Men's Health Journal. 2020; 4(1): e10

ORIGINAL RESEARCH

Comparison of Lasix and Methyldopa in Controlling Hypertension in preeclampsia patients: A Double-Blind Randomized Clinical Trial

Setareh Siamansoori[1], Elahe Afshari[2], Maryam Palizdar[3], Mohammad Ali Hosseini[3]*

1. Shahid Akbarabadi Clinical Research Unit, Iran University of Medical Science, Tehran, Iran.
2. Iran University of Medical Sciences, Tehran, Iran.
3. Student Research Committee, Qazvin University of Medical Sciences, Qazvin, Iran.

Received: April 2020; Accepted: June 2020; Published online: July 2020

Abstract: **Introduction:** Preeclampsia is a specific gestational syndrome that reduces organ perfusion due to vascular spasm and endothelial activation. Despite the use of magnesium sulfate, the patient's blood pressure sometimes remains uncontrolled, and therefore, it is necessary to use other medications, especially diuretics and Methyldopa. Hence, the aim of this study was to compare Lasix and Methyldopa in controlling postpartum hypertension in preeclampsia patients after magnesium sulfate treatment. **Methods:** This double-blind randomized clinical trial was carried out on 100 women with preeclampsia referred to Akbar Abadi Hospital-Iran. In the first 24 hours after the termination of pregnancy, the participants' blood pressure was measured and those with a blood pressure of 140/90 to 160/100 were divided into two groups. In the first and second 24 hours, and then one week after the intervention, systolic and diastolic blood pressure as well as diuresis and drug complications in the two groups were assessed and compared. The present study was registered in the Iranian Registry of Clinical Trials (IRCT) under the ID of IRCT20180114038349N1. **Results:** The mean age of individuals was 29.93 ± 6.65 in the Methyldopa group, and 32.35 ± 4.85 in the Lasix group (P = 0.479). Systolic and diastolic blood pressure had a substantial reduction in both groups, but there was no significant difference between the two groups (P> 0.05). Systolic blood pressure was reduced by 31 mmHg (reduction from 146 to 115) in the methyldopa group and 30 mmHg (reduction from 145 to 114) in the Lasix group. Furthermore, the reduction in diastolic blood pressure was 25 mmHg (from 95 to 70) in the methyldopa group, and 21 mmHg in the Lasix one (from 91 to 70). **Conclusion:** The present study showed that using Lasix and methyldopa was effective enough in changing blood pressure in patients with preeclampsia, and the effects observed in the two groups were the same. Therefore, it could have a great impact on the wellbeing of couples.

Keywords: Lasix; Methyldopa; Preeclampsia; Pregnancy; Hypertension

Cite this article as: Siamansoori S, Afshari E, Palizdar M, Hosseini M A. Comparison of Lasix and Methyldopa in Controlling Hypertension in preeclampsia patients: A Double-Blind Randomized Clinical Trial. Mens Health J. 2020; 4(1): e10.

1. Introduction

Blood pressure disorders, bleeding, and infections, account for maternal mortality in developing countries, and cause a majority of complications and deaths associated with pregnancy (1). Blood pressure disorders are among the most common abnormalities that occur during pregnancy (1-3). Preeclampsia is a specific pregnancy syndrome characterized by high blood pressure and proteinuria (4, 5).

The incidence rate of preeclampsia is about 5%. In saying that, a significant variation of this disorder has been reported (6-8). Some of its serious complications are end-organ involvement including heart failure, pulmonary edema, involvement of liver and coagulation system, and ultimately HELLP syndrome (Hemolysis Elevation of Liver Enzyme Low Tumble)(9). There is also the possibility of brain involvement and seizure, and even maternal death. On another note, due to the problems with uterine placental bloodstream, IUGR (Intrauterine Growth Retardation) and IUFD (Intrauterine Fetal Death) may occur, too (10, 11).

***Corresponding Author:** Mohammad Ali Hosseini Email: smahoseini@gmail.com Address: Qazvin University of Medical Sciences, Shahid Bahonar Boulevard, Qazvin, Iran Tel /Fax: +(98)9128128285/+(98)2122038462

Regarding the great importance of preeclampsia and its risks of maternal and infant complications and mortality, providing methods to reduce hypertension during pregnancy is very important. The use of antihypertensive, to increase the length of pregnancy or reduce prenatal outcomes in pregnant women with different types and severity of hypertension, has been highly considered by physicians and researchers. Despite decades of extensive research, the onset or exacerbation of gestational hypertension is unknown, and hypertensive disorders are still among the most important unresolved issues in obstetric medicine and midwifery (12). In general, preeclampsia is a specific gestational syndrome in which organ perfusion is reduced due to vascular spasm and activation of endothelium (13, 14). Therefore, treatments such as magnesium sulfate mainly focus on this issue and affect vasodilatation (15-17).

In preeclampsia trend, a reduction in urine volume is usually indicative of the worsening of the disease, and spontaneous diuresis translates into improved conditions. Thus, in the treatment of preeclampsia, the development of diuresis is considered a therapeutic goal (18, 19). For example, in choosing a crystalloid solution suitable for preeclampsia patients, ringer is preferred to normal saline, due to causing faster diuresis.

Today, there is a consensus around the world over the use of magnesium sulfate as a selective treatment for preeclampsia and eclampsia. The drug is used at a dose of 2-4 grams of acetate and 1-5 grams per hour by injection in a solution until 24 hours after lowering blood pressure. But its beneficial mechanism is ambiguous. Although high-concentration magnesium ion has a direct effect on smooth muscle relaxation, the magnesium that affects preeclampsia does not significantly reduce systemic blood pressure (1, 20, 21). Therefore, it is necessary to use other medications, especially diuretics and methyldopa. Diuretics are used in different types of high blood pressure. In order for methyldopa to work more effectively and to reduce fluid retention, a diuretic is usually prescribed. Therefore, the aim of this study was to compare Lasix with methyldopa in controlling postpartum hypertension in preeclampsia patients after magnesium sulfate treatment. To the best of our knowledge, this is the first study comparing the effects of Lasix with methyldopa in controlling postpartum hypertension in preeclampsia patients.

2. Material and Methods

This study was a double-blind randomized clinical trial carried out on women with preeclampsia who referred to Shahid Akbar Abadi Hospital in Tehran, Iran. The study was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran. It was then registered in the Iranian Registry of Clinical Trials website (IRCT) and received a clinical trial code number IRCT20180114038349N1. An informed consent was obtained from all participants in the study, after examining the inclusion and exclusion criteria. The women with preeclampsia who had received magnesium sulfate in the first 24 hours after the termination of pregnancy and were admitted to the ICU with a blood pressure of 140/90 to 160/100, were included in the study. While pregnant women with complicated pregnancies, such as GDM, heart diseases, kidney diseases, sensitivity to Lasix and methyldopa, and major adverse drug complications, were excluded.

After examining the inclusion and exclusion criteria, women were randomly assigned to the control and intervention groups with an allocation ratio of 1:1 in blocks of four and six. Opaque sealed envelopes numbered sequentially with the group type written in them were used for allocation concealment. The envelopes were prepared by a researcher not involved in data collection. The envelopes were opened after completing the pre-intervention questionnaires. Therefore, before random assignment of participants, researcher and participants were unaware of what participants were assigned to each group (Allocation Concealment). The first group received 20 mg oral tablet of Lasix twice a day, and the second group received 250 mg oral tablet of methyldopa 3 times a day. The primary outcome in this study was systolic and diastolic blood pressure measured at the beginning of the study and 6 hours, 48 hours, and one week, after the intervention. Another outcome studied was diuresis, which was measured in both groups in the first and second 24 hours after the intervention. The sample size in this study was calculated to be 50 people in each group by taking into account the results of previous studies with the mean and standard deviation of 131 ± 13 and 138± 13, 80% power and Îś = 0.05.

2.1. Statistical Data Analysis

The results were presented as mean and standard deviation (mean ± SD) for quantitative variables, and as numbers and percentages for those of qualitative categorical nature. To compare quantitative and qualitative variables, the t-test and the chi-square test were used, respectively. The independent t-test was also used to determine the changes in the indicators in both intervention and control groups. The significance level was considered lower than 0.05. The SPSS 24 software was used to analyze the data.

3. Results

The average women's age was 29.93 ± 6.65 in the Methyldopa group, and 32.35 ± 4.85 in the Lasix group (P = 0.479). Besides, the mean BMI and children's weight in the Methyldopa group were 28.95 ± 4.82 and 2444.58 ± 744.59, respectively, while they were 27.84 ± 4.13 and 2721.0±887.59 in the Lasix group. The differences were not statistically significant (P =

Table 1: Comparison of baseline data in the two groups

Variables	Methyldopa group(n=50)	Lasix group(n=50)	P-Value
Age	29.93 ± 6.65	32.35 ± 4.85	0.479
BMI	28.95 ± 4.82	27.84 ± 4.13	0.277
Infant Wieght	2444.58 ± 744.59	2721.0 ± 887.59	0.668

Table 2: Comparison of systolic blood pressure in both groups at baseline and 6 hours, 46 hours, and 1 week after intervention

Variables	Time	Methyldopa group(n=50)	Lasix group(n=50)	P -Value
Systolic Blood Pressure	Base line	146.66 ± 7.78	145.55 ± 7.26	0.922
	After 6 hours	129.16 ± 12.40	132.22 ± 12.01	
	After 48 hours	119.58 ± 12.87	119.44 ± 6.34	
	After 1 week	115.00 ± 5.22	114.44 ± 5.27	

0.277) (P = 0.669) (Table 1).

Comparison of the systolic blood pressure in both groups showed that there was a significant decrease in the systolic blood pressure at different times in both groups, but this difference was not statistically significant (F = 0.010, P = 0.922). However, it could be said that the systolic blood pressure was reduced by 31 mmHg (reduction from 146 to 115) in the methyldopa group and 30 mmHg (reduction from 145 to 114) in the Lasix group (Table 2).

Also, there was a major reduction in blood pressure at different times in both groups, but there was no significant difference between the two groups in terms of diastolic blood pressure (F = 0.005, P = 0.974). The reduction was 25 mmHg (from 95 to 70) in the methyldopa group, and 21 mmHg in the Lasix one (from 91 to 70) (Table 3).

In both groups, there was a noteworthy decrease in hemoglobin count in the first and the second 24 hours compared to the baseline, but the difference was not statistically significant (F = 0.593, P = 0.448) (Table 4). Furthermore, diuresis increased in both groups within the second 24 hours compared to the first one after the intervention, but the difference was not significant (P = 0.541) (Table 4). Moreover, no side effects related to the medication were seen in either intervention groups

4. Discussion

Postpartum blood pressure is a common phenomenon and is often a cause of concern. After giving birth to a child, increased intravascular hydrostatic pressure, increased capillary permeability, and low vascular oncotic pressure may occur. As a result of this fluid mobilization process, the central pressure and the overall pulmonary-capillary pressure are increased. This may cause pulmonary edema. Therefore, diuretics may be a preferable option for the treatment of hypertension in such situations20. In the present study, the comparison of systolic and diastolic blood pressure in the two groups showed a significant decrease in both blood pressure types at different times, but this difference was not statistically significant. There was a decrease in blood pressure in both groups, but this decrease was higher in the Methyldopa group.

In terms of decreased blood pressure, the results of this study were consistent with those of the study conducted by Ascarelli et al. In their study, Ascarelli et al. showed that postpartum systolic blood pressure was reduced significantly within 2 days after delivery only in patients with severe preeclampsia who received Lasix (22). In a study to evaluate the effects of Lasix, a total of 108 pregnant women with severe preeclampsia and over-150 mmHg hypertension were included within the first 24 hours after delivery. The results showed that there was no significant difference in the mean systolic and diastolic as well as the Mean Arterial Pressure (MAP) between the two groups at admission. One of the reasons why the results of this study were not significant could be attributed to the small sample size.

The study by Ascarelli et al. had a larger sample size than that of the present study, and obtained significant results. Despite the importance of pregnancy-induced hypertension, few studies have been done on the therapies for postpartum management of such patients. In a study conducted by FIDLER et al. in England (1982), the patients were randomly divided into two groups to be treated with Timolol or methyldopa (40 patients in each group). The results showed that treatment of high blood pressure (diastolic blood pressure of 105-95 mm Hg) with methyldopa (750-3000 mg / day) was not significantly different from treatment with Timolol (15-60 mg / day) in 80 patients during the study period (9 days), and had the same effect on the patients' blood pressure (18, 23). At the end of the study, it was concluded that Timolol could be an appropriate alternative for methyldopa in the treatment of high blood pressure 12. A study by Firoz et al. in 2014 showed that methyldopa could help control gestational blood pressure in 56% of cases (24). Another result of

Table 3: Comparison of diastolic blood pressure in both groups at baseline and 6 hours, 46 hours, and 1 week after interventionComparison of diastolic blood pressure in both groups at baseline and 6 hours, 46 hours, and 1 week after intervention

Variables	Time	Methyldopa group(n=50)	Lasix group(n=50)	P-Value
	Base line	95.00 ± 7.97	91.50 ± 7.47	
Diastolic Blood	After 6 hours	78.75 ± 9.07	81.00 ± 11.97	0.947
Pressure	After 48 hours	71.25 ± 3.76	73.00 ± 4.83	
	After 1 week	70.41 ± 1.44	70.50 ± 1.58	

Table 4: Comparison of mean hemoglobin in both groups at baseline and 24 and 48 hours after intervention

Variables	Time	Methyldopa group(n=50)	Lasix group(n=50)	P -Value
	Base line	13.03 ± 1.22	13.00 ± 1.39	
Hemoglobin	After 24 hours	11.89 ± 1.38	12.31 ± 1.52	0.448
	After 48 hours	11.06 ± 1.38	11.71 ± 1.03	
Diuresis	After 24 hours	1740.02 ± 150.65	1659.90 ± 145.53	0.541
	After 48 hours	1967.34 ± 175.34	2011.11 ± 164.42	

this study was a significant reduction in hemoglobin count in the first and second 24 hours compared with the baseline in both groups, but this difference was not statistically significant. The results also showed a significant decrease in diuresis during the second 24 hours after the intervention in both groups, compared to the first 24 hours which was not statistically significant. In a study by Magee et al. in Canada (2013), it was suggested that adding some other drugs, including nifedipine and methyldopa, did not have much effect on the treatment of uncontrolled postprandial blood pressure, while Lasix could be somewhat useful for controlling blood pressure (25).

This is the first study in the world comparing Methyldopa group with a Lasix one in terms of reducing blood pressure, and this could be considered a strength of the present study. On the other hand, measurement of blood pressure at different times would naturally better reflect the effect. In this study, it was possible to select a larger sample size in the two groups, and the researchers could also measure more variables to compare the effects.

5. Conclusion

The present study showed that the use of Lasix and methyldopa had the necessary efficacy to change the blood pressure in preeclampsia patients, although the results were insignificant. It seems that the effect of this drug in reducing blood pressure is due to its conversion to Îś-methyl norepinephrine. Central Îś-methyl norepinephrine reduces the sympathetic flow and thus decreases blood pressure.

In 2005, Ascarelli et al. (22), designed a randomized trial involving 264 women with preeclampsia at the postpartum stage. The patients were randomly divided into a group of 20 mg of furosemide per day and a non-treated one. In women with mild illness, there was a similar situation in terms of blood pressure control, regardless of receiving treatment or placebo. However, the patients with severe preeclampsia who were under treatment, showed a lower mean systolic blood pressure on the second day, compared to those treated with placebo.

Studying the need for additional drugs showed that there was no significant difference in the methyldopa and Lasix groups in terms of taking additional drugs for controlling blood pressure. The hemoglobin count measurements in the first and second 24 hours, showed that there was no significant difference between the two groups in terms of reduced hemoglobin count in the first and second 24 hours. Hence, it seems that these two drugs are effective for patients with preeclampsia and have the same benefits. Therefore, it could have a great impact on the wellbeing of couples. In saying that, more research with appropriate sample sizes is needed to further verify this claim.

6. Appendix

6.1. Acknowledgements

This paper is derived from a medical doctorate thesis of Iran Medical Sciences University. We would like to extent our sincere gratitude to Dr.Nasiri for his invaluable contribution to this work.

6.2. Author contribution

All the authors have the same contribution.

6.3. Funding/Support

None.

6.4. Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

1. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstetrics & Gynecology. 2003;102(1):181-92.
2. Sibai BM. Prevention of preeclampsia: a big disappointment. American journal of obstetrics and gynecology. 1998;179(5):1275-8.
3. Haghighi L, Hashemi N, Moradi Y, Barzegar N, Najmi Z. The Association Between Menarche Age and First Offspring Sex Ratio. Shiraz E-Medical Journal. 2016;17(1).
4. Rath W, Fischer T. The diagnosis and treatment of hypertensive disorders of pregnancy: new findings for antenatal and inpatient care. Deutsches ÃĎrzteblatt International. 2009;106(45):733.
5. Haghighi L, Nohesara S, Moradi Y, Rashidi M, Moridi M. Psychological Disorders in Women with Spontaneous Preterm Delivery. Shiraz E-Medical Journal. 2016;17(10).
6. Lisonkova S, Joseph K. Incidence of preeclampsia: risk factors and outcomes associated with early-versus late-onset disease. American journal of obstetrics and gynecology. 2013;209(6):544. e1-. e12.
7. Nordqvist M, Jacobsson B, BrantsÃęter A-L, Myhre R, Nilsson S, Sengpiel V. Timing of probiotic milk consumption during pregnancy and effects on the incidence of preeclampsia and preterm delivery: a prospective observational cohort study in Norway. BMJ open. 2018;8(1):e018021.
8. Smith GN, Walker M, Tessier JL, Millar KG. Increased incidence of preeclampsia in women conceiving by intrauterine insemination with donor versus partner sperm for treatment of primary infertility. American journal of obstetrics and gynecology. 1997;177(2):455-8.
9. Brown MA, Lindheimer MD, de Swiet M, Assche AV, Moutquin J-M. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Taylor & Francis; 2001.
10. Moser M. Working group report on high blood pressure in pregnancy. The Journal of Clinical Hypertension. 2001;3(2):75-88.
11. Pham T, Steele J, Stayboldt C, Chan L, Benirschke K. Placental mesenchymal dysplasia is associated with high rates of intrauterine growth restriction and fetal demise: a report of 11 new cases and a review of the literature. American journal of clinical pathology. 2006;126(1):67-78.
12. Chandiramani M, Shennan A. Hypertensive disorders of pregnancy: a UK-based perspective. Current opinion in obstetrics and gynecology. 2008;20(2):96-101.
13. Erez O, Romero R, Espinoza J, Fu W, Todem D, Kusanovic JP, et al. The change in concentrations of angiogenic and anti-angiogenic factors in maternal plasma between the first and second trimesters in risk assessment for the subsequent development of preeclampsia and small-for-gestational age. The Journal of Maternal-Fetal & Neonatal Medicine. 2008;21(5):279-87.
14. Mehdizadeh Kashi A, Moradi Y, Chaichian S, Najmi Z, Mansori K, Salehin F, et al. Application of the World Health Organization Quality of Life Instrument, Short Form (WHOQOL-BREF) to patients with endometriosis. Obstetrics & gynecology science. 2018;61(5):598-604.
15. Barton JR, Sibai BM. Prediction and prevention of recurrent preeclampsia. Obstetrics & Gynecology. 2008;112(2):359-72.
16. Grotegut CA. Prevention of preeclampsia. The Journal of clinical investigation. 2016;126(12):4396-8.
17. Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi J-M. Pre-eclampsia: pathophysiology, diagnosis, and management. Vascular health and risk management. 2011;7:467.
18. FTDLER J, SMITH V, SWIET M. A randomized study comparing timolol and methyldopa in hospital treatment of puerperal hypertension. BJOG: An International Journal of Obstetrics & Gynaecology. 1982;89(12):1031-4.
19. Hoorsan H, Majd HA, Chaichian S, Mehdizadehkashi A, Hoorsan R, Akhlaqghdoust M, et al. Maternal Anthropometric Characteristics and Adverse Pregnancy Outcomes in Iranian Women: A Confirmation Analysis. Archives of Iranian Medicine (AIM). 2018;21(2).
20. Belfort MA, Anthony J, Saade GR, Allen Jr JC. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. New England Journal of Medicine. 2003;348(4):304-11.
21. Meibodi MR, Mossayebi E, Najmi Z, Moradi Y. Normal labor curve is affected by fetus gender: A cohort study. Medical journal of the Islamic Republic of Iran. 2017;31:93.
22. Ascarelli MH, Johnson V, McCreary H, Cushman J, May WL, Martin JN. Postpartum preeclampsia management with furosemide: a randomized clinical trial. Obstetrics & Gynecology. 2005;105(1):29-33.
23. Firoz T, Magee L, MacDonell K, Payne B, Gordon R, Vidler M, et al. Oral antihypertensive therapy for severe hypertension in pregnancy and postpartum: a systematic review. BJOG: An International Journal of Obstetrics & Gynaecology. 2014;121(10):1210-8.
24. Magee L. Prevention and treatment of postpartum hypertension. 2013.