (Fig. 2A), although the mean TXB₂ level is relatively higher in the Group A at admission. The changes of TXB₂ levels in each individual patient at enrollment and 24 hours postpartum are shown in Fig. 1B. The ratios of 6-keto-PGF1 α to TXB₂ were 5.0 ± 0.6 and 6.2 ± 1.5 for Group A at admission and 24 hours postpartum, which were not statistically different from 7.1 ± 1.5 and 6.5 ± 1.7 for group B at the time of admission and 24 hours postpartum, respectively.

Fig. 3 shows the correlation of plasma TXB₂ levels with platelet counts at enrollment and 24 hours postpartum. The correlation of plasma TXB₂ levels with platelet counts in group A is shown in Fig. 3A, $y = 0.000 \times - 0.014$, $r^2 = 0.029$ (antepartum) and $y = 0.000 \times + 0.016$, $r^2 = 0.015$ (postpartum). The correlation of plasma TXB₂ levels with platelet counts in group B is shown in Fig. 3B, $y = -0.000 \times + 0.028$, $r^2 = 0.000$ (antepartum) and $y = -0.000 \times + 0.032$, $r^2 = 0.025$ (postpartum). No correlation was noticed between plasma TXB₂ levels with platelet counts in both groups.

DISCUSSION

In the present study, we measured prostacyclin and thromboxane levels by their stable metabolites of 6-keto PGF1 α and TXB₂ in the plasma samples obtained at enrollment and 24 hours postpartum from women with severe preeclampsia undergoing magnesium sulfate therapy. We found that TXB₂ levels remain unchanged at 24 hours postpartum compared

with levels at enrollment in women with preeclampsia. However, 6-keto PGF1 α levels were significantly lower 24 hours postpartum compared with those before delivery. The findings of reduced 6-keto PGF1 α levels with relative invariable TXB₂ levels after delivery are consistent in both groups. A pharmacokinetic study showed that the average half-life of magnesium was 5.2 hours (13). In the present study, the mean duration of magnesium sulfate infusion was approximately 10 hours postpartum in Group B, which is significantly shorter than the standard 24 hours postpartum magnesium sulfate infusion in Group A. Consistently, serum magnesium concentrations were also significantly lower in Group B patients than those in Group A patients. These data suggest that maternal magnesium concentration may not be the major regulator of prostacyclin levels in the maternal circulation before and within 24 hours after delivery in women with preeclampsia. Although an *in vitro* study by Watson and colleagues (5) found that prostacyclin production by endothelial cells was two-to five fold increased when cells were incubated with plasma obtained from women with preeclampsia undergoing magnesium sulfate therapy, these authors measured accumulated prostacyclin production in the cell culture plate. However, the prostacyclin levels we measured in the maternal plasma represent an *in vivo* dynamic changes in the maternal circulation. This may explain the discrepancy of our data and O'Brien's *in vivo* study (12) with the *in vitro* cell culture results (5). We believe that the changes in prostacyclin levels before and after delivery further indicate the important compensatory effects of this vasodilatory agent on the physiological adaptation to the increased blood volume and reduced vascular resistance during pregnancy.

Initially, we expected that thromboxane levels would be reduced after delivery. However, our results showed no significant changes for thromboxane levels at 24 hours postpartum compared with that at the enrollment. It is known that the platelet is a major source of thromboxane in the systemic circulation. Increased thromboxane levels in the maternal circulation have been demonstrated in women with severe preeclampsia compared with that in women with normal pregnancies (8–11). Since the present study did not include normal pregnant women, no comparison could be made for the thromboxane levels between normal and preeclamptic patients before and after delivery. However, a relative stable platelet count in the study patients (see Table 2) could, at least in part, explain the phenomena of comparative thromboxane levels before and after delivery. In this study, most patients were delivered less than 34 weeks of gestation and had been given steroids to promote fetal lung maturity. Both magnesium and steroids exert platelet inhibitory function (6,14). Therefore, inhibition of platelet activation and aggregation by magnesium and steroids could protect platelets from degranulation and thromboxane release in the study patients.

Consistent with previous reports (15), we also found that the ratio of 6-keto PGF1 α and TXB₂ was not significantly changed before delivery and 24 hours postpartum in both Group A and Group B, when patients were undergoing magnesium sulfate therapy. The stability of the ratio between prostacyclin and thromboxane may play a significant role in the physiological adaptation to reduce vascular resistance during pregnancy and control the vascular reactivity during the postpartum period. A higher level of prostacyclin before delivery may reflect compensatory effects of this vasodilator to offset increased maternal blood pressure during pregnancy in women with preeclampsia.

Acknowledgments

This study was supported in part by grants from National Institute of Health, National Institute of Child Health Development (HD36822) and National Heart, Lung, and Blood Institute (HL65997).

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Figure 1.

Plasma levels of 6-keto PGF1α in women with preeclampsia at admission and 24 hours postpartum. (A) shows the mean levels of 6-keto PGF1α at admission (*Pre*) and 24 hours postpartum (*Post*) in the group A and the group B. (B) shows the change of 6-keto PGF1α levels in each individual patient at admission (*Pre*) and 24 hours postpartum (*Post*) in Group A and Group B. * $p < 0.05$, respectively.

Figure 2. Plasma levels of TXB₂ in women with preeclampsia at admission and 24 hours postpartum. (A) shows the mean levels of TXB₂ at admission (*Pre*) and 24 hours postpartum (*Post*) in Group A and Group B. (B) shows the change of TXB₂ levels in each individual patient at admission (*Pre*) and 24 hours postpartum (*Post*) in Group A and Group B, respectively.

Figure 3.

Correlation of plasma TXB₂ levels with platelet counts at admission and 24 hours postpartum. There was no correlation of plasma TXB₂ levels with platelet counts at admission and 24 hours postpartum in both groups. The pattern of the correlation for TXB₂ levels to platelet counts was fairly similar in both groups at admission and 24 hours postpartum. Group A (Fig. 3A): $y = 0.000 \times -0.014$, $r^2 = 0.029$ (antepartum) and $y = 0.000 \times +0.016$, $r^2 = 0.015$ (postpartum); Group B (Fig. 3B): $y = -0.000 \times +0.028$, $r^2 = 0.000$ (antepartum) and $y = -0.000 \times +0.032$, $r^2 = 0.025$ (postpartum), respectively.

Table 1

Demographic data for patients who enrolled in this study.

Demographic Data	Group A (n = 27)	Group B (n = 23)	p Value
Maternal age*	24.4 ± 7.0	22.3 ± 5.3	0.237
Racial status			
Black	19	15	ns
White	8	8	ns
Gestational age*	34 ⁺⁴ ± 4 ⁺¹	32 ⁺⁴ ± 4 ⁺³	0.105
Primigravida (%)	62%	48%	ns
Blood pressure*			
Admit systolic	162.3 ± 17.9	167.6 ± 23.2	0.212
diastolic	100.7 ± 12.6	100.9 ± 15.5	0.957
12h pp systolic	146.2 ± 14.9	150.0 ± 18.3	0.416
diastolic	84.4 ± 12.0	89.3 ± 11.1	0.138
24h pp systolic	143.0 ± 15.5	148.6 ± 11.0	0.142
diastolic	83.2 ± 11.1	87.5 ± 9.8	0.154
Mode of delivery (%C/S)	59%	61%	ns

* Data are presented as mean ± S.D. ns = not significant.

Table 2Hours of MgSO₄ infusion, maternal MgSO₄ concentration and platelet count in the group A and the group B.

Variable	Group A (n = 27)	Group B (n = 23)	p Value
MgSO ₄ infusion (h°m') [*]			
Predelivery	18°03' ± 18°55'	16°00' ± 11.30'	0.589
Postpartum	24°00' ± 55'	9°57' ± 6°54'	<0.001
Maternal magnesium concentration (mg/dl) [*]			
Initial measure [#]	3.50 ± 1.10	3.80 ± 1.22	0.378
12 h postpartum	5.37 ± 1.08	4.85 ± 1.79	0.215
24 h postpartum	4.89 ± 1.04	3.24 ± 1.90	<0.001
Platelet count (10 ³ /μL) [*]			
Admission	231.30 ± 56.63	221.78 ± 50.60	0.537
12h postpartum	226.48 ± 50.69	218.50 ± 80.60	0.675
24h postpartum	226.22 ± 57.61	218.14 ± 90.45	0.706

^{*} Data are presented as mean ± S.D.

[#] 2 hours after bolus infusion.