Ain-Shams Journal of Anesthesiology

ORIGINAL ARTICLE Open Access

Impact of intravenous infusion of labetalol combined with magnesium sulfate versus hydralazine combined with magnesium sulfate on fetomaternal hemodynamics in severe preeclampsia

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Abstract

Objective: The aim of this study was to compare the effectiveness of two different protocols, labetalol with magnesium sulfate versus hydralazine with magnesium sulfate intravenous infusion with respect to their impact on maternal and fetal hemodynamics in severe preeclampsia.

Patients and methods: In this prospective comparative randomized study, a total of 50 pregnant women in severe preeclampsia with gestational age ≥ 32 weeks were randomly recruited into two groups. Group A: 25 patients received labetalol with magnesium sulfate, and group B: 25 patients received hydralazine with magnesium sulfate by intravenous infusion in an escalating manner according to response until the target blood pressure ≤ 145/95 mmHg was achieved. Blood pressure, maternal heart rate, fetal heart rate, and Doppler ultrasound indices of umbilical and middle cerebral arteries were studied before and after treatment.

Results: A significant reduction of the maternal blood pressure was achieved in both groups, with significant reduction of maternal heart rate in group A. No significant changes in the umbilical and middle cerebral arteries pulsatility index, resistance index, and systolic/diastolic ratio before and after treatment were noted in both groups.

Conclusion: We concluded that both labetalol and hydralazine intravenous infusion regimens are well tolerated and effective in controlling severe hypertension in pregnant women with severe preeclampsia in combination with magnesium sulfate. Both drugs are reassuring as they are not related to any significant changes in fetoplacental circulation. Fetal heart rate did not change significantly after treatment in both groups.

Keywords: Preeclampsia, Labetalol, Hydralazine, Doppler indices

Background

Preeclampsia (PE) is a multi-system disorder of widespread vascular endothelial malfunction and vasospasm, characterized by new onset of hypertension and either proteinuria or end-organ dysfunction or both after 20 weeks of gestation in a formerly normotensive woman. Albeit most influenced pregnancies convey at term or close term with adverse maternal and fetal outcome, these pregnancies are at expanded danger for maternal and fetal mortality or morbidity worldwide (Hutcheon et al. 2011). Preeclampsia is further sub classified into, mild and severe, early onset and late-onset syndrome (American College of Obstetricians and Gynecologists; Hypertension in Pregnancy 2013).

Preeclampsia has a complex pathophysiology; the essential etiopathogenesis being played by the placenta (Roberts and Cooper 2001), as defective invasion of the spiral arteries by cytotrophoblast cells is detected during preeclampsia (Fisher et al. 2009). This might be because of the nitric oxide pathway that controls the vascular tone. Increased uterine arterial resistance triggers higher

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sensitivity to vasoconstriction and subsequently chronic placental ischemia and oxidative stress, which cause intrauterine fetal growth retardation (FGR) and death. In addition, oxidative stress actuates release of substances into the maternal circulation such as free radicals, cytokines, and vascular endothelial growth factor 1. These abnormalities are in charge of endothelial dysfunction (Roberts 1998), with vascular hyperpermeability, and hypertension.

Doppler velocimetry provides a direct exhibition of this process, because it may detect the persistence of high resistance in utero-placental vessels that are suggestive of a reduced placental and fetal perfusion (Neilson and Alfirevic 1998). Furthermore, the presence of abnormal flow-velocity waveforms is frequently associated with impaired oxygen and substrate accessibility to the fetus, fetal growth retardation, and high maternal and perinatal mortality (Schneider and Schulman 1995). Pulsatility index which represents the variability of the flow velocity in a vessel, equal to the difference between the peak systolic (S) and minimum diastolic (D) velocities divided by the mean velocity during the cardiac cycle. It is the most dependable marker of the degree of resistance in a specific blood vessel. Increased umbilical artery pulsatility index is commonly associated with adverse perinatal outcome (Yoon et al. 1994). Another data from Doppler waveform analysis is the peak systolic velocity (*S*) to peak diastolic velocity (*D*) ratio (*S*:*D* ratio) which seems to be the most commonly used due to its simplicity. A less common simple index is the resistive index also known as Pourcelot index that represents pulsatile blood flow and reflects the resistance to blood flow induced by microvascular network distal to the site of measurement (RI) [RI = (*S*–*D*)/*S*] (Schulman et al. 1984).

Maternal mortality from PE was most commonly attributed to intracerebral hemorrhage, ischemic heart disease, stroke, and eclampsia. There is general consensus that these maternal risks should be managed as a critical situation that is best done in the intensive care unit till proper control of blood pressure and guarding against eclampsia (Brown et al. 2000).

Magnesium sulfate ($MgSO_4$) is the drug of choice for prophylaxis and treatment of eclamptic seizures (Sibai and Eclampsia 1990; Witlin and Sibai 1998). Although magnesium is a unique calcium antagonist exerting cardioprotective effect and causing arterial relaxation that may subsequently decrease peripheral and cerebral vascular resistance and arterial blood pressure (Altura et al. 1987), but it ought not be considered primarily an anti-hypertensive agent, as there are different medications more qualified for that purpose (Roberts 2004). Recent guidance recommends treatment of severe hypertension of pregnancy with labetalol, hydralazine, or nifedipine as first-line alternative anti-hypertensives within the critical care setting. All three agents have their proponents and detractors (National Institute of Health and Clinical Excellence 2010; Rey et al. 1997).

Labetalol is predominantly a non-selective *ß*-blocker with some selective α1-blocking effects with a ratio of α/β blockade 1:7 (Schulman et al. 1984; Louis et al. 1984), which reduces the systemic vascular resistance without changes in cerebral, renal, and coronary blood flow (Pearce and Wallin 1994). It has low lipid solubility, thus reduced placental transfer occurs (Varon and Marik 2003), but specific concerns have been raised about the risk of neonatal bradycardia (Vigil-De Gracia et al. 2006). While hydralazine belongs to nitrate group so has a direct vasodilator effect, its onset is after 5–8 min and has duration of 4–8 h. Some adverse effects related to hydralazine have been reported as reflex tachycardia, hemolytic anemia, vasculitis, glomerulonephritis, and a lupus-like syndrome (Magee et al. 1999). The aim of our study was to compare the effectiveness of two different protocols labetalol with $MgSO_4$ versus hydralazine with $MgSO_4$ intravenous infusion in controlling severe hypertension in preeclamptic women with respect to their impact on maternal and fetal hemodynamics.

Patients and methods

This prospective comparative randomized study was carried out at Ibn Sina Medical College Hospital, Jeddah, Saudi Arabia from October 2013 till August 2015. A total of 50 pregnant women in severe PE with gestational age ≥ 32 weeks were recruited in this study. This study was approved by the Hospital Research Ethics Committee and has been performed in accordance with the ethical standards as in Declaration of Helsinki (1964) and its later amendments, and a written informed consent was obtained from each participant.

All patients fulfilled the following criteria:

- Singleton pregnancy
- Gestational age ≥ 32 weeks documented by last menstrual period and ultrasonography.
- Blood pressure (BP) ≥ 160/110 mmHg measured at least in two occasions 4 h apart while the patient is at bed rest and proteinuria ≥ 300 mg/24 h urine collection. In patients with new onset of hypertension with absence of proteinuria, but associated with new onset of thrombocytopenia, or impaired liver function, or pulmonary edema, or cerebral or visual disturbance (American College of Obstetricians and Gynecologists; Hypertension in Pregnancy 2013).
- Maternal heart rate ≥ 60 and ≤ 110 bpm.
- Acceptable cardiotocograph (CTG)
- No history of cardiac, liver, or renal diseases.

We excluded any patient with one of the following:

- Patients with eclampsia (with or without intracerebral hemorrhage).
- Patients with renal disorders (oliguric and/or high serum creatinine and blood urea).
- Patients with fetal distress (abnormal CTG).
- Patients with known allergy to any of the used drugs.

These patients were admitted to obstetrics and gynecology department initially then transferred to intensive care unit (ICU). These patients were randomly classified into two equal groups. Randomization was performed using computer generated list by means of sequentially numbered, sealed envelopes indicating their medication. Group A: 25 pregnant women with severe PE treated with $MgSO_4$ and labetalol intravenous infusion. Group B: 25 pregnant women with severe PE treated with$MgSO_4$ and hydralazine intravenous infusion.

The two groups received 4 g of $MgSO_4$ intravenously over 20 min as a loading dose, at the same time we started either anti-hypertensive drugs. $MgSO_4$ intravenous infusion was continued at a rate of 1 g/h for 24 h.

Labetalol (Trandate™, 5 mg/ml, Aspen): available in 20 ml ampoules containing 100 mg labetalol (5 mg/ml). Start infusion at a rate of 5 ml/h (25 mg/h), titrate the dose until the targeted BP was obtained or the maximum dose had been reached (150 mg/h).

Hydralazine (Apresoline, 20 mg dry ampoules, Amdipharm): reconstituted with 0.9% sodium chloride (1 mg/ml) and start infusion at a rate of 2 mg/h titrate the dose until the targeted BP was obtained or the maximum dose had been reached (10 mg/h).

In both groups, the target blood pressure should be SBP between 110 and 145 mmHg, and DBP between 60 and 95 mmHg maintained for at least 4 readings within the last 60 min.

Maternal hemodynamic assessment

All patients were attached to monitor on admission to ICU with continuous monitoring of the maternal ECG, oxygen saturation, respiratory rate, non-invasive blood pressure, maternal temperature, urine output, and reflexes.

Blood pressure evaluation

Maternal blood pressure was measured with the arm at the level of the heart using an appropriately sized cuff with the automated non-invasive blood pressure monitor and confirmed by mercury sphygmomanometer every 15 min. The trial was abandoned, and appropriate measures were done in case of non-reassuring fetal status, significant maternal hypotension (≤ 90/60 mmHg), or maternal hypertension resistant after the maximum dose of the studied drug.

Fetal hemodynamic assessment

Study of fetal vessels was performed using a color Doppler and pulsed Doppler system with a 3.5 MHz transducer. The pulsatility index (PI), resistance index (RI), and systolic pressure/diastolic pressure (S/D) ratio of umbilical artery (UA) and middle cerebral artery (MCA) of the fetus were recorded at the time of admission to the ICU with acute severe hypertension and after the treatment when the target maternal blood pressure was achieved and during a period of fetal rest.

The pulsed Doppler samples were placed in the lumen of the umbilical artery away from the placental and fetal cord insertion, at the mid portion of the umbilical artery. For MCA, an axial view of fetal head was obtained at the level of cerebral peduncles, then the color Doppler was used to visualize the circle of Willis, and the Doppler samples were placed within 1 cm of the origin of MCA (Arbellie et al. 1987). During the course of treatment, the fetuses were monitored electronically (CTG) on a continuous basis.

The primary end point for our study was divided into maternal catastrophic events including development of fits, antepartum hemorrhage, and severe persistent hypotension (BP) less than 90/60 mmHg and fetal catastrophic events, like fetal bradycardia.

Statistical analysis

The data were collected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version20) software. Arithmetic mean, standard deviation, for categorized parameters chi-square test was used, while for numerical data *t* test was used to compare two groups. The level of significance was 0.05.

Sample size calculation

The required sample size has been calculated using the Med Calc statistical software VAT. Ver 17.2 registration number is BE 0809 344,640. Med Calc Software is a corporate member of the American Statistical Association and a member of the International Association for Statistical Computing (IASC). By using this constant in the program, it is estimated that a sample size of 25 patients in either study group (total 50 patients).

Results

Fifty pregnant women in severe PE with gestational age ≥ 32 weeks were randomized in the study into two equal groups. In group A, 24 out of 25 patients were investigated and only 1 patient was excluded during the trial period due to pathological FHR traces; on the other hand, in group B, 2 patients were excluded, the first one due to severe hypotension 80/60 mmHg, palpitations, chest pain together with poor CTG readings, and the

second one due to poor response to hydralazine. The patients' criteria of the study participants are illustrated in Table 1. There were no statistically significant differences between the two groups as regards maternal age, body mass index (BMI), parity, and gestational age.

Regarding maternal hemodynamic, in group A, the mean systolic blood pressure (SBP) decreased significantly from (171.25 ± 9.88) to (115.79 ± 5.40) mmHg ($P = 0.001$), and the mean diastolic blood pressure (DBP) decreased significantly from (116.33 ± 7.08) to (80.80 ± 7.81) mmHg ($P = 0.001$). While in group B, the mean SBP and DBP decreased significantly from (173.85 ± 9.16 and 119.92 ± 4.33) mmHg to (126.46 ± 6.83 and 79.08 ± 3.04) mmHg respectively. ($P = 0.001$, 0.001) Comparing both groups, the post-treatment SBP decreased more significantly in labetalol group than in hydralazine group ($P = 0.001$), while there were no statistically significant differences in post-treatment DBP between both groups (Fig. 1). In group A, the mean maternal heart rate (MHR) decreased significantly from (85.13 ± 5.25) to (75.21 ± 6.59) beat/min ($P = 0.025$), while in group B there was insignificant changes (83.31 ± 7.65 vs 89.23 ± 7.94) beat/min ($P = 0.073$). On the other hand, the fetal heart rate (FHR) showed insignificant changes in both groups (Fig. 2).

Regarding fetal Doppler study, the mean UA (PI) before and after treatment in group A (1.03 ± 0.08 vs 1.00 ± 0.07) and in group B (1.04 ± 0.08 vs 1.02 ± 0.079) respectively, showed insignificant changes ($P = 0.114$, 0.266) (Fig. 3). In group A, no statistically significant differences were observed before and after treatment regarding UA (RI) and *S:D* ratio (RI 0.63 ± 0.04 vs 0.62 ± 0.02, $P = 0.344$; *S:D* 2.71 ± 0.34 vs 2.67 ± 0.18, $P = 0.340$). While in group B, these pre- and post-treatment values also showed insignificant differences (RI 0.62 ± 0.03 vs 0. 0.64 ± 0.03, $P = 0.063$; *S:D* ratio 2.68 ± 0.24 vs 2.83 ± 0.28, $P = 0.071$). Comparing between group A and B, these parameters did not show any significant changes before or after treatment (Figs. 3 and 4).

MCA Doppler study showed that, in group A, the mean PI, RI, and *S:D* ratio values did not show any significant changes before and after treatment (1.64 ± 0.12, 0.78 ± 0.031 and 4.45 ± 0.56 vs 1.58 ± 0.119, 0.77 ± 0.03 and 4.61 ± 0.69 respectively) ($P = 0.076$, 0.416, 0.241). While in group B, pre- and post-treatment showed also insignificant changes (1.54 ± 0.12, 0.75 ± 0.03 and 4.62 ± 0.66 vs 1.60 ± 0.11, 0.78 ± 0.04 and 4.67 ± 0.69 respectively) ($P = 0.093$, 0.087, 0.098). Comparing between the two groups, MCA Doppler indices did not show any significant changes before or after treatment Figs. 5 and 6).

Table 1 Patients' criteria in groups A and B

	Group A	Group B	*P* value
Age (years) mean ± SD	27.42 ± 3.40	25.20 ± 4.31	0.062
Gestational age (weeks) mean ± SD	35.05 ± 1.75	34.8 ± 1.89	0.29
Parity mean ± SD	0.50 ± 0.72	0.38 ± 0.62	0.23
Body nass index (BMI) mean ± SD	27.96 ± 1.88	28.34 ± 2.71	0.26

Data presented as mean ± SD

Discussion

Preeclampsia is a pregnancy complication characterized by hypertension and signs of damage to other organ systems. Despite the fact that the cause is not completely comprehended, variables thought to have a part include genes, the immune response, the placenta, and maternal vascular disease (Roberts and Cooper 2001). The target of treating extreme hypertension is to avoid organ damage and congestive heart failure without influencing utero-placental perfusion (Vigil-De Gracia et al. 2006).

A Cochrane systematic review reported that $MgSO_4$ reduces the incidence of eclamptic fits (Duley et al. 2003), with reports of transient reduction or no changes in BP, at 30 min after 2–5 g of intravenous $MgSO_4$in the management of preeclampsia. The potential for a transient decrease of BP 30 min after administration ought to be considered when anti-hypertensives are co-regulated (Magee et al. 2008).

Three short-acting anti-hypertensive agents, hydralazine, labetalol, and nifedipine, are usually used to control serious hypertension in women with severe preeclampsia, which necessitates immediate interventions (Rey et al. 1997). Recently, a Cochrane systematic review considered the effectiveness of these anti-hypertensives for treatment of severe hypertension during pregnancy and inferred that there is no confirmation that one anti-hypertensive drug is desirable over the others for improving outcome for women with serious hypertension during pregnancy, and their babies (Duley et al. 2013).

Six trials have compared parenteral hydralazine with labetalol (Magee et al. 2011). Magee et al. (2003), in a meta-analysis of randomized controlled trials of short-acting anti-hypertensives for severe hypertension in pregnancy, concluded that parenteral hydralazine was associated with more antagonistic impacts including maternal hypotension, caesarean section, and fetal heart rate abnormalities ($n = 21$ trials, 1085 women). Hydralazine was a more effective anti-hypertensive when compared with parenteral labetalol specifically in a subgroup analysis. It ought to be noticed that labetalol was associated with more neonatal bradycardia (Vigil-De Gracia et al. 2006).

In our study, we compared intravenous infusion of combination of labetalol with $MgSo_4$ versus hydralazine with $MgSo_4$. Our outcomes are in concurrence with

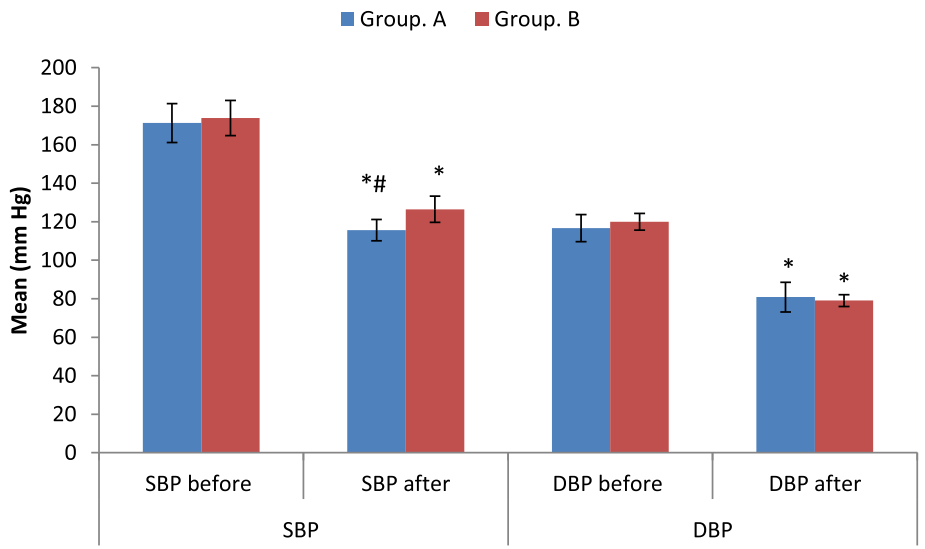

Fig. 1 Maternal systolic and diastolic blood pressure before and after treatment in both groups. *Significant decrease after in the two groups, # significant difference between the two groups after treatment

previously published trials (Magee et al. 2011; Nombur et al. 2014), as both regimens were effective in controlling severe hypertension, with the target blood pressure achieved significantly in most cases within the same median time (40 min). On the contrary to these studies, we recorded a significant reduction in the MHR in labetalol group, while we did not demonstrate any noteworthy changes in the hydralazine group, and this may be attributed to the infusion of the drug.

Just three patients were excluded from our study, two patients in group B, one of them developed hypotension (80/60), tachycardia, chest pain, and poor CTG readings, so she was excluded from the study with prompt resuscitation by stoppage of drug infusion and giving fluid challenge till blood pressure had been stabilized and expedited delivery, the other patient was excluded due to persistent hypertension albeit maximum infusion rate of 15 mg/h had been reached for around 60 min that necessitated giving a combination of labetalol and hydralazine till target blood pressure was achieved. On the other hand a single patient was excluded from group A due to pathological FHR traces which required stoppage of drug infusion, lateral positioning, IV fluids, and expedited delivery.

The medical impacts of $MgSO_4$ on fetal hemodynamic in preeclampsia and eclampsia have been studied few times before (Belfort et al. 1993). Souza et al. (2010) demonstrated that UA and MCA (RI) and (PI) values were significantly reduced 20 min after injection of

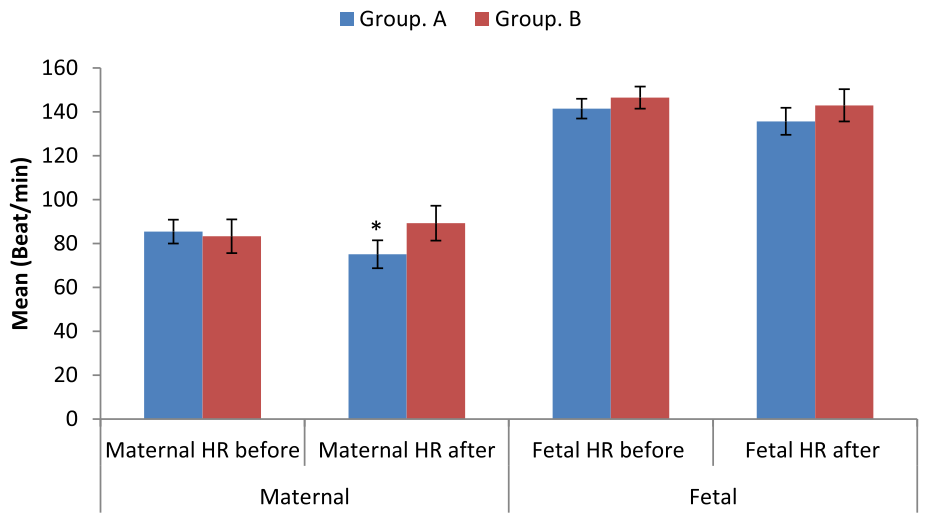

Fig. 2 Maternal and fetal heart rate before and after treatment in both groups. *Significant decrease from before value

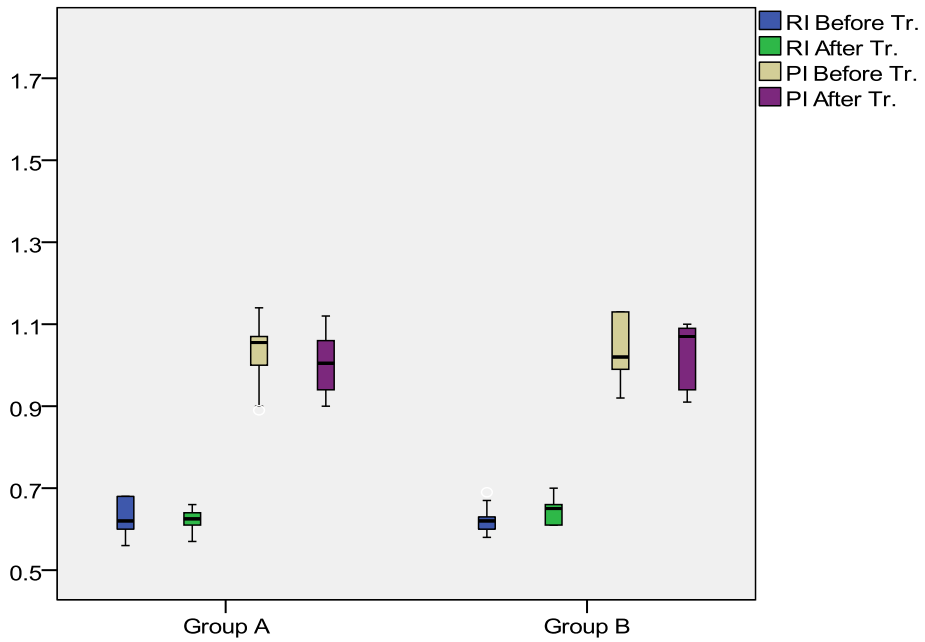

Fig. 3 Umbilical artery pulsatility index (PI) and resistance index (RI) before and after treatment in both groups

MgSO4, while in different studies these parameters demonstrated no critical changes (Belfort et al. 1993), This was disclosed to be because of lesser affectability (just 10–15%) of umbilical vessels secondary to pathological changes in the vessel wall, making them less flexible (Belfort et al. 1995). Dasgupta's et al. (Dasgupta et al. 2012), in a randomized placebo controlled trial after full dosage of prophylactic magnesium sulfate in preeclampsia, reported that post-magnesium sulfate UA and MCA (PI) dropped fundamentally in contrast with pre-magnesium sulfate. In another study done by Twickler et al. (Twickler et al. 2010), no significant effects on fetal cerebral blood flow were detected.

Albeit anti-hypertensive drugs may increase the uteroplacental flow, but blood pressure reduction may cause adverse effects, reducing uteroplacental flow and

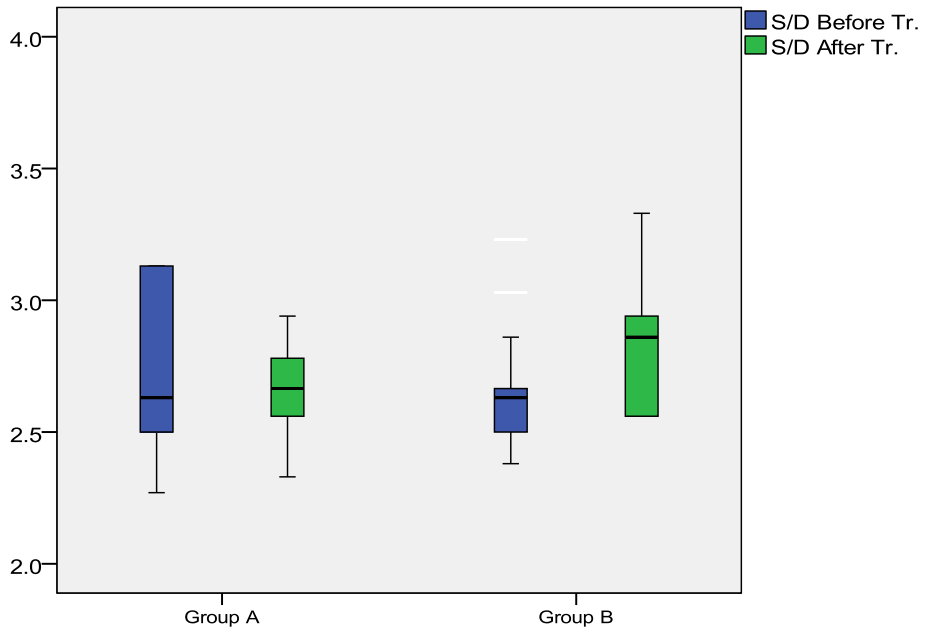

Fig. 4 Umbilical artery *S:D* ratio before and after treatment in both groups

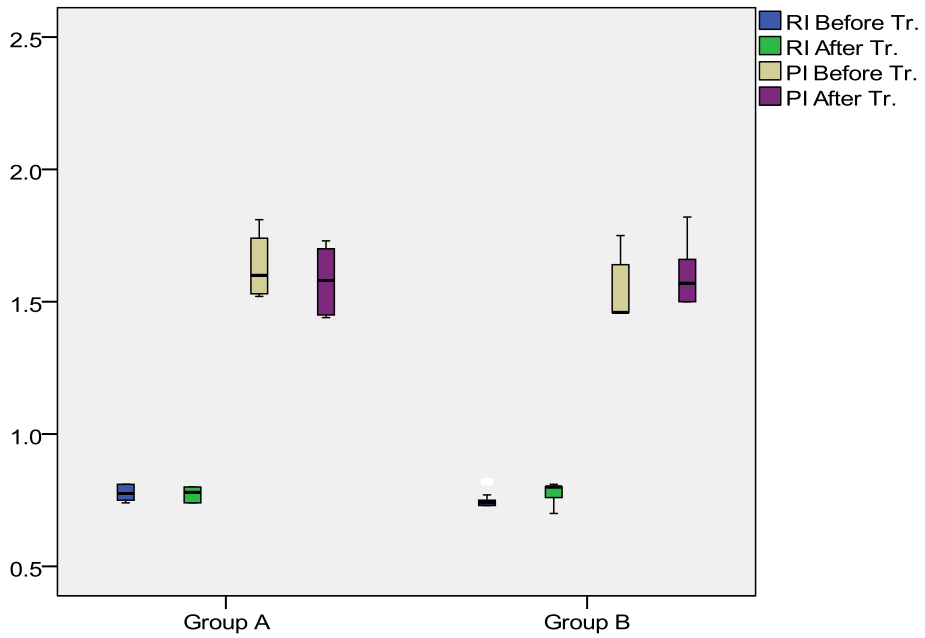

Fig. 5 Middle cerebral artery pulsatility index (PI) and resistance index (RI) before and after treatment in both groups

worsening the intra-uterine conditions. Several studies documented that the use of hydralazine and labetalol were not identified with any significant changes in UA and MCA flow velocity waveforms (Baggio et al. 2011; Mahmoud et al. 1993).

In agreement with the previously mentioned studies, the results of our study also showed that in both groups, UA and MCA Doppler indices did not show any significant changes before and after treatment until blood pressure had been controlled hypothesizing no negative impact of hydralazine or labetalol in combination with $MgSO_4$ on fetoplacental circulation.

Also, no noteworthy chronotropic impacts on fetal heart rate were recorded either by hydralazine or labetalol, and no neonatal or maternal mortality in either group. Actually, adrenergic receptor blockers are unrealistic to

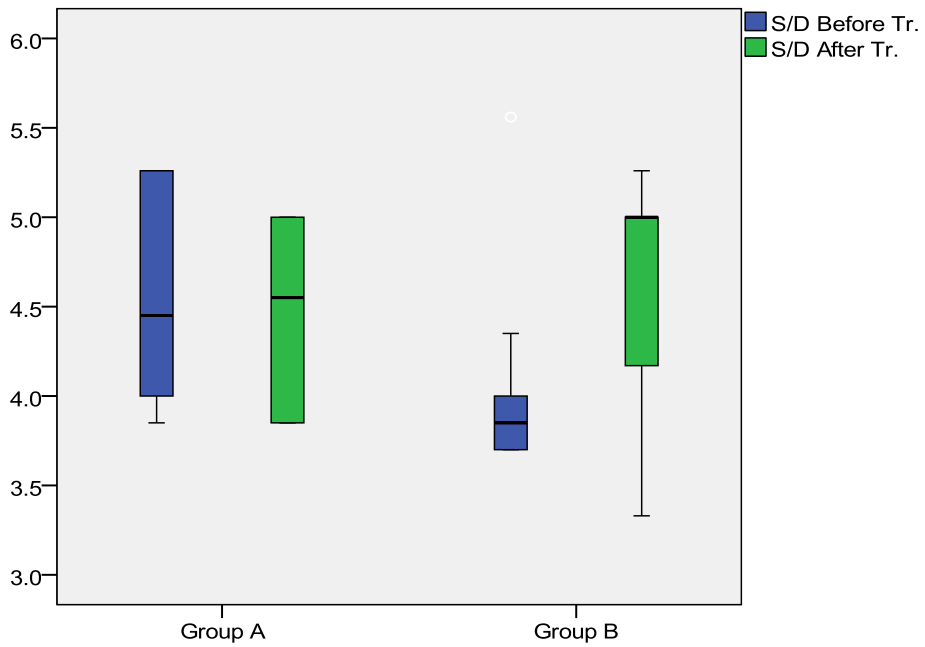

Fig. 6 Middle cerebral artery *S/:D* ratio before and after treatment in both groups

influence placental vessels as they are without adrenergic nerves. Umbilical resistance has been appeared to be principally controlled by hormones, autacoids substances, and oxygen pressure (Belfort et al. 1993).

Conclusion

Both studied regimens are well tolerated and effective in controlling severe hypertension in severe preeclampsia, as they are reassuring on fetomaternal hemodynamics. Results of our study point to more extensive studies with larger patient numbers are required to support conclusions about the effects of MgSO4 when co-administered with anti-hypertensive drug on fetomaternal hemodynamics.

Abbreviations

BMI: Body mass index; BP: Blood pressure; CTG: Cardiotocograph; DBP: Diastolic blood pressure; FGR: Fetal growth retardation; FHR: Fetal heart rate; IASC: International Association for Statistical Computing; ICU: Intensive care unit; MCA: Middle cerebral artery; $MgSO_4$: Magnesium sulfate; MHR: Maternal heart rate; PE: Preeclampsia; PI: Pulsatility index; RI: Resistance index; S/D: Systolic/diastolic; SBP: Systolic blood pressure; SPSS: Statistical Package for Social Sciences; UA: Umbilical artery; WFI: Water for injection

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

Authors' contributions

TNI and MAY contributed to the conception and design of the study. Both organized the data collection, reviewed and greatly contributed to the interpretation of results, checked the statistical analysis, and revised the manuscript critically for important intellectual content. AMR and AA performed the data collection and organized data preparation. All authors actively discussed the manuscript, critically reviewed its comprehensive content, and finally approved the version to be submitted for publication.

Ethics approval and consent to participate

The study protocol was approved by the Scientific Research Ethics Committee at Ibn Sina National College Hospital (1S-09/13-10). There was an informed consent for all patients approved to participate.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Received: 23 August 2018 Accepted: 7 January 2019
Published online: 21 February 2019

References

Altura BM, Altura BT, Carella A, Gebrewold A, Murakawa T, Nishio A (1987) Mg^{2+}-Ca^{2+} interaction in contractility of vascular smooth muscle: Mg^{2+} versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. Can J Physiol Pharmacol 65:729–745

American College of Obstetricians and Gynecologists; Hypertension in Pregnancy (2013) Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 122:1122–1131

Arbellie P, Ronuin A, Besun M, Patat F, Pourcelot L (1987) Exploration of the fetal cerebral blood flow by duplex Doppler-linear array system in normal and pathological pregnancies. Ultrasound Med Bial 13:329–337

Baggio MR, Martins WP, Calderon AC et al (2011) Changes in fetal and maternal Doppler parameters observed during acute severe hypertension treatment with hydralazine or labetalol: a randomized controlled trial. Ultrasound Med Biol 37:53–58

Belfort MA, Saade GR, Kenneth JM (1993) The effect of magnesium sulfate on maternal and fetal blood flow in pregnancyinduced hypertension. Acta Obstet Gynecol Scand 72:526–530

Belfort MA, Saade GR, Suresh M, Johnson D, Vedernikov YP (1995) Human umbilical vessels: responses to agents frequently used in obstetric patients. Am J Obstet Gynecol 172:1395–1403

Brown MA, Hague WM, Higgins J et al (2000) The detection, investigation and management of hypertension in pregnancy: executive summary. Aust N Z J Obstet Gynaecol 40:133–138

Dasgupta S, Ghosh D, Seal SL, Kamilya G, Karmakar M, Saha D (2012) Randomized controlled study comparing effect of magnesium sulfate with placebo on fetal umbilical artery and middle cerebral artery blood flow in mild preeclampsia at ≥34 weeks gestational age. J Obstet Gynaecol Res 38:763–771

Duley L, Gulmezoglu AM, Henderson-Smart DJ (2003) Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. Cochrane Database Syst Rev. 2003(2):CD000025.

Duley L, Meher S, Jones L (2013) Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev. 2013(7):CD001449. https://doi.org/10.1002/14651858.CD001449.pub3.

Fisher SJ, McMaster M, Roberts M (2009) Chesley's Hypertensive Disorders in Pregnancy. Academic Press Elsevier, Amsterdam The placenta in normal pregnancy and preeclampsia

Hutcheon JA, Lisonkova S, Joseph KS (2011) Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol 25:391–403

Louis WJ, McNeil JJ, Drummer OH (1984) Pharmacology of combined alpha-beta-blockade. I Drugs 28(Suppl 2):16–34

Magee LA, Abalos E, von Dadelszen P, Sibai B, Easterling T, Walkinshaw S (2011) How to manage hypertension in pregnancy effectively. Br J Clin Pharmacol 72:394–401

Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P (2003) Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. BMJ 327:955–960

Magee LA, Helewa M, Rey E, Cote AM, Douglas J, Gibson P, Gruslin A, Lange I, Leduc L, Logan AG, Smith GN, STIRRHS Pre-eclampsia Scholars, Cardew S, Firoz T, Moutquin J-M, von Dadelszen P. SOGC Clinical Practice Guideline: diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. JOGC 2008; 30: S1–48

Magee LA, Ornstein MP, von Dadelszen P (1999) Fortnightly review: management of hypertension in pregnancy. BMJ 318:1332–1336

Mahmoud TZ, Bjornsson S, Calder AA (1993) Labetalol therapy in pregnancy induced hypertension: the effects on fetoplacental circulation and fetal outcome. Eur J Obstet Gynecol Reprod Biol 50:109–113

National Institute of Health and Clinical Excellence. Hypertension in Pregnancy, The management of hypertensive disorders during pregnancy. Clinical guidelines CG107 Issued: August 2010. Accessible on http://guidance.nice.org.uk/CG107. Last accessed 26 Dec 2010

Neilson JP, Alfirevic Z (1998) Doppler ultrasound in high risk pregnancies. In: Neilson JP, Crowther CA, Hodnett ED, Hofmeyr GJ (eds) Pregnancy and Childbirth Module of the Cochrane Database of Systematic Reviews, Cochrane Collaboration; issue 1. Update Software, Oxford

Nombur LI, Agida ET, Isah AY, Ekele BA (2014) A comparison of hydralazine and labetalol in the management of severe preeclampsia. J Women's Health Care 3:6

Pearce CJ, Wallin JD (1994) Labetalol and other agents that block both alpha and beta-adrenergic receptors. Cleve Clin J Med 61:59–69

Rey E, LeLorier J, Burgess E, Lange IR, Leduc L (1997) Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy. CMAJ 157:1245–1254

Roberts JM (1998) Endothelial dysfunction in preclampsia. Semin Reprod Endocrinol 16:5–15
Roberts JM (2004) Pregnancy-related hypertension. In: Creasy RK, Resnik R, Iams JD (eds) Maternal-fetal medicine: principles and practice. Saunders, Philadelphia, pp 884–887
Roberts JM, Cooper DW (2001) Pathogenesis and genetics of preeclampsia. Lancet 357:53–56
Schneider EP, Schulman H (1995) Doppler ultrasound in obstetrics and gynecology. In: Copel JA, Reed KL (eds) Hypertension. Raven Press, New York, pp 147–155
Schulman H, Fleischer A, Stern W, Farmakides G, Jagani N, Blattner P (1984) Umblical velocity wave ratios in human pregnancy. Am J Obstet Gynecol 148:985–990
Sibai BM, Eclampsia VI (1990) Maternal-perinatal outcome in 254 cases. Am J Obstet Gynecol 163:1049–1055
Souza AS, Amorim MM, Coutinho IC, Lima MM, Noronha Neto C, Figueroa JN (2010) Effect of the loading dose of magnesium sulfate (MgSO4) on the parameters of Doppler flow velocity in the uterine, umbilical and middle cerebral arteries in severe preeclampsia. Hypertens Pregnancy 29:123–134
Twickler DM, McIntire DD, Alexander JM, Leveno KJ (2010) Effects of magnesium sulfate on preterm fetal cerebral blood flow using Doppler analysis: a randomized controlled trial. Obstet Gynecol 115:215
Varon J, Marik PE (2003) Clinical review: the management of hypertensive crises. Crit Care 7:374–384
Vigil-De Gracia P, Lasso M, Ruiz E, Vega-Malek JC, de Mena FT, Lopez JC (2006) Severe hypertension in pregnancy: hydralazine or labetalol. A randomized clinical trial. Eur J Obstet Gynecol Reprod Biol 128:157–162
Witlin AG, Sibai BM (1998) Magnesium sulfate therapy in preeclampsia and eclampsia. Obstet Gynecol 92:883–889
Yoon BH, Lee CM, Kim SW (1994) An abnormal umbilical artery waveform: a strong and independent predictor of adverse perinatal outcome in patients with preeclampsia. Am J Obstet Gynecol 171:713–721