Sflt-1 Levels As An Indicator of The Effectiveness of Antihypertensive Agents In Gestational Hypertension

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Abstract.
Gestational hypertension is reported to increase maternal morbidity and mortality, linked to higher levels of soluble fms-like tyrosine kinase-1 (sFlt-1) that lead to endothelial dysfunction. Methyldopa and nifedipine are thought to improve the angiogenic profile, but there are limited data on the effect on the sFlt-1 levels. Therefore, this study aimed to evaluate how methyldopa alone and the combination of methyldopa with nifedipine affect sFlt-1 levels and mean arterial pressure (MAP) in cases of gestational hypertension. This prospective observational study included 30 patients with gestational hypertension who were divided into the methyldopa monotherapy (n=15) and methyldopa-nifedipine combination group (n=15). sFlt-1 levels were calculated utilizing the enzyme-linked immunosorbent assay (ELISA) method in the first 24 hours of hospitalization (prepartum) and 24 hours after delivery (postpartum). The results showed that the combination group experienced a decrease in sFlt-1 levels and MAP by 23.8% ($p<0.05$) and 13.1% ($p<0.001$), respectively. These values were greater than those of the monotherapy group, which only reduced sFlt-1 levels by 18.8% ($p>0.05$) and MAP by 10.4% ($p<0.05$). A more consistent decrease in sFlt-1 levels was observed in five patients with severe preeclampsia who received additional magnesium sulphate ($MgSO_4$). In conclusion, methyldopa monotherapy and the combination of methyldopa-nifedipine reduced sFlt-1 and MAP levels. This result made sFlt-1 levels a marker of the effectiveness of antihypertensive therapy in gestational hypertension.

Keywords: *sFlt-1, Mean Arterial Pressure, Methyldopa, Nifedipine, Preeclampsia and Magnesium Sulfate.*

I. INTRODUCTION

Gestational hypertension and maternal mortality rates are increasing significantly in developing countries. According to a previous study, this condition accounts for 5-10% of maternal deaths[1]. The total of maternal deaths in Indonesia rises annually, with the leading causes in 2019 being 1,280 and 1,066 cases of hemorrhage and gestational hypertension, respectively[2]. Hypertensive disorders in pregnancy are characterized by the gestational stage and the clinical context in which increased blood pressure is initially identified. According to international guidelines, these illnesses are often classified into four categories. Chronic or pre-existing hypertension is high blood pressure that is present before pregnancy or is found before 20 weeks of gestation.

Gestational hypertension, on the other hand, is high blood pressure that starts after 20 weeks and goes away after the pregnancy ends[3]. Pregnancy accompanied by chronic or gestational hypertension may subsequently proceed to more severe clinical disorders, including preeclampsia, eclampsia, and HELLP syndrome[4].One of the main causes of gestational hypertension is abnormal placental development, which can lead to less oxygenation of the placenta and hypoxic stress[5]. In these situations, the placenta releases a number of biologically active mediators, such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), as well as inflammatory cytokines, reactive oxygen species, and angiotensin II type 1 receptor agonistic autoantibodies. All of these things can hurt the vascular endothelium[6]. By sequestering placental growth factor and vascular endothelial growth factor and interfering with angiogenic signaling, elevated sFlt-1 concentrations exacerbate this process.

Systemic vasoconstriction, compromised endothelial integrity, decreased renal perfusion, decreased glomerular filtration, proteinuria, and elevated blood pressure are all consequences of this disruption[6,7,8]. In chronic hypertension, a similar sequence may happen. Poor blood flow to the uterus and placenta can cause placental hypoxia, raise the release of antiangiogenic factors, lower the levels of angiogenic mediators like PlGF and VEGF, and eventually lead to endothelial dysfunction and preeclampsia[9].

Biomarkers like sFlt-1 are widely used to predict preeclampsia early, 4-5 weeks before clinical manifestations[10]. Elevated sFlt-1 levels in preeclampsia are strongly linked to endothelial dysfunction and widespread metabolic shifts. Furthermore, high sFlt-1 levels are positively linked to greater endothelial cell damage, oxidative stress, and altered mitochondrial function. This angiogenic imbalance also acts as an active mediator of vascular damage, contributing to increased peripheral resistance and blood pressure[11].

Placental growth factor is a key proangiogenic protein that facilitates vascular adaptation during pregnancy by enhancing endothelial proliferation, boosting placental vascular development, and inducing vasodilation in the uterine circulation. On the other hand, sFlt-1 is an antiangiogenic protein since it is a soluble splice form of VEGF receptor-1. sFlt-1 lowers the availability of VEGF and PlGF for receptor activation and decreases their ability to promote blood vessel growth by binding them in the blood. In preeclampsia, the combination of lower PlGF activity and higher placental sFlt-1 expression has become more important for both diagnosing and treating the disease3.
Women with preeclampsia usually have lower amounts of PlGF in their blood and higher levels of sFlt-1. It is significant that these angiogenic balance anomalies may be identifiable prior to the manifestation of clinical illness. Consequently, the sFlt-1/PlGF ratio has assumed a significant role in the specialized evaluation of women exhibiting symptoms or signs indicative of hypertensive disorders in pregnancy, especially for pinpointing those at an elevated risk of developing preeclampsia within the following 1-4 weeks[12].

Preeclampsia signifies an imbalance in the maternal equilibrium of proangiogenic and antiangiogenic circulating substances, numerous of which have been studied as biomarkers throughout pregnancy. The sFlt-1/PlGF ratio consistently exhibits a rise prior to and during the clinical phase of the disease, hence affirming its applicability in both diagnostic and prognostic contexts. This changed angiogenic profile is sometimes seen as a sign of more general placental dysfunction[13].
Antihypertensive therapy in pregnancy aims to gradually reduce blood pressure to prevent maternal-fetal hypoperfusion and improve placental hypoxia[14,15]. Meanwhile, methyldopa is a central α2-adrenergic agonist that have direct effect in reducing sFlt-1 production through cAMP inhibition in placental trophoblasts[1,16]. Nifedipine, a calcium channel blocker, acts as a peripheral vasodilator, improving uteroplacental perfusion and reducing placental hypoxia[17]. In Indonesia, nifedipine and methyldopa are commonly used because labetalol is not widely available[18].

Studies on the combination of methyldopa and nifedipine to reduce sFlt-1 levels remain limited. Therefore, the study objective is to analyze the effect of methyldopa monotherapy versus the combination of methyldopa and nifedipine on reducing sFlt-1 levels and MAP in patients with gestational hypertension. The study analyzes the ability of sFlt-1 as an indicator of drug effectiveness in just 24 hours.

II. METHOD

Population and Sample

The study included all hospitalized patients diagnosed with gestational hypertension. A total of 30 patients who met the inclusion criteria were recruited as the study sample through purposive sampling. The inclusion criteria consisted of (1) patients interpreted with gestational hypertension, with or without complications (2) patients who underwent labor, and (3) those who were willing to

sign informed consent. Meanwhile, the exclusion criteria included (1) patients who withdrew during the study, (2) patients who died or were hospitalized for less than 24 hours after delivery. This study was supported ethically by the Airlangga University Hospital Research Ethics Committee, with approval number 083/KEP/2023.

Antihypertensive Regimen

Antihypertensive medications were administered either singly or in combination during the prepartum hospitalization period and up to 24 hours postpartum. Doses consisted of oral methyldopa 250-500 mg taken three times a day, oral nifedipine 10 mg one to three times daily, or nifedipine OROS 30 mg once day. In patients with severe hypertension, an additional 10 mg of oral nifedipine was administered, and blood pressure was monitored at 30 and 60 minutes after administration.

Blood Sampling and Examination

A 0.5 mL venous blood sample was drawn within the first 24 hours of hospitalization (prepartum). This process was repeated in the first 24 hours after delivery (postpartum). The blood was centrifuged to split the serum, which was subsequently stored at -80°C, and sFlt-1 levels were determined using Elisa.

Magnesium Sulfate ($MgSO_4$) Administration

Magnesium sulfate ($MgSO_4$) was administered intravenously to five patients with severe preeclampsia as seizure prophylaxis according to ACOG guidelines 11. The regimen involved an initial 4-gram IV dose over 20-30 min, followed by a maintenance infusion of 1-2g per hour for 24 hours postpartum.

Methods

Study Design

This observational study took place at the Department of Obstetrics and Gynecology, Universitas Airlangga Hospital in Surabaya, from June to August 2023.

Operational Definition and Classification

hypertension was classified according to ACOG19 and POGI20 guidelines into mild and severe categories. Mild hypertension is characterized by a systolic blood pressure of 140–159 mmHg or a diastolic blood pressure of 90–109 mmHg. Severe hypertension was characterized by a systolic blood pressure of at least 160 mmHg or a diastolic blood pressure of at least 110 mmHg. MAP was determined with the formula: MAP = (2 × diastolic + systolic)/3. The target blood pressure reduction was set to <140/90 mmHg for mild hypertension and <160/110 mmHg for severe hypertension. sFlt-1 levels were determined using an ELISA assay with a Bioenzy kit. The normal reference range of sFlt-1 in normal pregnancy was defined as 0.895–3.382 ng/mL[1].

Blood Pressure Measurement

Blood pressure was routinely monitored every 6 hours during the antenatal period and for the first 24 hours postpartum. Measurements were taken close to the time of blood sampling.

III. RESULTS AND DISCUSSION

Patient Characteristics by Therapy Group

total of 30 patients participated in this study, divided into a methyldopa monotherapy (n=15) and a methyldopa–nifedipine combination group (n=15). In the monotherapy group, the majority of patients had chronic hypertension and severe uncomplicated preeclampsia, each with a percentage of 33.3%. The combination group was primarily composed of patients with more severe hypertension, with 60% having severe preeclampsia (33.3%) or superimposed preeclampsia (26.7%). This result showed that combination therapy was recommended for patients with higher-risk, complex pregnancies.

Comparison of Prepartum-Postpartum sFlt-1 and MAP Levels per Therapy Group

In the methyldopa alone group, there was a significant reduction in sFlt-1 levels by 18.8% and 10.4% as evidenced by p-values of 0.211 and 0.016, respectively. Meanwhile, in the methyldopa-nifedipine combination group, the decrease was greater in both cases at 23.8% (p=0.024) and 13.1% (p<0.001), respectively. These results showed that the combination of the two drugs provided a synergistic effect.

Methyldopa suppressed sFlt-1 production in trophoblasts through cAMP inhibition, while nifedipine improved uteroplacental blood flow, thereby reducing placental hypoxia that triggers sFlt-1 release[21,22]. Methyldopa was effective in lowering blood pressure, but it did not significantly reduce sFlt-1 levels in the first 24 hours postpartum. This was because the effect on sFlt-1 production required a longer duration or higher doses[16]. Previous studies have indicated that in preeclampsia, sFlt-1 levels rise progressively throughout pregnancy, as well as the sFlt-1/PlGF ratio doubled within a week, reflecting ongoing placental pathological activity due to hypoxia and oxidative stress. Although the placenta was still in utero, sFlt-1 production remained high or continued to increase. After delivery, sFlt-1 levels declined rapidly, following an exponential pattern with a half-life of approximately 1.4 ± 0.3 days, reaching <1% within about a week, confirming that the placenta was the primary source of sFlt-1 in preeclampsia[23]. Therefore, the combination of the two drugs theoretically provided more stable blood pressure control as well as comprehensive improvement in vascular function than monotherapy.

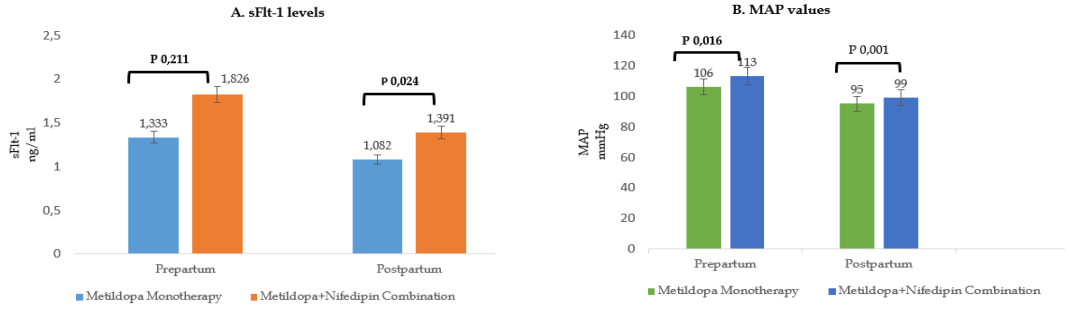
Antihypertensive therapy in preeclampsia improved uteroplacental perfusion and reduced placental hypoxia, potentially suppressing sFlt-1 release and reducing the sFlt-1/PlGF ratio. However, changes in these angiogenic biomarkers were generally slower than the reduction in blood pressure, because MAP reflects a rapid hemodynamic response. sFlt-1 as well as the sFlt-1/PlGF ratio reflected more gradual placental pathophysiological processes[24].

Table I. Comparison of Prepartum-Postpartum sFlt-1 and MAP Levels per Therapy Group

Group	Parameter	Prepartum (Mean ± SD)	Postpartum (Mean ± SD)	Δ Mean ± SD	p-value
Methyldopa Monotherapy (n=15)	sFlt-1 (ng/mL)	1.333 ± 0.803	1.082 ± 1.070	0.251 ± 1.037	0,211
	MAP (mmHg)	106 ± 6	95 ± 11	11 ± 14	0,016
Methyldopa+Nifedipine Combination (n=15))	sFlt-1 (ng/mL)	1.826 ± 1.362	1.391 ± 1.105	0.434 ± 0.702	0,024
	MAP (mmHg)	113 ± 11	99 ± 9	15 ± 11	0,001

*Data are presented as mean ± standard deviation. sFlt-1: soluble fms-like tyrosine kinase-1; MAP: mean arterial pressure; $MgSO_4$: magnesium sulfate; SD: standard deviation; Δ: prepartum-postpartum mean difference

Figure 1. Comparison of the percentage reduction in sFlt-1 and MAP levels between the methyldopa monotherapy and methyldopa-nifedipine combination groups. (A) sFlt-1 levels and (B) MAP values. The combination group showed a greater reduction in sFlt-1 (23.8% vs. 18.8%; p<0.05) and a greater reduction in MAP (13.1% vs. 10.4%; p<0.001). Data are presented as means.



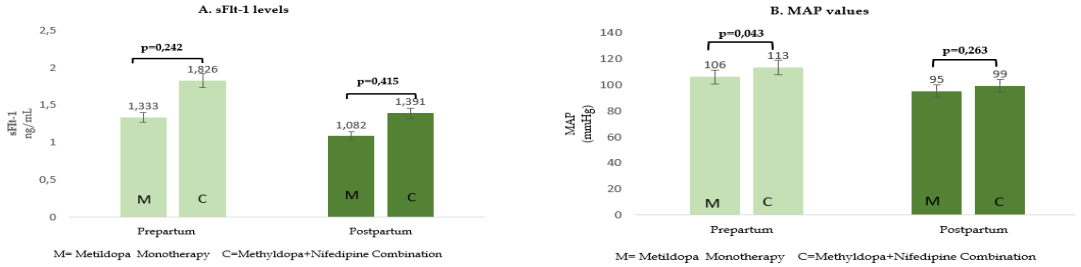
Analysis of Intergroup Difference Test

A t-test analysis was carried out to compare sFlt-1 and MAP levels between the two treatment groups. In the prepartum phase, the methyldopa-nifedipine combination group had a higher mean sFlt-1 level than methyldopa monotherapy (1.826 ± 1.362 ng/mL vs. 1.333 ± 0.803 ng/mL), but the disparity was not statistically significant (p=0.242). This result showed the greater clinical severity in the combination group. In the postpartum phase, both groups exhibited a decrease in sFlt-1 levels,

with the mean remaining higher in the combination group (1.391 ± 1.105 ng/mL vs. 1.082 ± 1.070 ng/mL), but no significant difference was observed (p=0.415). These results showed relatively comparable effectiveness between the two treatment regimens in the management of gestational hypertension based on angiogenic biomarker profiles.

In the prepartum phase, the mean MAP in the combination group was higher than monotherapy (113 ± 11 mmHg vs. 106 ± 6 mmHg), with a statistically significant disparity (p=0.043). In the postpartum phase, both groups showed a decrease in MAP without a significant difference (99 ± 9 mmHg vs. 95 ± 11 mmHg; p=0.263). These results suggested that despite the higher baseline blood pressure in the combination group, both regimens were comparable in effectiveness in reducing MAP until the **postpartum phase**.

Figure 2. Comparison of prepartum and postpartum sFlt-1 and MAP levels between the methyldopa monotherapy and methyldopa-nifedipine combination groups. (A) sFlt-1 levels. There were no significant differences between the groups in the prepartum (p=0.242) or postpartum (p=0.415) phases. (B) MAP values. MAP in the combination group was significantly higher in the prepartum phase (p=0.043), but comparable in the postpartum phase (p=0.263). Data are presented as mean ± SD



Analysis of the Relationship between MAP Decrease and sFlt-1 Levels

The decrease in MAP and sFlt-1 levels was not linearly correlated due to the different mechanisms and kinetics. MAP provided a more rapid response to the vasodilatory effects of antihypertensives, usually within minutes to hours. However, sFlt-1 had a longer half-life of approximately 1.4 days. The decline was lower and strongly influenced by placental separation during labor[23,25]. These differences in mechanisms contributed to the lack of a perfect linear relationship between the two parameters.

Blood pressure and sFlt-1 appear to be closely related, with higher sFlt-1 levels being linked to higher blood pressure readings. One explanation could be that elevated sFlt-1 decreases the availability of vasodilatory factors like prostacyclin (PGI2) and nitric oxide (NO) while increasing the production of vasoconstrictor mediators like endothelin-1 (ET-1) and thromboxane A2 (TxA2). This imbalance may lead to endothelial dysfunction and elevated blood pressure[9,26].

On the other side, improper placentation and placental hypoxia may result from increased blood pressure itself further reducing placental perfusion. This hypoxic environment reduces angiogenic mediators including PlGF and VEGF and increases the release of antiangiogenic factors, especially sFlt-1. The vascular endothelium may also be directly harmed by hypertension. In combination, these pathways can raise systemic vascular resistance and help cause preeclampsia[27]. Persistent hypertension has also been associated with high antiangiogenic factor levels following delivery. sFlt-1 levels decrease after placental delivery, however this decrease takes time. Consequently, women with severe hypertensive problems or organ involvement during pregnancy, particularly those with preeclampsia, may persist in experiencing hypertension or even deteriorating clinical symptoms throughout the postpartum period[28].

Perdigao et al. found a strong correlation between postpartum hypertension and greater prepartum sFlt-1/PlGF ratios[29]. Similarly, Minhas et al. showed a correlation between blood pressure during pregnancy and postpartum sFlt-1 levels. Patients in that study were divided into two groups: women with uncontrolled blood pressure (≥140/90 mmHg) and women with chronic hypertension whose blood pressure was regulated during pregnancy (<140/90 mmHg). Prepartum sFlt-1 levels were substantially higher in women with uncontrolled blood pressure (4218.5 pg/mL) than in women with

regulated blood pressure (3056.0 pg/mL). The uncontrolled group's postpartum systolic blood pressure was likewise higher, with a median value of 165.5 mmHg as opposed to 153.0 mmHg in women whose blood pressure had been managed during pregnancy[30].

In this study, the mean prepartum sFlt-1 level was already in the normal range, which may be due to the fact that antihypertensive medicine was given before the sFlt-1 test. Postpartum sFlt-1 levels further declined, indicating a potential positive response after therapy. However, this result should be regarded with caution because the observed reduction may possibly be a result of physiological changes that occur following placental delivery and cannot be exclusively attributed to antihypertensive medication.

Profile of sFlt-1 and MAP Levels in PEB Patients Receiving $MgSO_4$ in the Methyldopa+Nifedipine Combination Group

In five PEB patients receiving $MgSO_4$, there was a 29.6% and 15.1% decrease in sFlt-1 ($p=0.043$) and MAP ($p=0.001$), respectively. The $MgSO_4$ group indicated a greater and more consistent decrease in MAP (18 mmHg vs. 13 mmHg) compared to the non-$MgSO_4$ group. $MgSO_4$ had a vasodilatory effect through increased Nitric Oxide and prostacyclin, thereby improving endothelial function, increasing uteroplacental perfusion, and contributing to a reduction in blood pressure and antiangiogenic factors[28,31,32]. Therefore, $MgSO_4$ played a role as an anticonvulsant and was an essential vascular therapy in the management of preeclampsia[19]. Previous studies have shown that $MgSO_4$ therapy in patients with preeclampsia improved the angiogenic profile, as shown by decreases in sFlt-1 levels and the sFlt-1/PlGF ratio after therapy. This effect was thought to occur through improved endothelial function and increased uteroplacental perfusion, which suppressed the production of placental antiangiogenic factors. $MgSO_4$ theoretically reduced the sFlt-1/PlGF ratio through vasodilatory effects, improved endothelial function, and decreased oxidative stress. However, these effects were generally not dominant because $MgSO_4$ primarily acted as seizure prophylaxis in preeclampsia. The changes in angiogenic biomarkers were more pronounced when combined with antihypertensive therapy[22].

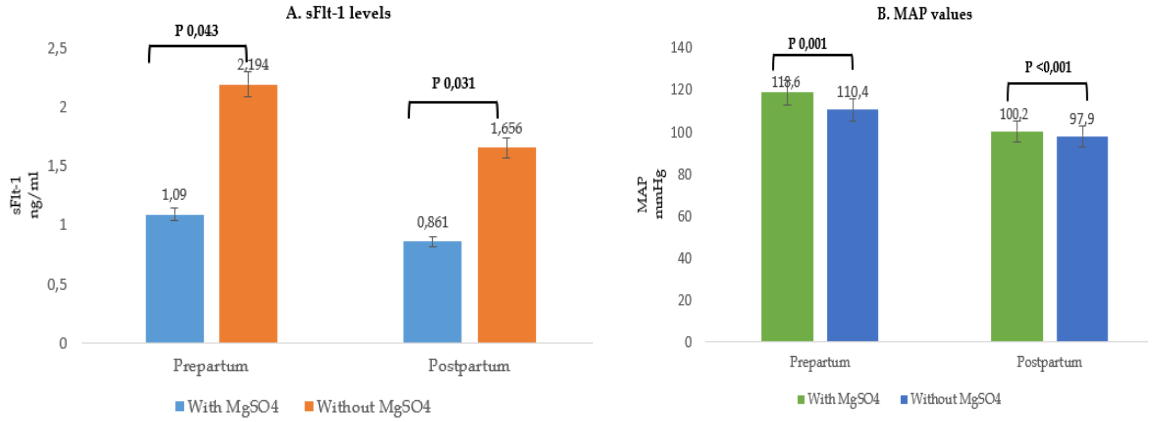
Table II. Profile of sFlt-1 and MAP Levels in severe preeclampsia Patients Receiving $MgSO_4$ in the Methyldopa+Nifedipine Combination Group

Group	Parameter	Prepartum (Mean ± SD)	Postpartum (Mean ± SD)	Δ Mean ± SD	P Value
With $MgSO_4$ (n=5)	sFlt-1 (ng/mL)	1.090 ± 0.888	0.861 ± 0.844	0.229 ± 0.208	0,043
	MAP (mmHg)	119 ± 10	100 ± 7	18 ± 7	0,001
Without $MgSO_4$ (n=10)	sFlt-1 (ng/mL)	2.194 ± 1.420	1.656 ± 1.150	0.538 ± 0.800	0,031
	MAP (mmHg)	110 ± 11	98 ± 11	13 ± 12	<0,001

Data are presented as mean ± standard deviation.

*sFlt-1: soluble fms-like tyrosine kinase-1; MAP: mean arterial pressure; SD: standard deviation; Δ: prepartum-postpartum mean difference

Figure 3. Comparison of sFlt-1 and MAP levels in severe preeclampsia patients with and without $MgSO_4$ administration in the methyldopa-nifedipine combination group. (A) sFlt-1 levels. (B) MAP values. The $MgSO_4$ group showed a greater (18 mmHg vs. 13 mmHg) and more consistent decrease in MAP. Data are presented as mean ± SD



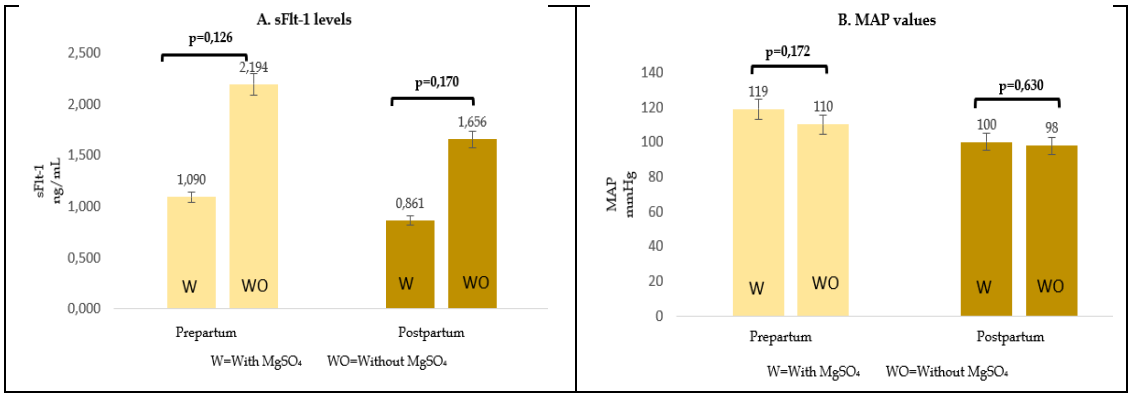
Difference Test Analysis of Patients with and without $MgSO_4$

A t-test analysis was carried out to assess the additional benefit of $MgSO_4$ on improving the angiogenic profile and hemodynamic parameters. In the prepartum phase, sFlt-1 levels in the group without $MgSO_4$ were higher than those with $MgSO_4$ (2.194 ± 1.420 ng/mL vs. 1.090 ± 0.888 ng/mL), but the discrepancy was not statistically significant (p=0.126). However, prepartum MAP in the group with $MgSO_4$ was higher (119 ± 10 mmHg vs. 110 ± 11 mmHg), also with a non-significant difference (p=0.172). This pattern reflected the clinical indication of $MgSO_4$ administration in patients with more severe hypertension, although the difference was not statistically significant.

the postpartum phase, sFlt-1 levels in the group without $MgSO_4$ remained higher (1.656 ± 1.150 ng/mL vs. 0.861 ± 0.844 ng/mL; p=0.170). Meanwhile, postpartum MAP was similar between groups (98 ± 11 mmHg vs. 100 ± 7 mmHg; p=0.630). Although there were no statistically significant differences, a noticeable clinical trend was apparent. The $MgSO_4$ group exhibited a greater (18 mmHg vs. 13 mmHg) and more consistent (smaller SD) reduction in MAP, suggesting a possible additional benefit of $MgSO_4$ for hemodynamic stability in patients with PEB. This result showed that $MgSO_4$ exerted a vasodilatory effect by increasing Nitric Oxide and prostacyclin, which enhanced endothelial function and decreased antiangiogenic factors[31,32].

This study is restricted by a small sample size (n=30) and an observational design. sFlt-1 levels were only measured twice, hence the kinetics of the decline could not be observed serially and within this time period, a decrease in sFlt1 levels was seen as an indicator of the effectiveness of antihypertensive drugs.

Figure 4. Analysis of the difference in sFlt-1 and MAP levels between the methyldopa monotherapy and methyldopa-nifedipine combination groups. (A) Prepartum and postpartum sFlt-1 levels. The difference was not significant in both phases (p=0.242 and p=0.415). (B) Prepartum and postpartum MAP values. MAP in the combination group was significantly higher in the prepartum phase (p=0.043), but comparable in the postpartum phase (p=0.263). Data are presented as mean ± SD



IV. CONCLUSION

In conclusion, both the methyldopa-nifedipine combination and methyldopa reduce sFlt-1 and MAP levels in gestational hypertension. $MgSO_4$ treatment in severe preeclampsia offers additional

benefits by improving the angiogenic profile. Therefore, sFlt-1 levels act as a marker to evaluate the effectiveness of antihypertensive medicine in gestational hypertension which can be seen within 24 hours.

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