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Original Article

COMPARISION OF EFFICACYAND SAFETY OF ORAL LABETALOL AND NIFEDIPINE IN PREECLAMPSIA: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Objective: To compare the efficacy and safety of oral Labetalol and Nifedipine in preeclampsia patients and to aid professionals in making appropriate therapeutic decisions in the management of preeclampsia.

Methods: A Prospective observational study with the total of 152 pregnant women with preeclampsia is conducted in a Tertiary Care Hospital in India. Pregnant women with preeclampsia prescribed with either oral labetalol or oral nifedipine were selected. Main outcome measures include monitoring of adverse effects of labetalol and nifedipine and efficacy of both drugs. Blood pressures were measured every 4 hrs using sphygmomanometer and average of three consecutive readings is recorded. The two groups were followed until delivery and are interviewed for any adverse reactions.

Results: The duration of days required for labetalol to normalize the high blood pressure is 5 days (5±2.63 d), and that of nifedipine is 7.5 days (7.5±3.83 d) with P value of 0.0015. Common adverse Drug reactions (ADR's) of the both drugs are pedal edema (50%, 47.36%), headache (44.7%, 26.31%), and orthostatic hypotension (9%, 7%) etc are compared.

Conclusion: Oral Labetalol is more efficacious than Oral Nifedipine, with an exception of more adverse effects and high cost.

Keywords: Preeclampsia, Safety, Efficacy, Labetalol, Nifedipine.

INTRODUCTION

Hypertensive disorders of pregnancy are an important cause of severe morbidity and mortality among both mother and fetus [1]. Pregnant women with hypertension have more chance to develop placental abruption, disseminated intravascular coagulation (DIC), cerebral hemorrhage, hepatic failure and acute renal failure [2].

Hypertensive disorders of pregnancy include Preeclampsia, Eclampsia, Chronic hypertension, gestational hypertension and preeclampsia superimposed on chronic hypertension [3, 4].

Among the pregnancy complicating hypertensive disorders, Pre-eclampsia and Eclampsia are the major causes of maternal and perinatal mortality and morbidity [1].

Preeclampsia is defined as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on 2 occasions at least 4 h apart after 20 w gestation in women with a previously normal blood pressure or ≥160 mmHg systolic or ≥110 mmHg diastolic, confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy and Proteinuria≥ 300 mg/24 h or a protein/creatinine ratio≥ 0.3 mg/d l or a dipstick reading of 1+reading [5].

Worldwide about 76,000 pregnant women die each year from preeclampsia and related hypertensive disorders. Fetal mortality rate is thought to be on the order of 5,00,000 per annum [6]. The prevalence of Preeclampsia in developing countries ranges from 1.8% to 16.7% [7].The Recent United Kingdom (UK) guidelines from the National Institute of Health and Clinical Excellence (NICE) recommend oral Labetalol as the first line choice in the treatment of hypertension in pregnancy [8].

Novelity of the study

Selection of antihypertensive agent is the major issue concerned with pre-eclampsia. National Institute of Health and Clinical Excellence Guidelines suggests that Labetalol, Nifedipine and Methyldopa are preferred choice of drugs. The use of anti-hypertensive drugs in pregnancy is controversial as most antihypertensive agents used in pregnancy are designated as Category 'C' stating that human studies are lacking. Clinicians vary in their choice of treatment for hypertension in pregnancy and there is uncertainty regarding potential benefits and harms of using antihypertensive drugs in pregnancy.

A meta-analysis study of Randomized controlled trials conducted for the assessment of efficacy, side effects and perinatal outcome of nifedipine compared with other antihypertensives for treating severe preeclampsia in pregnant women concluded that nifedipine is associated with greater effective control of blood pressure and prolongation of gestation, compared with other antihypertensive for women with severe preeclampsia [9].

A prospective study conducted in 2012 evaluated the effectiveness and safety of oral Labetalol and oral Nifedipine in pregnant women with Pregnancy induced hypertension (PIH) and concluded that labetalol is more effective than Nifedipine in controlling blood pressure whereas tachycardia (11 %) and occipital headache are more common with nifedipine [10]. Despite of various clinical trials conducted, there is seldom robustness in the treatment guidelines of preeclampsia. Therefore our study focuses on an assessment of safety and efficacy of oral labetalol and oral nifedipine in the control of hypertension in pregnancy.

MATERIALS AND METHODS

A Prospective Observational Study has been carried out on Comparison of Safety and Efficacy of oral Labetalol and oral Nifedipine in Pre-eclampsia patients in Obstetrics and Gynecology Department at Government General Hospital, Guntur for 6 months from 1st March 2014 to 31st August 2014.

The study is completely inpatient based; primary data was generated by studying patients admitted for the management of preeclampsia. Inclusion Criteria is pregnant women of age between

15-40 y with preeclampsia with elevated systolic blood pressure of ≥ 140 mmHg and diastolic blood pressure of ≥ 90 mmHg. Pregnant women with co-morbidities like Asthma/Obstructive Airway Disease and Heart Failure are excluded.

A total number of 152 patients who were prescribed with either Labetalol or Nifedipine were selected and included in the study. On admission detailed patient case history was collected which includes the details like age, obstetric and gynaecological history, past medical history, medication history, blood pressure, socioeconomic status. Blood Pressure is recorded using mercury sphygmomanometer. After diagnosing preeclampsia, written informed consent is taken and the trial group was treated with either Labetalol or Nifedipine.

Pregnant women receiving labetalol 100 mg twice daily are considered as group A and who are receiving Nifedipine 10 mg thrice a day (TID) are considered as group B. Dose was increased every 1-2 days if required, up to a maximum of Labetalol 2400 mg/d and Nifedipine 120 mg/d untill satisfactory Blood Pressure (BP) (≤120/80 mmHg) control was achieved. Average of three consecutive measurements is considered as Blood pressure (BP) reading and is monitored 4th hourly by sphygmomanometer. If blood pressure doesn't decrease even after increasing the dose to maximum, additional antihypertensive agent is added and the treatment is considered as failure.

Investigations Considered are complete hemogram, Liver function tests (LFT's), Renal function tests (RFT's), Serum uric acid, Fundoscopy, Ultrasound scan. Those patients with impending eclampsia were given Magnesium sulphate. Decision to continue with conservative management of pregnancy or to deliver and mode of delivery is made depending on maternal and fetal indications. Then patients were followed until delivery and the various modes of delivery were noted. The patients were interviewed for the drug adverse effects. Later consultation was made with the physician and the data were documented. Finally, the documented data was analyzed using Microsoft excel version and statistical methods (t test) to find p value to compare the two treatment groups.

RESULTS

A comparative study consisting of 152 pregnant women, 76 pregnant women with preeclampsia treated with Labetalol(Group A) and 76 pregnant women with preeclampsia treated with Nifedipine(Group B) is undertaken to study the safety & efficacy of the drugs. Both the two groups had comparable demographics and their characteristics are represented in table 1.

Table 1: Characteristics of pregnant women randomised to oral nifedipine or oral labetalol

Characteristic (range)	Labetalol	Nifedipine
Age Group (15-40 y)	24.23±3.64	23.6±4.28
Primi's	17	22
Gravidity (1-3)	2	2
Parity (0-3)	1	1
Systolic Blood Pressure (130-210)	162.36±20.72	146.05±9.16
Diastolic Blood Pressure (80-140)	105±12.46	95.26±6.87
Pulse rate (80-105)	87.94±4.39	86.39±2.74

Labetalol drug sample size-(n=76), Nifedipine sample size-(n=76), The Age wise distribution of pregnant women with Preeclampsia is as shown in fig. 1.

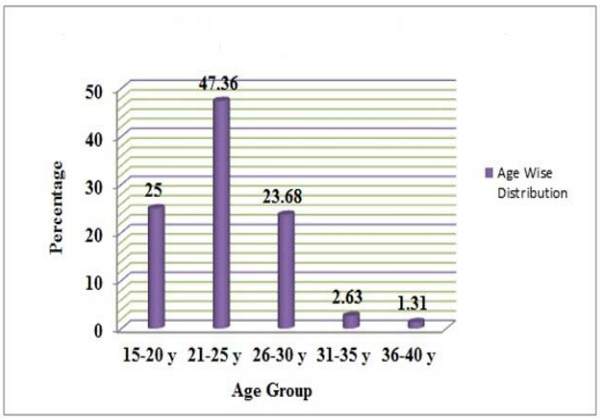

Fig. 1: Age wise distribution of pregnant women with preeclampsia. In our study, we observed that 21–25 years aged pregnant women are more prominent with Preeclamspia followed by age group 15-20 y and 26-30 y

Primi's is more prone to pre-eclampsia than females with second and third gravidity and is as shown in fig. 2.

On individual assessment of the adverse effects of Labetalol and Nifedipine, patients on labetalol has experienced side effects mostly Pedal edema (22%), Headache (20%), Sweating (10%), Orthostatic Hypotension (9%), Blurred vision (9%), Chills &Rigors (7%), Facial Edema (7%) etc and side effects observed mostly due to Nifedipine are Pedal edema (31%), Headache (17%), Sweating (10%), Orthostatic Hypotension (7%), Dizziness (7%), Cough (7%), Facial Edema (5%) etc.

On comparison of common adverse effects of the both drugs, Labetalol and Nifedipine, we found Pedal edema (50%, 47.36%), Headache (28.94%, 26.31%), Sweating (23.68%, 15.78%), Orthostatic Hypotension (21.05%, 10.52%), Blurred Vision (21.05%, 2.63%), Chills and Rigors (15.78%, 7.89%), Facial Edema (15.78%, 7.89%), Dizziness (10.52%, 10.52%), Nausea & Vomiting (10.52%, 0), Bronchospasm (7.89%, 2.63%), Fever (7.89%, 5.26%) respectively. We found Labetalol (Group A) has experienced more adverse effects than Nifedipine and is as shown in fig. 3 and in table 2.

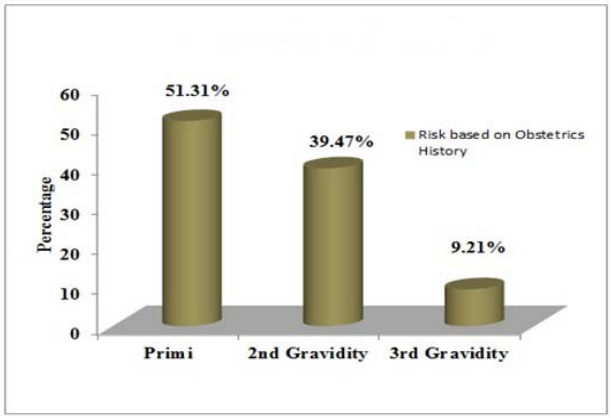

Fig. 2: Risk based on obstetrics history

Comparing the efficacy between labetalol and nifedipine is as shown in fig. 4, Duration of days required for Labetalol is 5 days (5±2.63 d), Nifedipine is 7.5 days (7.5±3.83 d) and Duration of Hours required

for Labetalol is 120 h (120±63.12) and 180 h for Nifedipine (180±91.92) with P value of 0.0015 and are as listed in table 3. There is significant difference between both the treatment groups.

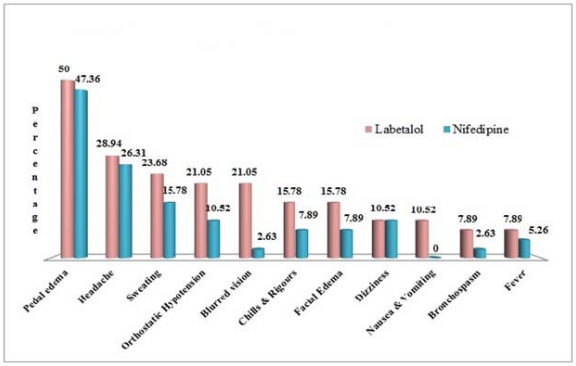

Fig. 3: Comparison of adverse effects of labetalol and nifedipine

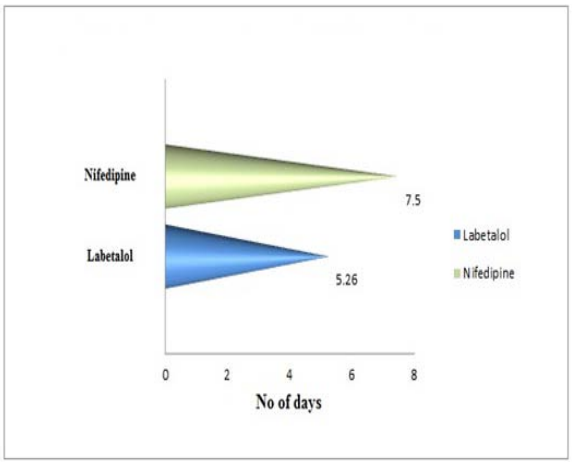

Fig. 4: Comparison of efficacy of labetalol and nifedipine

Table 2: Comparison of adverse effects of oral labetalol and nifedipine

Adverse effect	Labetalol (n=76)		Nifedipine (n=76)	
	No of Patients	Percentage	No of patients	Percentage
Pedal Edema	38	50	36	47.36
Headache	22	28.94	20	26.31
Sweating	18	23.68	12	15.78
Orthostatic Hypotension	16	21.05	8	10.52
Blurred Vision	16	21.05	2	2.63
Chills & Rigors	12	15.78	6	7.89
Facial Edema	12	15.78	6	7.89
Dizziness	8	10.52	8	10.52
Nausea & Vomiting	8	10.52	0	0
Bronchospasm	6	7.89	2	2.63
Fever	6	7.89	4	5.26
Cough	0	0	8	10.52
Anasarca	0	0	2	2.63
Periorbital Edema	0	0	2	2.63

*n-sample size

Table 3: Comparision of efficacy of labetalol and nifedipine

Drug name	Labetalol (n=76)	Nifedipine (n=76)
Duration in days	5	7.5
Duration in Hours	120	180
mean±SD (d)	5±2.63	7.5±3.83
mean±SD (h)	120±63.12	180±91.92
P value: 0.0015		

SD: Standard Deviation,*n-Sample Size.

DISCUSSION

The Cochrane review on drugs for the treatment of very high blood pressure in pregnancy concluded that until better evidence is available, the choice of antihypertensive should depend on the clinician's experience and familiarity with a particular drug [11].

The appropriate selection of antihypertensive in pre-eclampsia is contraversial in the literature. Most commonly preferred choice of antihypertensive is Labetalol, Methyldopa, and Nifedipine in pre-eclampsia [12].

As per the National Institute for Health and Clinical Excellence (NICE) guidelines for hypertension in pregnancy, the preferred choice of drug is oral Labetalol to oral nifedipine and Methyldopa [8].

Main findings

In our study, we included 152 pregnant women with Group A(n=76), Group B(n=76). Group A is treated Labetalol and Group B with Nifedipine. Treatment Strategies are Labetalol 100 mg twice daily, Maximum Dosage 2400 mg/d; Nifedipine 10 mg Thrice a day (TID), Maximum Dosage 120 mg/d. If there is seldom improvement to normal dosage, the dosage was increased in increments to both treatment groups. Pregnant women were monitored for Blood Pressure every 4 h and adverse effects frequently. Based on the statistics, we observed that Labetalol is more effective than Nifedipine in controlling blood pressure whereas the safety concern, nifedipine has less frequency of side effects than labetalol.

Strengths and Limitations

The strengths of our study are the generalizability of results is due to the diversity of the study population from various regions and unbiased since there is no loss of data as it is a prospective study and there exists a chronological relationship between drug exposure and outcome.

The limitations of our study are Study population is heterogenous which includes both proteinuric and non-proteinuric pregnant women with high blood pressure and Blood pressure considered is

the highest single reading recorded among all four hourly measurements for the entire day.

Interpretation

The results of our study are similar to that of a prospective, randomized, open labeled study, the use of oral labetalol with oral nifedipine in hypertensive urgencies in the emergency department of obstetrics conducted by McDonald AJ *et al.* The pretreatment Blood pressure for labetalol was 195/127 mmHg which decreased to 154/100 mmHg and of nifedipine was 198/128 mm Hg, alleviated to 163/100 mm Hg (P>.2). No significant side effects occurred with either drug. Labetalol is effective when compared to nifedipine in pregnancy induced hypertensive emergencies [13].

However, they diverge from a Meta-analysis Study conducted by Liu QQ *et al.,* the study includes the assessment of the efficacy, side effects and perinatal outcome of nifedipine compared with other antihypertensives.

Compared with other antihypertensives, nifedipine contributed greater efficacy in controlling blood pressure (OR = 2.65, 95%CI: 1.65-4.25, P<0.01) [9].

A recent prospective study conducted by Nita K. Patela *et al.* in 2012 to evaluate the comparative effectiveness and safety of nifedipine, methyldopa and labetalol monotherapy in patients with Pregnancy induced hypertension (PIH) concluded that Labetalol was more effective than methyldopa and nifedipine in controlling blood pressure in patients with Pregnancy induced hypertension (PIH) providing sustenance for our study [10].

There was no major adverse event attributed to either drug regimens. Our data supports recent guidelines and expert opinion that oral labetalol is the suitable first-line antihypertensive for hypertensive emergencies of pregnancy.

CONCLUSION

From our study, we observed that Oral Labetalol is more efficacious than Oral Nifedipine, with an exception of more adverse effects and high cost. Hence most of the Health care professionals preferring Nifedipine to Labetalol. However, due to inter individual variation, prevalence of side effects may vary and due to their less severity, it's better to opt labetalol for effective control of blood pressure in preeclampsia.

Practical and research recommendations

In order to have an appropriate therapeutic decision making, further studies should be performed in the future with large homogenous study population for better results.

ABBREVIATION

ADR's-Adverse drug reactions, DIC-Disseminated intravascular coagulation, NICE-National Institute of Health and Clinical Excellence, PIH-Pregnancy induced hypertension, LFT's-Liver function tests, RFT's-Renal function tests, JSS-Jan Shikshan Sansthan, SD-Standard Deviation.

Details of ethics approval

Ethics Committee, Guntur Medical College and Govt. General Hospital, Guntur–522004, AP, India

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CONFLICT OF INTERESTS

Declared None

REFERENCES

1. Introduction to Preeclampsia. WHO recommendations for Prevention and Treatment of Pre-eclampsia and eclampsia. WHO Handbook for guideline development. Geneva, World Health Organization; 2010.
2. Preeclampsia Introduction. Hypertensive disorders of pregnancy. Queensland Maternity and Neonatal Clinical Guideline; 2010. p. 7.
3. Pre-eclampsia. Alabama perinatal excellence collaborative guidelines. Protocol; 2014.
4. Classification of Hypertensive Disorders. ACOG 2013;2:13-5.
5. Preeclampsia: Hypertension in pregnancy report of the american college of obstetricians and gynecologists' task force on hypertension in pregnancy. ACOG 2013;122:1122-31.
6. The impact of preeclampsia. Preeclampsia and Maternal Mortality: A Global Burden; 2013.
7. Kayode O Osungbade, Olusimbo K Ige. Public Health Perspectives of Preeclampsia in Developing Countries: Implication for Health System Strengthening. J Pregnancy 2011. doi.org/10.1155/2011/481095. [Article in Perss]
8. Management of Preeclampsia. Hypertension in Pregnancy Pathway. National Instituite for Health and Clinical Excellence (NICE); 2014.
9. Liu QQ, Yu YH, Gong SP, Huang LP. Clinical efficacy and perinatal outcome of nifedipine for severe preeclampsia: meta-analysis. Zhonghua Fuchanke Zazhi 2012;47:592-7.
10. Nita K Patel, Mansi Gadhavi, Dhaval Gorasia, Manish R Pandya. Comparative evaluation of antihypertensive drugs in the management of pregnancy-induced hypertension. Int J Basic Clin Pharmacol 2012;1:174-7.
11. Duley L, Henderson-Smart DJ, Meher S. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev 2006;19:CD001449.
12. Prevention of Preeclampsia. Hypertension in pregnancy report of the american college of obstetricians and gynecologists' task force on hypertension in pregnancy. ACOG 2013;122:27-9.
13. McDonald AJ, Yealy DM, Jacobson S. Oral labetalol versus oral nifedipine in hypertensive urgencies in the ED. Am J Emerg Med 1993;11:460-3.