European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 10, Issue 01, 2023

ORIGINAL RESEARCH

Management of Pregnancy induced hypertension (PIH) by Methyldopa versus labetalol - A randomized controlled trial

Madhu Digra[1], Yasmeen Kousar[2], Javid Iqbal[3], Ravinder Kumar[4]

[1]Assistant Professor Department of Obstetrics and Gynaecology, Government Medical College Kathua, Jammu and Kashmir, India.
[2]Government Medical College Jammu, Jammu and Kashmir, India.
[3]Government Medical College Jammu Jammu and Kashmir, India.
[4]Associate Professor, Department of Surgery, Government Medical College, Kathua, Jammu and Kashmir, India. India.

Received Date: 26/11/2022 Acceptance Date: 16/01/2023

ABSTRACT

Background: Pregnancy-related hypertension can alter the outcomes of pregnancy if left unmanaged. The complications associated with pregnancy-related hypertension include pre-eclampsia and eclampsia. Various medicines are available that can avoid these complications and lead to better outcomes of pregnancy. Material and Methods: The study was conducted on 250 patients with pregnancy-induced hypertension (PIH) that were prospectively enrolled over two years at a tertiary healthcare facility. After randomization of the patients into two groups, methyldopa or labetalol was administered to patients. The difference between the two groups was evaluated for the mode of labour, delivery, perinatal mortality, mean birth weight, Apgar score and neonatal intensive care (NICU) admissions. Result: There was no significant difference observed in the mode of labour, delivery, perinatal mortality, mean birth weight, Apgar score and neonatal intensive care (NICU) admissions between the patients undergoing management with methyldopa or labetalol. Conclusion: Overall, labetalol was found to have slightly better and safer outcomes for both the mother and the fetus in comparison to methyldopa.

Keywords: Pregnancy-induced hypertension, Pregnancy, Labor, Delivery.

Corresponding Author: Dr. Ravinder Kumar, Associate Professor, Department of Surgery, Government Medical College, Kathua, Jammu and Kashmir, India.
Email: dr.ravinderchambyal@gmail.com

INTRODUCTION

Pregnancy-related hypertensive illnesses account for 30% of instances of chronic hypertension and 70% of cases of gestational hypertension, which includes preeclampsia and eclampsia[1]. A systolic blood pressure of ≥160 mm Hg and a diastolic blood pressure of ≥110 mm Hg are indicative of severe pregnancy-induced hypertension (PIH). Proteinuria >300 mg/24 hours urination and severe PIH are two symptoms of severe pre-eclampsia[2,3]. Several complications are associated with hypertension, and a considerable risk of maternal cerebral vascular injury when mean arterial pressure exceeds 140 mm of Hg. Therefore, it is advised that BP ≥160/110 mm Hg with or without proteinuria (>300 mg/24 hrs. urination) be recognized as hypertensive urgency[4].

PIH affects around 6–8% of pregnancies worldwide[5,6]. One fatality from complications like pre-eclampsia and eclampsia occurs every three minutes globally[7]. By using hypertension medications, this development into a bad feto-maternal result can be avoided[8][9].

PIH is treated with a variety of medications such as methyldopa, labetalol, and nifedipine, which are indicated as the first-choice medications on a global scale[10,11,12]. Methyldopa has been used extensively to treat PIH because it lowers blood pressure by acting centrally on alpha 2 receptors and reducing sympathetic nerve activity[13,14]. Although a substantial dosage and a 12 to 24-hour window are needed for a sufficient therapeutic response, long-term blood pressure management is made possible[15]. Labetalol has a combination of alpha- and beta-blocking action, which helps to reduce peripheral vascular resistance while having little to no effect on cardiac output. Labetalol is more quickly acting and is administered orally or by injection. Furthermore, it is superior to other beta-blockers in that it does not enter the foetal circulation, cross the placenta, or risk foetal bradycardia[16]. Due to these advantages, labetalol is becoming a first-line treatment for PIH[17]. This study aims to assess the effectiveness of methyldopa vs labetalol in the management of PIH and pregnancy outcomes.

MATERIAL AND METHODS

Study subjects: In this study, 250 patients with PIH were prospectively enrolled over two years from September 2017 to October 2019 at a tertiary healthcare facility, regardless of patient age, parity, or socioeconomic status.

The study procedures and protocols were approved by the institutional ethics committee. Informed consent was obtained for all the participants that were enrolled in the study.

Inclusion and Exclusion criteria: The study comprised singleton pregnancies with systolic BP≥ 150 mm Hg and diastolic BP≥95 mm Hg, and gestational age ranging from 20 weeks to 38 weeks. Patients with a history of hypertension before pregnancy, patients who had previously taken antihypertensive medications in the current pregnancy, and patients whose blood pressure was less than 170/110 mm Hg were excluded from the study. Additionally, patients with a history of metabolic disorders, diabetes, cardiovascular disease, respiratory disease, collagen disorder, or Rhesus isoimmunization were excluded from the study.

Study design: Eligible patients were allocated into two groups using computer-generated random numbers after obtaining written informed consent.

Group - I: patients were treated with methyldopa.

Group - II: patients were treated with labetalol.

As per the randomization chart, antihypertensive medication with either methyldopa or labetalol was administered to patients with systolic blood pressure ≥ 150mm Hg and diastolic blood pressure ≥95 mm Hg as specified in our inclusion criteria.

To manage blood pressure, the methyldopa dose was initiated at 750 mg per day (250 mg three times a day) and increased every 2-3 days, as necessary. There was a daily maximum dosage of 3000 mg. On the other hand, the dosage of labetalol was increased by 100 mg every 2-3 days until the desired response was achieved, starting with a daily dose of 300 mg (100 mg three times daily). The maximum daily dose administered was 800 mg.

Response status and categorization: The primary goal of the investigation was to lower blood pressure under 140/90 mm Hg and maintain it below the limit. The patients who showed this response were deemed, responders. Patients who developed imminent eclampsia symptoms while receiving therapy and patients with uncontrolled blood pressure even after receiving the highest recommended dose of the medication and requiring the addition of additional antihypertensive medications were marked as nonresponders. All PIH patients were hospitalized and kept under observation until their diastolic blood pressure dropped below 90 mm Hg, at which point they were followed up every week as outpatients. The side effects were documented along with a response to both medicines was monitored until the

patients gave birth. Labour was induced by medicinal or surgical means in patients who reacted to therapy but did not experience spontaneous labour by the time they reached term gestation. Delivery was accelerated in non-responders or when the risk to the mother or fetus was greater if pregnancy persisted.

Other variables: The birth weight of the infant, the gestational age at delivery, the mode of delivery (spontaneous or induced), the baby's Apgar score at 1 and 5 minutes, and the decision on the requirement for the baby to be admitted to a neonatal special care unit were recorded.

Results

The investigation was conducted on 250 patients that were randomly divided into Group-I (n=125) and Group II (n=125). The difference in the mode of labour was evaluated between Group-I and Group II. Spontaneous labour was observed in 42% of patients in Group-I in comparison to 48% of patients in Group II. The need for inducing labour via medical or surgical methods was observed in 46% of patients in Group-I and 38% of patients in Group II. 12% of patients in Group-I had elective lower segment Cesarian section (LSCS) before the onset of labour in Group-I whereas 14% of patients had elective LSCS before the onset of labour in Group II. Based on the analysis, there was no significant difference in the mode of labour between the study groups (p-value = 0.7).

The difference in the mode of delivery was evaluated between Group-I and Group II. In Group-I, there were 62% of the patients underwent a normal vaginal delivery, as opposed to 70% of patients in Group II. The instrumental delivery in the form of forceps or ventose was conducted in 6% of the patients in Group-I and 4% of the patients in Group II. Caesarean section was performed in 32% of the patients in Group-I and 26% of patients in Group II. There was no significant difference in the mode of delivery in the two groups (p=0.6). The main indications for cesarean section in both groups are shown in Table no. 1.

Table 1: Showing indications for caesarean section

Indication	**Group-I (n = 125)**		**Group-II (n = 125)**	
	Counts	**%**	**Counts**	**%**
Elective (CPD, malpresentation)	8	6.4	9	7.2
Impending eclampsia	12	9.6	11	8.8
Acute fetal distress	9	7.2	9	7.2
Failure of induction	5	4	6	4.8
IUGR	7	5.6	4	3.2
Prolonged leaking	3	2.4	-	-
Antepartum haemorrhage	-	-	1	0.8

The evaluation of the perinatal outcomes was performed to highlight the differences between Group-I and Group II (table 2). The parameters used for the evaluation of perinatal outcomes include perinatal mortality, mean birth weight, Apgar score and neonatal intensive care (NICU) admissions. Although, there was no statistically significant difference between the two groups in this study (p-value = 0.49). However, there were 06 perinatal mortalities (03 neonatal mortality and 03 stillbirths) in group I as opposed to none in group 2. The mean Apgar score at 1 minute was 8.71 (SD=1.46) in the methyldopa group in comparison to 8.82 (SD=1.93) in the labetalol group, while the mean Apgar score at 5 minutes was 9.68 (SD=1.32) in methyldopa group in comparison to 9.76 (SD=0.77) in labetalol group. The differences observed were not statistically significant (p-value = 0.5). Apgar score was observed to be better in group II and there were fewer NICU admissions and birth weights>3kg in more patients in group II but none of the differences was statistically significant as shown in Table 2.

Table 2: Showing the perinatal outcome in the study groups

Perinatal outcome	Group-I (n = 125)		Group-II (n = 125)		P- value
	Counts	%	Counts	%	
Live births	120	96	125	100	
Perinatal mortality	6	4.8	-	-	NS
a. Stillbirthrth	3	2.4	-	-	
b. Neonatal death	3	2.4	-	-	
Mean birth weight (in kg)	2.57(SD=0.42)		2.62(SD=0.33)		0.2
Birth wt>3kg.	60	48	65	52	NS
Apgar Score ≤8 at 1 min	38	30.4	25	20	NS
≤8 at 5 min	18	14.4	13	10.4	0.9
NICU Admissions	25	20	20	16	NS

Maternal complications during labour included placental abruption (2% in the methyldopa group), postpartum haemorrhage (6% in the methyldopa group and 2% in the labetalol group) and vulval hematoma over episiotomy site (2% in labetalol group). However, no maternal death was observed in the groups of our study.

DISCUSSION

The occurrence of hypertension in pregnancy may be attributed to the gravid state after 20 weeks of pregnancy. Reports suggest that various complications in pregnancy arise from hypertensive disorder mostly with the rise in mean arterial pressure above 140 mm of Hg. Although, fetus delivery is the definitive treatment, however, various drugs are available to maintain maternal blood pressure and reduce complications. The present guidelines from the National Institute for Health and Clinical Excellence, UK emphasise the administration of labetalol (oral or intravenous), intravenous hydralazine or oral nifedipine to the inpatient cases for severe hypertension during pregnancy as first-line alternative antihypertensive within the critical care setting[18].

In this study, perinatal mortality was not observed in patients administered with the labetalol group and only a few cases were observed to exhibit perinatal mortality in methyldopa groups. An earlier evaluation by Gupta et al[19] also reported no statistical difference in the perinatal mortality between patients undergoing treatment with labetalol and methyldopa. No perinatal loss was observed in another investigation by Mahmoud et al[20] on patients undergoing treatment with labetalol.

The drugs did not seem to have any effect on the mean birth weight in both group. This observation was by the investigation by Gupta et al[19] that reported no significant difference in the mean birth weight after administration of labetalol or methyldopa. Another investigation reported mean birth weight of babies in group A (labetalol) was 2013.33±778.367gm and in group B (Methyldopa) was 2311.11±779.92gm conducted by Kalsoom et al[21]. Kalsoom et al[21] reported that the frequency of SGA babies was higher in women treated with labetalol (37.8%) than in those treated with methyldopa (13.3%). These were contradictory findings to our study. In the case of the mean Apgar score, there was no significant difference observed between the two groups. In this study, few cases were reported that required admission to NICU, neonatal jaundice and meconium aspiration syndrome without any significant difference in the two study groups.

Overall, in this study no statistically significant difference was observed in mean birth weight, stillbirth rate, neonatal deaths, mean Apgar score at 1 and 5 min, the number of babies admitted to NICU and neonatal complications between the two groups. Our findings are in agreement with investigations conducted by Gupta et al[19], Lamming et al[22] and Qarmalawi et al[23] on perinatal outcomes with labetalol and methyldopa.

CONCLUSION

Labetalol is an effective antihypertensive drug in pregnancy-induced hypertension and it is safe for both the mother and the fetus. Perinatal outcomes were better with the administration of labetalol as compared to methyldopa, but the differences were not statistically significant.

REFERENCES

1. Long P, Oats J. Preeclampsia in twin pregnancy. Severity and pathogenesis Aust N Z J Obstet Gynaecol. 1987; 27:1.
2. Cunningham FG, Leveno KJ, Bloom SL, et al. Pregnancy hypertension. Text book of Williams Obstetrics. 23rd ed. New York: McGraw-Hill 2010; 706-57.
3. Walfisch A, Hallack M. Hypertension. In: James DK. High risk pregnancy. 3rd ed. Philadelphia: Elseiver 2006; 772-97.
4. Raheem IA, Saaid R, Omar SZ, et al. Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. Br J Obstet Gynecol. 2012;119(1):78-85.
5. Saxena S, Srivastava PC, Thimmarau KV, Mallick AK, Dalmia K, Das B. Socio-demographic Profile of Pregnancy Induced Hypertension in a Tertiary Care Centre. Sch. J. App. Med. Sci., 2014; 2(6D):3081-086
6. Muti M, Tshimanga M, Notion GT, Bangure D, Chonzi P. Prevalence of pregnancy induced hypertension and pregnancy outcomes among women seeking maternity services in Harare, Zimbabwe. BMC Cardiovasc Disord. 2015; 15: 111-15.
7. Davis RL, Eastman D, McPhillips H, Raebel MA, Andrade SE. Risks of congenital malformations and perinatal events among infants exposed to calcium channel and beta-blockers during pregnancy. Pharmacoepidemiology and drug safety. 201; 20(2):138-45.
8. Subhedar B, Inamdar S, Hariharan C, Subhedar S. Comparison of efficacy of labetalol and methyldopa in patients with pregnancy-induced hypertension. Int J Reprod Contracept Obstet Gynecol. 2013; 2(1):27-34
9. Townsend R, Brien PO, Khalil A. Current best practice in the management of hypertensive disorders in pregnancy Integr Blood Press Control. 2016; 9: 79–94.
10. Magee LA, von Dadelszen P, Singer J. Can adverse maternal and perinatal outcomes be predicted when blood pressure becomes elevated? Secondary analyses from the CHIPS (Control of Hypertension in Pregnancy Study) randomized controlled trial. Acta Obstet Gynecol Scand. 2016; 95:763–76.
11. Magee LA, Namouz-Haddad S, Cao V, Koren G, von Dadelszen P. Labetalol for hypertension in pregnancy. Expert Opin Drug Saf. 2015; 14(3):453-61.
12. Hypertension in Pregnancy. NICE clinical guidelines 107-RCOG.Published:1/08/2010.https://w.w.w.rcog.uk.
13. Molvi SN, Mir S, Rana VS, Jabeen F, Malik AR. Role of antihypertensive therapy in mild to moderate pregnancy-induced hypertension: a prospective randomized study comparing labetalol with alpha methyldopa. Archives of gynecology and obstetrics. 2012; 285(6):1553-62.
14. Easterling TR, Pharmacological Management of Hypertension in Pregnancy Semin Perinatol. 2014; 38(8): 487–95.

15. Togarikar SM. Efficacy of methyldopa versus nifedipine in mild and severe pregnancy induced hypertension. Int J Reprod Contracept Obstet Gynecol. 2017;6:4544-48.
16. Dharwadkar MN, Kanakamma MK, Dharwadkar SN, Rajagopal K, Gopakumar C, et al. Study of Methyl Dopa Versus Labetalol in Management of Preeclampsia and Gestational Hypertension. Gynecol Obstet. (Sunnyvale) 2014;4: 242.
17. Sushrut D, Girija. Labetalol - An Emerging First-line Drug for Pregnancy-induced Hypertension. Indian Journal of Clinical Practice. 2013; 23(10): 640-44
18. National Institute of Health and Clinical Excellence. Hypertension in pregnancy. The management of hypertensive disorders during pregnancy. Clinical guidelines CG107 Issued: August 2010. http://guidance.nice.org.uk/CG107.
19. Gupta M, Gupta U, Kumar S. Evaluation of labetalol in pregnancy induced hypertension. J Obstet Gynaecol India. 1995; 45 (3): 349-355.
20. Mahmoud TZK, Bjornsson S, Calder AA. Labetalol therapy in pregnancy induced hypertension: the effects on fetoplacental circulation and fetal outcome. Eur J Obstet Gynecol Rep Biology. 1993; 50:109-113.
21. Shabana Kalsoom S, Majeed N, Riaz M, Tariq S. Labetalol Versus Methyldopa: Comparison of Frequency of Small for Gestational Age in the Treatment of Pregnancy Induced Hypertension. Journal of Rawalpindi Medical College (JRMC). 2018; 22(4): 346-349.
22. Lamming GD, Broughton PF, Symonds E.M. Comparison of the alpha and beta blocking drug, labetalol and methyldopa in the treatment of moderate and severe preganancy induced hypertension. Clin Exp Hypertens. 1980; 2(5):865-895.
23. El-Qarmalawi AM, Morsy AH, Al-Fadly A, Obeid A, Hashem M. Labetalol versus methyldopa in the treatment of pregnancy induced hypertension. Int. J. Gynaecol Obstet. 1995; 49 (2):125-30.