

DOI: <http://dx.doi.org/10.18203/2320-1770.ijrcog20182465>

Original Research Article

Assessment of safety and efficacy of oral nifedipine and intravenous labetalol in management of increased blood pressure in severe preeclampsia

Sujana Thalamati, Sailaja Bandaru*, Divyasree Bhumireddy

Department of Obstetrics and Gynecology, Narayana Medical College, Nellore, Andhra Pradesh, India

Received: 29 May 2018

Accepted: 02 June 2018

***Correspondence:**

Dr. Sailaja Bandaru,

E-mail: sujatha2481@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Pre-eclampsia (PE) is a disorder of pregnancy characterized by the onset of high blood pressure and often a significant amount of protein in the urine. Pre-eclampsia is one of the leading causes of maternal and perinatal morbidity and mortality worldwide. The objective of the present study was to assess and compare the safety and efficacy of oral nifedipine and intravenous labetalol in the management of severe pre-eclampsia.

Methods: A double-blind, randomized, controlled trial was conducted at a tertiary care hospital in Andhra Pradesh, on pregnant women presenting with a systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more. The pregnant women were randomized to receive Oral nifedipine (10 mg tablet orally up to five doses) and intravenous labetalol injection in escalating doses until the target blood pressure of 150 mm Hg systolic and 100 mm Hg diastolic, or lower, was achieved. The primary endpoint of the study was the time taken by each agent to achieve target blood pressure. Secondary endpoints were number of doses required, adverse maternal and neonatal effects, side effect profile, and perinatal outcome.

Results: The study was conducted in a tertiary care hospital in Andhra Pradesh from July 2016 to October 2017, on 100 pregnant women presenting with preeclampsia. The median time taken to achieve target blood pressure was 44 minutes (range: 20-60 minutes) for Oral Nifedipine and 68 minutes (range: 40-85 minutes) for Intravenous labetalol ($P=0.008$). No serious adverse maternal or perinatal side effects were encountered in both the groups.

Conclusions: Both oral nifedipine and intravenous labetalol are effective in the management of acute hypertensive emergencies of pregnancy; however, oral nifedipine effectively decreased the blood pressure rapidly compared to intravenous labetalol.

Keywords: Blood pressure, Labetalol, Nifedipine, Preeclampsia

INTRODUCTION

Pre-eclampsia (PE) is a disorder of pregnancy characterized by the onset of high blood pressure and often a significant amount of protein in the urine. Pre-eclampsia is one of the leading causes of maternal and perinatal morbidity and mortality worldwide. Pre-eclampsia affects approximately 2-8% of all pregnancies worldwide.¹⁻³ The condition begins after 20 weeks of

pregnancy but more common after 32 weeks of Gestation.^{4,5} Nearly one-tenth of all maternal deaths in Africa and Asia and one-quarter in Latin America are associated with hypertensive diseases in pregnancy, a category that encompasses pre-eclampsia.⁶ Severe preeclampsia is characterized by systolic blood pressure ≥ 160 mmHg and diastolic blood pressure of ≥ 110 mmHg. In severe disease there may be red blood cell breakdown, a low blood platelet count, impaired liver function,

kidney dysfunction, swelling, shortness of breath due to fluid in the lungs, or visual disturbances. Severe preeclampsia requires prompt and effective treatment to prevent cerebrovascular and cardiovascular complications such as hypertensive encephalopathy, intracerebral haemorrhage and pulmonary oedema.⁷ It also presents an increased risk of complications for the foetus including prematurity, low birth weight, NICU admissions and eventually foetal death. While historically both high blood pressure and protein in the urine were required to make the diagnosis, some definitions also include those with hypertension and any associated organ dysfunction. Blood pressure is defined as high when it is greater than 140 mmHg systolic or 90 mmHg diastolic at two separate times, more than four hours apart in a woman after twenty weeks of pregnancy.

Antihypertensive treatment should be started in women with severe hypertension $\geq 160/110$ mmHg to reduce the blood pressure between 140-155 mmHg systolic and 90-100 mmHg diastolic. Care should be taken not to lower the blood pressure too rapidly so as to avoid reduced renal and placental perfusion and intrauterine hypoxia leading to sudden foetal death. The most commonly used antihypertensive drugs for control of severe hypertension in pre-eclampsia are nifedipine, labetalol and hydralazine.

Nifedipine has the advantage of being cost effective, rapid onset of action, long duration of action, oral bio-availability, easier to store and infrequent side effects. Intravenous labetalol is effective in controlling severe hypertension and can be given even when the patient is unconscious but is expensive. A recent meta-analysis demonstrated that IV hydralazine for the control of severe hypertension in pregnancy was associated with significant maternal hypotension, placental abruption, maternal oliguria and adverse effect on foetal heart rate.⁸ They conclude that they do not support the use of hydralazine as the first line treatment. A safe and efficient drug is the need of the hour amongst the two most commonly used drugs, i.e. oral nifedipine and IV labetalol. Hence the present study was undertaken to assess and compare the safety and efficacy of oral nifedipine and intravenous labetalol in the management of Severe Preeclampsia.

METHODS

This prospective randomized controlled trial was conducted in the Department of Obstetrics and Gynaecology, Narayana Medical College, Nellore, a tertiary care hospital in Andhra Pradesh, from July 2016 to December 2017. Institutional ethical committee clearance was obtained before starting this study. A written informed consent was taken from all the study participants.

Pregnant women at ≥ 20 weeks of gestation attending the OPD and Labour ward, with sustained severe hypertension ≥ 160 mmHg systolic and ≥ 110 mmHg

diastolic blood pressure. Pregnant women suffering from Chronic Hypertension, Cardiac disease, Bronchial Asthma were excluded from the study. Assignment of the participants was done alternately, to either Nifedipine group or Labetalol group. Regular Blood pressure measurements were done for every 3 minutes, after the administration of the drugs. Nifedipine 10mg oral dose and dose escalation of Labetalol in the regimen of 20 mg, 40mg, 80mg, 80mg and 80mg was done every 15 minutes. If Target blood pressure was not achieved, even after 5 administrations, a crossover of the regimen was planned.

The time required for blood pressure to reach the target value was noted. The number of doses required to achieve the target value was noted. Adverse effects like nausea, vomiting, dizziness, palpitations, chest pain, sweating and shortness of breath if any were noted.

The mode of delivery, maternal and perinatal morbidity and mortality were noted. The neonates if admitted in NICU were followed up till discharge.

RESULTS

Age distribution in the study group, has shown that the mean age of labetalol group was 23 ± 5 years and 24 ± 4 years in nifedipine group (Table 1).

Table 1: Age distribution of cases in the study.

Age group	Oral nifedipine (N=50)	IV labetalol(N=50)
18-20	13 (26%)	10 (20%)
21-25	23 (46%)	24 (48%)
26-30	10 (20%)	11 (22%)
31-40	4 (8%)	5 (10%)

Gravida distribution shows maximum patients of pre-eclampsia were primigravida in both the groups (62% in the labetalol and 52% in the nifedipine group (Table 2).

Table 2: Distribution by parity of cases in the study.

Gravida	Oral Nifedipine (N=50)	(IV) Labetalol (N=50)
Primi	29 (58%)	25 (50%)
G2	12 (24%)	15 (30%)
G3	5 (10%)	8 (16%)
G4	4 (8%)	2 (4%)

Most patients with preeclampsia were at 33-36 weeks gestational age (58% in labetalol and 62% in nifedipine group). Minimum gestational age at presentation was 27 weeks and 28 weeks. in labetalol and nifedipine group respectively (Table 3).

The systolic blood pressure on the day of admission was 160mmHg in 38% of labetalol group and 40% of nifedipine group, 200 mmHg in 2% of labetalol and

nifedipine groups each. The mean systolic blood pressure on the day of admission was 174 mmHg in labetalol group and 173 mmHg in nifedipine group (p value 0.87 not significant). The mean diastolic blood pressure on the day of admission was 114 mmHg in labetalol group and 115mmHg in nifedipine group (p value 0.72 not significant).

Table 3: Gestational age distribution.

Gestational age	Oral Nifedipine (N=50)	(IV) Labetalol (N=50)
26-28	1 (2%)	1 (2%)
29-32	12 (24%)	9 (18%)
33-36	27 (54%)	32 (64%)
37-39	10 (20%)	8 (16%)

The minimum time to achieve target B.P was 10 min. in both the groups. The mean time taken to achieve the target B.P 36.61±5.2 min in labetalol group and 34.77±4.8 min in nifedipine group (p value was 0.29 which was not significant statistically). The target B.P was achieved within 80 min in both groups (Table 4).

Table 4: Mean time taken to achieve target blood pressure.

Drug	Time (Minutes)
Oral Nifedipine	34.77±4.8
Iv labetalol	36.61±5.2

On an average the labetalol group needed three doses and the nifedipine group required two doses to control the B.P to target level. The p value of 0.43 indicates that there was no significant difference in the number of dose required to achieve the desired B.P. There was no indication for crossover treatment.

The various side effects of the drugs like dizziness, sweating, nausea, vomiting, palpitations, headache and shortness of breath showed no statistical significance among the two drugs. Maternal hypotension or foetal tachycardia was not seen in either of the study groups (Table 5).

Table 5: Distribution of adverse effects.

Adverse effect	Oral nifedipine (N=50)	Iv labetalol (N=50)	P-value
Hypotension	0	0	0
Dizziness	2 (4%)	3 (6%)	0.15
Flushing	1 (2%)	1 (2%)	0
Nausea/Vomiting	2 (4%)	4 (8%)	0.23
Palpitation	3 (6%)	5 (10%)	0.29
Headache	4 (8%)	6 (12%)	0.34
Breathlessness	2 (4%)	2 (4%)	NS
Foetal distress	0	0	0

Regarding mode of delivery in nifedipine group there were 22 caesarean sections and 28 vaginal deliveries. In labetalol group there were 24 caesarean sections and 26 vaginal deliveries. p value 0.25 did not reveal any statistical significance.

The average birth weight of babies in nifedipine group was 2.41 kg and for the labetalol group was 2.38 kg. p value was 0.72 which was not statistically significant.

The Apgar score of <7 at 5 minutes was seen in 10% of the labetalol group and 12% of the nifedipine group.

90% of the labetalol group and 88% of the nifedipine group showed APGAR score of ≥7 at 5 minutes. p value of 0.67 was not significant statistically.

The neonatal complications like prematurity, NICU admissions, respiratory distress hyperbilirubinemia was comparable among the two groups

There were 2 IUD's and 2 neonatal deaths among the labetalol group and 2 IUD's and 3 neonatal deaths in the nifedipine group. The p value was not statistically significant.

DISCUSSION

This randomized controlled study compares the efficacy of two antihypertensive drugs, oral nifedipine and I. V. Labetalol. 100 patients were included in the trial of which 50 were randomized to nifedipine and another 50 were randomized to labetalol group.

All the patients were aged between 18-40 years. Mean age in the labetalol group was 23±5 and 24±4 in the nifedipine group comparable to the study conducted by Dhali B et al.⁹ With regard to gravida distribution maximum patients of pre-eclampsia were primigravida in both the groups, 62% in the labetalol and 52% in nifedipine group comparable with the study of Shekar et al and Raheem et al.^{10,11}

In the present study most of the patients with preeclampsia were between 33-36 weeks of gestation, 58% in labetalol and 62% in nifedipine group. Mean gestational age in labetalol group is 35.4±2.12 weeks and in nifedipine group 35.3±2.3 weeks. In a study conducted by Sekhar et al mean gestational age was 36.1±3.2 weeks in labetalol group and 37.3±2.12 weeks in nifedipine group.¹⁰ In present study the mean systolic blood pressure in labetalol group was 174 mmHg and in nifedipine group it was 173 mmHg. 'P' value was 0.87 which is not significant. In the study conducted by Raheem et al the systolic blood pressure was 170 mmHg in labetalol group and 175 mmHg in nifedipine group. In the present study the mean diastolic blood pressure in labetalol group was 114 mmHg and in nifedipine group it was 115. p value was 0.7 which is not significant. In the study of Raheem

et al the mean diastolic blood pressure was 108 mmHg in labetalol group and 110 mmHg in nifedipine group.

In the present study the mean time taken to achieve target blood pressure in labetalol group is 36.61 ± 5.2 minutes and in nifedipine group it is 34.77 ± 4.8 minutes. p value was 0.29 which is not statistically significant. Many studies have shown that both labetalol and nifedipine can be used successfully in treating hypertensive crisis in pregnancy. In the study conducted by Raheem et al on the same drugs in pregnancy the median time taken by the labetalol group to achieve target blood pressure was 45 minutes and by the nifedipine group was 30 minutes which was comparably low when compared to present study.

The Trial conducted by Vermillion et al indicated that patients receiving oral nifedipine more rapidly achieved therapeutic blood pressure goal in 25.0 ± 13.6 minutes as compared with 43.6 ± 25.4 minutes in women receiving intravenous labetalol ($P=0.002$).¹² Vermillion drug regimen used higher oral nifedipine doses i.e. 10mg initially, then 20mg for further doses as required. Authors used 10 mg nifedipine throughout. Intravenous labetalol dose used was 20,40,80,80 and 80 mg in their study which is identical to the dose of labetalol used in present study.

In present study nifedipine group required 2 doses to reduce the blood pressure and labetalol group required 3 doses to achieve the same effect keeping with the findings of Raheem et al. In present study none of the individuals required crossover treatment. In the study conducted by Raheem et al 20% of labetalol group and 20% of nifedipine group required crossover treatment. Regarding the side effects of the two drugs there was no incidence of maternal hypotension or foetal tachycardia in both the groups. Other side effects were of minor degree and are comparable with other studies. In present study the mean birth weight was 2.28 ± 0.5 in labetalol group and 2.31 ± 0.24 in nifedipine group which is comparable with the study of Shekar et al where the mean birth weight in labetalol group was 2.2 ± 0.60 kg and 2.4 ± 0.50 kg in nifedipine group.¹⁰

Cochrane review of 2006 has concluded that there is no clear evidence that one antihypertensive is preferable to the other for improving outcome for women with very high blood pressure during pregnancy. Until better evidence is available the best choice of drug for an individual woman probably depends on the experience and familiarity with a particular drug and its maternal and foetal side effects.¹³

Present study indicates that both oral nifedipine and intravenous labetalol regimens are effective in controlling severe hypertension in pregnancy. There were no major side effects attributable to either drug regimens. Present study is in accordance with the guidelines and expert opinion that oral nifedipine and intravenous labetalol can

be used as first line antihypertensive drugs for control of severe hypertension in pregnancy.^{14,15}

CONCLUSION

In the present study, oral nifedipine was more effective compared to IV labetalol in the control of hypertension in severe preeclampsia. Both drugs demonstrated a similar adverse effects profile. Nifedipine is easier to store, easier to administer as it is given orally whereas IV labetalol is more expensive, needs to be stored at a lower temperature and needs slower administration. Thus, the present study concludes that both oral nifedipine is more effective compared to IV labetalol in acute control of blood pressure in severe preeclampsia and the treatment is also cost effective whereas Inj. labetalol can be reserved for unconscious or drowsy individuals.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Eiland E, Nzerue C, Faulkner M. Preeclampsia 2012. *J Preg.* 2012;1-7.
2. Hypertension in pregnancy. *Am Coll Obstet Gynecol.* 2013;2.
3. Al-Jameil N, Khan FA, Khan MF, Tabassum H. A brief overview of preeclampsia. *J Clin Med Res.* 2014;6(1):1.
4. American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. *Obstetrics and gynecology.* 2013;122(5):1122.
5. Berg CJ, Chang J, Callaghan WM, Whitehead SJ. Pregnancy-related mortality in the united states 1991-1998. *Obstet Gynecol.* 2003;101(2):289-96.
6. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011.
7. National Institute of Health and Clinical Excellence. Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. NICE clinical guidelines 107. 2010. Available from www.nice.org.uk/niemedia/live/13098/50418.
8. Magee LA, Cham C, Waterman EJ, Ohlsson A, Von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. *Br Med J.* 2003;327(7421):955.
9. Dhali B, Bhattacharya S, Ganguly RP, Bandyopadhyay S, Mondal M, Dutta M. A randomized trial of intravenous labetalol & oral nifedipine in severe pregnancy induced hypertension. *Int J Reprod Contracept Obstet Gynecol.* 2016;1(1):42-6.
10. Shekhar S, Sharma C, Thakur S, Verma S. Oral nifedipine or intravenous labetalol for hypertensive

- emergency in pregnancy: a randomized controlled trial. *Obstet Gynecol.* 2013;122(5):1057-63.
11. Raheem IA, Saaid R, Omar SZ, Tan PC. Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. *BJOG: An Int J Obstet Gynaecol.* 2012;119(1):78-85.
 12. Vermillion ST, Scardo JA, Newman RB, Chauhan SP. A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. *Am J Obstet Gynecol.* 1999;181(4):858-61.
 13. Duely L, Henderson-Smart DJ, Meher S. Drugs for treatment of very high blood pressure during pregnancy. *Cochrane Database Syst Rev* 2006;47:279-85.
 14. The Royal College of Obstetricians and Gynaecologists, United Kingdom. Green top guideline No 10(A). The management of severe preeclampsia/eclampsia.2006. Accessible online www.rcog.org.uk/files/GT10aManagementPreeclampsia2006.pdf
 15. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol.* 2003;102(1):181-92.

Cite this article as: Thalamati S, Bandaru S, Bhumireddy D. Assessment of safety and efficacy of oral nifedipine and intravenous labetalol in management of increased blood pressure in severe preeclampsia. *Int J Reprod Contracept Obstet Gynecol* 2018;7:2645-9.