Soluble vascular cell adhesion molecule-1 and magnesium sulfate with nifedipine treatment in Indonesian women with severe pre-eclampsia

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Abstract: *Background:* Endothelial cell activation in pre-eclampsia is associated with elevated soluble vascular cell adhesion molecule-1 (sVCAM-1) levels. The objective of the study was to determine whether sVCAM-1 levels in Indonesian women with pre-eclampsia were similar to other ethnic studies and to determine the effects of magnesium sulfate with nifedipine on blood pressure. *Methods:* A total of 61 pregnant women were admitted, who had normal pregnancy ($n = 25$) and severe pre-eclampsia ($n = 36$). Blood sampling was performed at admission to the study, 1 h after placental separation, and 24 h postpartum. sVCAM-1 and blood pressure levels were determined. *Results:* The mean ages in normal pregnancy ($n = 25$) and in severe pre-eclampsia ($n = 36$) are 30.0 ± 3.4 years and 27.1 ± 6.1 years, respectively. Significantly elevated sVCAM-1 was seen in pre-eclampsia. No significant variation in sVCAM-1 levels during the study periods was seen in both groups of cohorts. Magnesium sulfate infusion and nifedipine significantly lowered the blood pressure level. *Conclusion:* Elevated sVCAM-1 levels were also seen in Indonesian women with severe pre-eclampsia. The placenta may not be the only source of elevated sVCAM-1 and that endothelial dysfunction persists beyond the postpartum period. Magnesium sulfate together with nifedipine significantly lowered blood pressure. The determination of elevated sVCAM-1 in pregnancy as a risk marker for endothelial dysfunction is therefore suggested.

Keywords: sVCAM-1, normal pregnancy, magnesium sulfate, nifedipine, blood pressure, pre-eclampsia

Introduction

Pre-eclampsia, characterized by hypertension and proteinuria occurring after mid-gestation, is a severe complication of human pregnancy with worldwide reported incidence of between 2% and 8% [1, 2]. It is characterized by an elevated blood pressure and proteinuria and develops after 20 weeks of gestational age. In Indonesia, pre-eclampsia and eclampsia are among the leading cause of maternal and perinatal mortalities. The etiology and pathology of pre-eclampsia are not completely understood. Endothelial cell damage or activation is considered to be the pathophysiological basis for the disease [3–5] and is still the central issue in the pathogenesis of pre-eclampsia involving the release of cell adhesion molecules [6]. Adhesion molecules play a central role in endothelial cells–leukocytes adherence and the subsequent migration of leukocytes into perivascular tissue. Soluble vascular cell adhesion molecule-1 (sVCAM-1) was the first adhesion molecule to be identified in soluble form in higher concentrations in pre-eclampsia and is used as a marker for endothelial activation/dysfunction [7]. VCAM-1 functions as a transmembrane receptor for the vascular endothelial cell membrane and recruits leukocytes to the site of inflammation [8, 9]. Increased expression of sVCAM-1 was seen in moderate and further increased levels in

severe pre-eclampsia compared with pregnant control group [10, 11]. sVCAM-1 serum levels do not show a diurnal rhythm and do not correlate with systemic blood pressure levels or urinary secretion [12]. There is strong evidence-based global support for prompt treatment of women who develop pre-eclampsia, thus promoting survival of mother and baby. Magnesium sulfate has been the drug of choice for prevention of seizures by lowering blood pressure levels in patients with pre-eclampsia and eclampsia. The intravenous administration of magnesium sulfate leads to an increase in maternal heart rate and a decrease in blood pressure [13]. Several possible mechanisms of action have been proposed including acting as a vasodilator in the cerebral circulation to relieve vasoconstriction, protecting the blood–brain barrier to decrease cerebral edema formation, and acting as a central anticonvulsant [14]. The use of nifedipine, a calcium-channel blocker, to treat hypertension has been recommended to use in pre-eclampsia [15]. It significantly reduced the systemic blood pressure without adversely affecting the expected course of pregnancy.

The objective of the study was to determine whether circulating levels of sVCAM-1 levels in Indonesian women presenting with pre-eclampsia were similar to other ethnic group studies and to determine the effects of magnesium sulfate infusion together with calcium-channel blocker, nifedipine, to lower blood pressure levels. The analysis was done by following admission to the study, 1 h after placental separation, and 24 h postpartum compared with normal pregnancy.

Methods

The study received ethical approval from the Health Research Ethical Committee (No: 43/KOMET/FK USU/2014), Medical School, University of North Sumatra, Indonesia. It was conducted in the Department of Obstetrics and Gynaecology at Adam Malik Hospital, Faculty of Medicine, University of North Sumatra, Dr. Pirngadi Hospital, and Sundari Hospital in Medan, Indonesia. Pre-eclampsia was defined by increased blood pressure of greater than 140 mmHg systolic or 90 mmHg diastolic on two occasions at least 6 h apart. It was regarded as severe if the systolic blood pressure rises to a level above 160 mmHg or diastolic to a level greater than 110 mmHg with proteinuria (dipstick 3+).

Sample size

With the postulation that there is at least a 2-fold difference in sVCAM-1 levels between pre-eclampsia and controls, a moderate Cohen's effect size of 0.8 would require 25 subjects in each group for a power of 80% and two-sided 5%.

Subjects

The pregnant subjects diagnosed earlier with severe pre-eclampsia and proteinuria were referred from various clinics and surrounding hospitals for intensive management at the University Department of Obstetrics and Gynaecology, Adam Malik Hospital. They were in their third trimester of pregnancy. Severe pre-eclamptic patients when admitted were given with magnesium sulfate intravenous infusion of loading dose of 4 g/h (bolus) and maintenance dose of 1 g/h mainly to prevent seizure and discontinued by 48 h of infusion. Nifedipine, a calcium-channel blocker, was given simultaneously orally at dosage of 3×10 mg over 24 h. The subjects were admitted to the study after giving written informed consent and fulfilled the inclusion criteria, which are pre-eclamptic pregnancy and gestational age above 20 weeks. The exclusion criteria are history of hypertension, diabetes mellitus, and hyperlipidemia. Normal uncomplicated pregnant subjects were also recruited after giving written informed consent; they were normotensive and admitted for delivery at the hospital. A total of 61 pregnant subjects were admitted to the study after written informed consent was given, normal pregnancy ($n = 25$) and severe pre-eclampsia ($n = 36$).

Blood pressure was determined in all subjects prior to blood sampling at admission to the study, 1 h after placental separation, and 24 h postpartum. An additional measurement was made for pre-eclampsia after 2–4 h of magnesium sulfate infusion. This was to determine if there were any significant differences in blood pressure or sVCAM-1 levels before and after the initial magnesium sulfate infusion. The total dosage of magnesium sulfate given to each patient was recorded.

Blood sampling

A clean venipuncture was performed and about 5 mL of plain blood was collected in vacutainer for serum preparation. After about 2 h, the clotted blood was centrifuged at 2,500*g* for 15 min and the serum aliquots stored at –70 °C until analysis. Blood sampling was performed at admission to the study, 1 h after placental separation, and 24 h postpartum. In pre-eclampsia, additional blood sampling was performed between 2 and 4 h after first loading dose of magnesium sulfate infusion.

Laboratory analysis

sVCAM-1 levels were determined by a quantitative sandwich enzyme immunoassay technique (Quantikine, R&D Systems Inc., Minneapolis, MN, USA). The sensitivity for the assay ranged from 0.17 ng/mL to 1.26 ng/mL with a mean detectable dose of 0.6 ng/mL. The assay was performed at Prodia Laboratory in Jakarta, Indonesia.

Statistical Analysis

Statistical Package for Social Sciences (SPSS 22, IBM Corp, Armonk, NY, USA) was used to perform statistical analysis. One-way analysis of variance (ANOVA) was performed to test for variations in the parameters studied, and the independent *t*-test and Mann–Whitney test for differences between groups were also performed. A *P*-value of <0.05 was considered to be statistically significant.

Results

Characteristics of patients with severe pre-eclampsia and pregnancy outcome compared with normal pregnancy

In normal healthy pregnant subjects ($n = 25$), the mean age at admission to the study was 30.0 ± 3.4 years and, for severe pre-eclampsia ($n = 36$), mean age of 27.1 ± 6.1 years. Pre-eclampsia patients were further divided into pregnancy outcome (pre-term labor $n = 22$, mean age 27.0 ± 6.9 years) and full-term labor ($n = 14$, mean age 27.4 ± 5.0 years). No statistical significant differences in age were seen between normal pregnancy and pre-eclampsia and between pre- and full-term labor. The gestational age at admission to the study in normal pregnancy was mean 37.4 ± 1.0 weeks and significantly earlier gestation in severe pre-eclampsia of mean 34.2 ± 2.5 weeks ($P \leq 0.001$). Due to no progress in clinical condition and the persistence of hypertension, 22 pre-eclamptic patients at mean gestation 32.7 ± 2.0 weeks when admitted had their pregnancy terminated by cesarean section at gestation mean 33.9 ± 2.0 weeks (pre-term labor) except for one who had normal delivery. The remaining 14 pre-eclamptic patients admitted at mean gestation 36.5 ± 1.1 weeks continued to full term and were delivered at mean gestation 38.1 ± 1.4 weeks. Most of the patients had cesarean sections (pre-eclampsia, 94.4%) including normal pregnant women who had previous cesarean sections have requested for such delivery in the present study (72%). The birth weights of babies born to women with severe pre-eclampsia was significantly lower ($P \leq 0.05$) and mainly seen in pre-term labor ($P \leq 0.001$) with no differences seen in those who reached full-term labor when compared to babies born to normal pregnant women *(Table I)*.

sVCAM-1 levels in severe pre-eclampsia compared to normal pregnancy

ANOVA showed no significant variation in sVCAM-1 levels at admission to the study, after placental separation, and 24 h postpartum both in normal pregnancy and severe pre-eclampsia. Moreover, sVCAM-1 levels were not influenced by delivery or at 24 h postpartum from admission to study in both pre-eclampsia and normal pregnancy cohorts. However, significantly elevated sVCAM-1 levels ($P \leq 0.001$) were seen in severe pre-eclampsia and in either pre- or full-term labor compared with normal pregnancy. No significant differences in sVCAM-1 levels between pre- and full-term labor were seen and between admission to the study and 2–4 h after magnesium sulfate bolus infusion. Similarly, there was no significant variation in sVCAM-1 levels between pre- and full-term labor in severe pre-eclampsia. As 94.4% (34/36) of pre-eclamptic women had cesarean sections, its effects on sVCAM-1 levels were not significantly different after placental delivery and 24 h postpartum from admission to the study *(Table II)*.

Magnesium sulfate infusion and nifedipine effects on blood pressure levels in severe pre-eclampsia

The total dosage of magnesium sulfate given to each pre-eclamptic patient was mean 52.42 ± 7.0 g (range 36–62 g) over 48 h (this does not exceed the maximum dose of 30–40 g/day). Nifedipine, a calcium-channel blocker, was given orally 3×10 mg per 24 h even at the postpartum period. Significantly elevated ($P \leq 0.001$) blood pressure levels at admission to the study and

Table I. Characteristics of patients with severe pre-eclampsia (pre- and full-term labor) compared with normal pregnancy. Mann–Whitney *t*-test mean (SD)

			Severe pre-eclampsia	
	Normal pregnancy	Severe pre-eclampsia	Pre-term labor	Full-term labor
N	25	36	22	14
Age, years	30.0 (3.4)	27.1 (6.1)	27.0 (6.9)	27.4 (5.0)
Gestation (weeks) at admission	37.4 (1.0)	34.2 (2.5)***	32.7 (2.0)***	36.5 (1.1)*
Gestation (weeks) at delivery	38.3 (1.0)	35.6 (2.7)***	33.9 (2.0)***	38.1 (1.4)
Mode of delivery, caesarean/vaginal	18/7	34/2	21/1	13/1
Birthweight (g)	2976.0 (268.1)	2665.7 (676.0)*	2347.6 (631.4)***	3142.9 (416.4)

*$P < 0.05$; ***$P < 0.001$

Table II. sVCAM-1 levels in severe pre-eclampsia compared with normal pregnancy and between pre- and full-term labor. Mann–Whitney *t*-test and one-way analysis of variance (ANOVA)

	sVCAM-1 [mean (SD), ng/mL]				
	At admission to study	2–4 h $MgSO_4$	1 h after placental separation	24 h postpartum	ANOVA *P*
Normal pregnancy					
$n = 25$	598.5 (136.9)	–	565.3 (127.3)	580.0 (139.0)	0.68
Severe pre-eclampsia					
$n = 36$	1208.5 (624.1)	1205.8 (572.4)	1383.2 (2018.4)	1017.2 (398.0)	0.64
P	<0.001		<0.001	<0.001	
Severe pre-eclampsia (pre-term labor)					
$n = 22$	1144.1 (539.0)	1154.9 (452.5)	1573.2 (2400.0)	992.6 (365.0)	0.53
P	<0.001		<0.001	<0.001	
Severe pre-eclampsia (full-term labor)					
$n = 14$	1473.6 (758.2)	1394.1 (739.0)	1098.6 (546.0)	1061.3 (469.3)	0.38
P	<0.001		<0.001	<0.001	
Severe pre-eclampsia (pre- vs. full-term labor)					
P	0.14	0.43	0.94	0.98	–

post-delivery periods were seen in severe pre-eclampsia compared to uncomplicated normal pregnancy cohorts which showed no significant variations during the points of study. Magnesium sulfate infusion with nifedipine significantly lowered ($P \leq 0.001$) the blood pressure levels in severe pre-eclampsia by 24 h postpartum even though it remained significantly higher than in normal pregnancy. No significant differences in blood pressure levels between pre- and full-term labor in pre-eclampsia cohorts at points were seen in the study *(Table III)*. The routine monitoring of neurological status (like level of alertness, patellar reflexes, respiratory rate, and urinary output) in severe pre-eclampsia patients was carried out and no seizures were observed during the period of study.

Table III. Magnesium sulfate infusion and nifedipine effects on blood pressure levels in severe pre-eclampsia compared with normal pregnancy. Mann–Whitney *t*-test and one-way analysis of variance (ANOVA)

	Blood pressure level [mean (SD), mmHg]				
	At admission to study	2–4 h $MgSO_4$	1 h after placental separation	24 h postpartum	ANOVA *P*
Normal pregnancy ($n = 25$)					
Systolic	123.2 (7.5)	–	121.6 (5.5)	122.8 (7.4)	0.69
Diastolic	74.8 (7.1)	–	72.8 (7.4)	74.8 (5.1)	0.47
Severe pre-eclampsia ($n = 36$)					
Systolic	193.5 (15.0)[a]	182.9 (14.7)	169.1 (13.3)[abe]	157.8 (11.2)[abe]	<0.001
Diastolic	107.7 (7.0)[a]	100.3 (3.0)	96.2 (6.0)[abe]	88.9 (5.2)[abe]	<0.001
Severe pre-eclampsia (pre-term labor, $n = 22$)					
Systolic	192.4 (12.6)[a]	181.9 (12.9)	168.2 (14.0)[acf]	157.3 (12.0)[acf]	<0.001
Diastolic	107.1 (7.2)[a]	104.2 (21.8)	95.0 (6.7)[acf]	88.2 (5.0)[acf]	<0.001
Severe pre-eclampsia (full-term labor, $n = 14$)					
Systolic	196.4 (17.4)[a]	185.0 (16.5)	171.3 (11.3)[adg]	158.6 (10.3)[adg]	<0.001
Diastolic	107.1 (6.1)[a]	101.4 (3.6)	98.0 (4.1)[adg]	90.0 (5.5)[adg]	<0.001
Severe pre-eclampsia (pre- vs. full-term labor)					
P	NS		NS	NS	NS

NS = not significant;
[a]$P \leq 0.001$ compared to normal pregnancy; [b]severe pre-eclampsia; [c]pre-term labor; [d]full-term labor ($P \leq 0.001$) compared with admission to study; [efg]$P \leq 0.001$ between 24 h postpartum and after placental separation

Discussion

Pre-eclampsia is characterized by hypertension and proteinuria occurring after mid-gestation with worldwide reported incidence of between 2% and 8% [1, 2]. Women who received no prenatal care were more than seven times likely to die from complications of pre-eclampsia than women receiving any prenatal care [16]. It is also known that a more powerful predisposition factor of poor placentation to establish an adequate utero-placental blood flow is a characteristic feature of pre-eclampsia [17]. The etiology and pathology of pre-eclampsia is not completely understood and is thought to result from generalized endothelial dysfunction [3–5, 18]. Dysfunctional maternal endothelial cells and activated circulating leukocytes could also release inflammatory molecules into the blood in pre-eclampsia. Cytokine-induced endothelial cell activation leads to expression of adhesion molecules on the endothelial surface, and the level of changes that depends on cytokine concentration has been suggested [19]. Elevated sVCAM-1 levels using multiplex suspension array method have also been reported in pre-eclampsia [20]. The placenta has been reported to be the potential source for circulating inflammatory cytokines in pre-eclampsia [21, 22]. Adhesion molecules play an important role in endothelial cell–leukocyte interaction, and increased levels are believed to be indicators of endothelial dysfunction in pre-eclampsia [23]. Elevated levels of sVCAM-1 in pre-eclamptic women support the concept of primary endothelial cell involvement in the pathogenesis of pre-eclampsia and, in healthy pregnant women, suggest a high predictive risk in developing pre-eclampsia [24]. Elevated sVCAM-1 levels were associated with severe pre-eclampsia and not with mild pre-eclampsia and normal pregnancy [11, 25–28] and were suggested that it may be useful in predicting pre-eclampsia severity. Elevated levels of sVCAM-1 in early- and late-stage gestation pregnancy that were consistently associated with pre-term delivery have also been observed [29]. In our study, Indonesian women with severe pre-eclampsia were also found to have elevated sVCAM-1 levels. Elevated levels were also seen in both pre- and full-term labor. Moreover, delivery and 24 h postpartum had no influence on sVCAM-1 levels observed from admission to study in both cohorts. No significant variation in sVCAM-1 levels was seen in either normal pregnancy or pre-eclampsia even by 24 h postpartum suggesting that the placenta may not be the only potential source for the elevated sVCAM-1. Elevated sVCAM-1 level is known to be associated with endothelial dysfunction, and then our results showed that this condition did not resolved immediately after delivery or by 24-h postpartum indicating that endothelial dysfunction still persists beyond the postpartum period. The timeline for the levels to decline to normal state has not been determined. Cesarean section had no effect on the sVCAM-1 levels in either normal pregnancy or severe pre-eclampsia. Only 38.9% of pre-eclamptic women reached full-term pregnancy. Measurement of circulating sVCAM-1 has high prevalence value and may recognize up to 55% of pregnant women who will later develop a severe pregnancy-related complication [6] and this may be useful in predicting the severity of the disease [10, 28].

Magnesium sulfate infusion has been the recognized treatment to prevent seizures and lower blood pressure level in pre-eclampsia and eclampsia due to its vasodilator effect [30, 31]. Similarly, nifedipine, a calcium-channel blocker, given orally has been recommended for the treatment of hypertension in pre-eclampsia without adversely affecting the expected course of pregnancy. We did not observe any incidence of sudden onset of hypotension during the course of oral nifedipine or magnesium sulfate infusion treatment, and blood pressure was routinely measured at periodic intervals during the day besides at the time point of blood sampling for the study. Routine interval measurement of blood pressure is recommended as the parallel treatment that may cause sudden onset of hypotension should be noted. Routine monitoring of neurological status was carried out during the period of study. Our record showed that neurological status was not affected by magnesium sulfate infusion in our patients and neither seizures nor maternal or infant mortality was observed. Magnesium sulfate together with nifedipine treatment significantly reduced blood pressure levels by 24-h postpartum from admission to the study even though it remained elevated above the normal pregnant group.

In conclusion, significantly elevated sVCAM-1 levels were also found in Indonesian women with severe pre-eclampsia. The levels remain elevated after placental separation and 24 h postpartum indicating that the placenta may not be the only source for the elevated sVCAM-1 seen and that endothelial dysfunction still persists beyond the postpartum period. Magnesium sulfate infusion together with nifedipine reduced the blood pressure levels in 24-h postpartum. Neither seizures nor maternal or infant mortality was observed. The determination of elevated sVCAM-1 in pregnancy as a risk factor for endothelial dysfunction is, therefore, suggested.

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Authors' contribution: HPP designed the study, enrolled patients, recorded clinical data, analyzed data, and contributed to the manuscript production. HH and RHR contributed to the design of the study, data analysis, and reviewed the manuscript. SCLK contributed to the design of the study, statistical analysis, manuscript production, and approved the final manuscript. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: The authors declare no conflict of interest.

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