FETO-MATERNAL OUTCOME OF INTRAVENOUS LABETALOL AND ORAL NIFEDIPINE IN SEVERE PRE-ECLAMPSIA- A COMPARATIVE STUDY

Gynaecology

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ABSTRACT

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. When it arises, the condition begins after 20 weeks of pregnancy.

Aims And Objectives: 1. to determine the efficacy and safety of oral nifedipine for treatment of severe hypertension of pregnancy compared with intravenous labetalol.

2. To compare the time taken to reach the therapeutic goal blood pressure after using intravenous labetalol & oral nifedipine in severe pregnancy induced hypertension.

3. The time taken to achieve a blood pressure of less than 150/100 mmHg.

4. To compare the maternal and perinatal outcome among the subjects using nifedipine over labetalol.

Material And Method: PROSPECTIVE RANDOMISED INTERVENTIONAL COMPARITIVE TRAIL. One and half year.

Conclusion: Our present study compares the efficacy of oral Nifedipine and IV Labetalol in reaching the therapeutic goal. From the results of our study we can conclude that nifedipine required less time for reaching target BP as compare to labetalol. Less no of dose of nifedipine was used for the rapid control of blood pressure in severe hypertension in pregnancy. So, Nifedipine may be preferable as it is a simple, less time and is an oral regimen.

KEYWORDS

Intravenous Labetalol, Oral Nifedipine and Pre-eclampsia.

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.¹ When it arises, the condition begins after 20 weeks of pregnancy.^{2,3} 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.^{3,4} Pre-eclampsia increases the risk of poor outcomes for both the mother and the baby.³ If left untreated, it may result in seizures at which point it is known as eclampsia.²

Risk factors for pre-eclampsia include obesity, prior hypertension, older age, gestational diabetes, and diabetes mellitus.^{2,4} It is also more frequent in a woman's first pregnancy and if she is carrying twins.² The underlying mechanism involves abnormal formation of blood vessels in the placenta amongst other factors.² Most cases are diagnosed before delivery. Rarely, pre-eclampsia may begin in the period after delivery.³ 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.⁵⁻⁹

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.³ Pre-eclampsia is routinely screened for during prenatal care.^{10,11}

Recommendations For Prevention Include:

aspirin in those at high risk, calcium supplementation in areas with low intake, and treatment of prior hypertension with medications.¹² In those with pre-eclampsia delivery of the baby and placenta is an effective treatment.⁶ When delivery becomes recommended depends on how severe the pre-eclampsia and how far along in pregnancy a woman is.⁴ Blood pressure medication, such as labetalol and methyldopa, may be used to improve the mother's condition before delivery.⁶ Magnesium sulfate may be used to prevent eclampsia in those with severe disease.⁴ Bedrest and salt intake have not been found to be useful for either treatment or prevention.¹³

Pre-eclampsia affects 2–8% of pregnancies worldwide.⁴ Hypertensive disorders of pregnancy (which include pre-eclampsia) are one of the most common causes of death due to pregnancy.⁶ They resulted in 46,900 deaths in 2015.⁷ Pre-eclampsia usually occurs after 32 weeks; however, if it occurs earlier it is associated with worse outcomes.⁶ Women who have had pre-eclampsia are at increased risk of heart

disease and stroke later in life.¹⁰ The word eclampsia is from the Greek term for lightning.¹⁴ The first known description of the condition was by Hippocrates in the 5th century BC.¹⁴

Pre-eclampsia affects approximately 2–8% of all pregnancies worldwide.^{12,53} The incidence of pre-eclampsia has risen in the US since the 1990s, possibly as a result of increased prevalence of predisposing disorders, such as chronic hypertension, diabetes, and obesity.¹⁰

Pre-eclampsia is one of the leading causes of maternal and perinatal morbidity and mortality worldwide.¹ 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.⁴

Eclampsia is a major complication of pre-eclampsia. Eclampsia affects 0.56 per 1000 pregnant women in developed countries and almost 10–30 times as many women in low-income countries as in developed countries.⁶

1. To determine the efficacy and safety of oral nifedipine for treatment of severe hypertension of pregnancy compared with intravenous labetalol.
2. To compare the time taken to reach the therapeutic goal blood pressure after using intravenous labetalol & oral nifedipine in severe pregnancy induced hypertension.
3. The time taken to achieve a blood pressure of less than 150/100 mmHg.
4. To compare the maternal and perinatal outcome among the subjects using nifedipine over labetalol

MATERIAL AND METHODOLOGY

A) Study Design-

It is a hospital based Prospective Randomised Interventional Comparative Trail.

B) Study Setting And Timelines

The study is to be conducted in rural based tertiary care hospital and medical college with time frame of one and half year from acceptance of synopsis.

C) Place Of Study

The proposed study to be conducted under the department of Obstetrics & Gynaecology, National Medical College and Hospital,

Kolkata, West Bengal.

D) Period Of Study: One and half year.

F) Sample Size / Design:

All pregnant mother with PIH fulfilling the inclusion criteria will be selected for study over 1½ year period. The cases will be categorised randomly generated by computer into the two groups; Group A: those who will receive IV Labetalol in escalating dose, Group B: those who will receive oral nifedipine.

H) Inclusion / Exclusion Criteria

Inclusion Criteria

Inclusion criteria for the study were patients with systolic BP ≥ 160 mm of Hg and diastolic BP ≥ 110 mm of Hg, proteinuria >300 mg / 24 hrs urine or $+1$ or greater in random urine dipstick, and the gestational age >34 weeks upto 41 weeks.

Exclusion Criteria

But the patients of eclampsia, known heart disease, DM or other medical disorders, systolic BP <160 mm of Hg, diastolic BP <110 , absence of significant proteinuria (<300 mg / 24 hrs of urine) and gestational age <34 weeks and more than 41 weeks were excluded from study population.

RESULT & DISCUSSION

200 patients were selected using above defined criteria, The cases were categorised randomly into the two groups; **Group A:** those who received IV Labetalol in escalating dose, **Group B:** those who received oral nifedipine. Present study was conducted October 2016 to June 2018.

Dhali B et al¹⁵ found that all the patients were aged between 19-35 yrs. In the Labetalol group 48% of the patients were between 25-29 years & in the Nifedipine group 42% of all the patients were between 25-29 years. The minimum age in both the group was 25.4 years.

We found that in group-A (Labetalol), the mean of age (mean $\pm$ s.d.) of patients was 24.5400 ± 3.7374 yrs with range 19.0000 - 34.0000 yrs and the median was 24.0000 yrs. In group-B (Nifedipine), the mean of age (mean $\pm$ s.d.) of patients was 24.5000 ± 3.6556 yrs with range 19.0000 - 34.0000 yrs and the median was 24.0000 yrs. Association of age in two groups was not statistically significant ($p=0.9391$).

Dhali B et al¹⁵ found that gestational age at presentation in each group. Most patients with pre-eclampsia belonged to 38-40 weeks of gestational age, 80% in the Labetalol group & 84% in the Nifedipine group.

Present study found that in In group-A (Labetalol), the mean of gestational age (mean $\pm$ s.d.) of patients was 37.6600 ± 2.3835 wks with range 34.0000 - 41.0000 wks and the median was 37.0000 wks. In group-B (Nifedipine), the mean of gestational age (mean $\pm$ s.d.) of patients was 37.0700 ± 2.0998 wks with range 34.0000 - 41.0000 wks and the median was 36.0000 wks. Association of gestational age in two groups was not statistically significant ($p=0.0647$).

Dhali B et al¹⁵ found that shows the gravida distribution of patients studied in each group with a range of primigravida to 4th gravid. Maximum patients of severe pre-eclampsia were primigravida in both the groups, 58% in the Labetalol group & 50% in the Nifedipine group. In group-A (Labetalol), 35(35.0%) patients had P0+0 parity, 57(57.0%) patients had P1+0 parity, 4(4.0%) patients had P1+1 parity and 4(4.0%) patients had P2+0 parity. In group-B (Nifedipine), 59(59.0%) patients had P0+0 parity, 35(35.0%) patients had P1+0 parity, 1(1.0%) patients had P1+1 parity, 4(4.0%) patients had P2+0 parity and 1(1.0%) patients had P3+0 parity. Association of parity in two groups was statistically significant ($p=0.0067$).

In group-A (Labetalol), 35(35.0%) patients had primi gravid, 57(57.0%) patients had second gravid and 8(8.0%) patients had third gravid. In group-B (Nifedipine), 59(59.0%) patients had primi gravid, 35(35.0%) patients had second gravid, 5(5.0%) patient had third gravid and 1(1.0%) patients had fourth gravid. Association of gravida in two groups was statistically significant ($p=0.0045$).

Dhali B et al¹⁵ found that spontaneous vaginal delivery was more in the Labetalol group i.e 28% when compared to the Nifedipine i.e 14%. A

significant higher incidence of induction of labour was found in the Nifedipine group i.e. 32%. Caesareans section rate was 46% and 54% in the Labetalol and Nifedipine group respectively.

We found that in group-A (Labetalol), 45(45.0%) patients had LSCS mode of delivery and 55(55.0%) patients had VD mode of delivery. In group-B (Nifedipine), 33(33.0%) patients had LSCS mode of delivery and 67(67.0%) patients had VD mode of delivery. Association of mode of delivery in two groups was not statistically significant ($p=0.0819$).

We found that in group-A (Labetalol), the mean of BMI (mean $\pm$ s.d.) of patients was 21.5290 ± 1.8869 with range 18.0000 - 25.3000 and the median was 22.0000. In group-B (Nifedipine), the mean of BMI (mean $\pm$ s.d.) of patients was 21.6590 ± 1.9131 with range 18.0000 - 25.3000 and the median was 22.0000. Association of BMI in two groups was not statistically significant ($p=0.6291$).

Dhali B et al¹⁵ found that comparison of systolic & diastolic BP of the two groups. Mean SBP was 186.2 ± 12 mm of Hg in the Labetalol group & 175 ± 12 mm of Hg in the Nifedipine group, which was statically not significant as 'P' value was 0.669.

Our study found that in group-A (Labetalol), the mean of SBP (initial) (mean $\pm$ s.d.) of patients was 180.3600 ± 9.7333 with range 166.0000 - 200.0000 and the median was 180.0000. In group-B (Nifedipine), the mean of SBP (initial) (mean $\pm$ s.d.) of patients was 180.3000 ± 9.5193 with range 166.0000 - 200.0000 and the median was 180.0000. Association of SBP (initial) in two groups was not statistically significant ($p=0.9649$).

Dhali B et al¹⁵ found that mean diastolic BP was 118.11 ± 8 mm of Hg in the Labetalol group and 112 ± 8 mm of Hg in the Nifedipine group which was also statistically insignificant and 'P' value was 0.745.

Raheem et.al¹⁶ the mean systolic BP was 175 (170-180) mm of Hg in Nifedipine group and 170 (165-180) mm of Hg in Labetalol group with 'P' value 0.25.

Patients received oral nifedipine achieved the goal therapeutic blood pressure more rapidly in 28.2 ± 11.7 minutes (mean $\pm$ SD) as compared with 48.4 ± 23.5 minutes in those received intravenous labetalol ($p=0.001$). The nifedipine group also required significantly fewer doses (3.5 ± 0.5 vs. 4.5 ± 1.5 ; $p=0.001$) to reach the goal blood pressure. Both drugs were ultimately effective in reaching the therapeutic goal because there were no failures requiring crossover in either study group.

We found that that in group-A (Labetalol), the mean of DBP (initial) (mean $\pm$ s.d.) of patients was 126.8800 ± 6.4843 with range 114.0000 - 140.0000 and the median was 128.0000. In group-B (Nifedipine), the mean of DBP (initial) (mean $\pm$ s.d.) of patients was 127.1200 ± 6.4843 with range 114.0000 - 140.0000 and the median was 128.0000. Association of DBP (initial) in two groups was not statistically significant ($p=0.7938$).

In group-A (Labetalol), the mean of SBP (target) (mean $\pm$ s.d.) of patients was 134.2000 ± 8.4734 with range 120.0000 - 148.0000 and the median was 134.0000. In group-B (Nifedipine), the mean of SBP (target) (mean $\pm$ s.d.) of patients was 134.5000 ± 8.7865 with range 120.0000 - 148.0000 and the median was 134.0000. Association of SBP(target) in two groups was not statistically significant ($p=0.8061$).

In group-A (Labetalol), the mean of DBP (target) (mean $\pm$ s.d.) of patients was 94.3000 ± 8.0120 with range 80.0000 - 108.0000 and the median was 94.0000. In group-B (Nifedipine), the mean of DBP (target) (mean $\pm$ s.d.) of patients was 93.0800 ± 8.0374 with range 80.0000 - 104.0000 and the median was 94.0000. Association of DBP (target) in two groups was not statistically significant ($p=0.2837$).

The results of the study conducted by Shekhar et.al⁵⁹ showed that the median time taken to achieve target blood pressure was 40 mins (interquartile range 20-60 mins) for Nifedipine and 60 mins (interquartile range 40-85 min) for Labetalol with a P value of 0.008.

Shekhar et.al¹⁷ concluded by their trial that oral Nifedipine had lowered blood pressure more quickly than that of intravenous Labetalol during hypertensive emergency in pregnancy.

In group-A (Labetalol), the mean of number of dose (mean $\pm$ s.d.) of

patients was 2.2100 ± 1.1397 with range 1.0000 - 5.0000 and the median was 2.0000. In group-B (Nifedipine), the mean of number of dose (mean $\pm$ s.d.) of patients was $1.3100 \pm .4861$ with range 1.0000 - 3.0000 and the median was 1.0000. Association of number of dose in two groups was statistically significant ($p < 0.0001$).

In group-A (Labetalol), the mean of time (mean $\pm$ s.d.) of patients was 44.2000 ± 22.7938 with range 20.0000 - 100.0000 and the median was 40.0000. In group-B (Nifedipine), the mean of time (mean $\pm$ s.d.) of patients was 26.2000 ± 9.7214 with range 20.0000 - 60.0000 and the median was 20.0000. Association of time in two groups was statistically significant ($p < 0.0001$).

Dhali B et al¹⁵ found that Mean birth weight was 2.48 ± 0.54 kg in the Labetalol group and 2.43 ± 0.59 kg in the Nifedipine group, which was statistically not significant ($P = 0.0689$).

We found that in group-A (Labetalol), the mean of birth weight (mean $\pm$ s.d.) of patients was $2.6810 \pm .2596$ with range 2.1000 - 3.4000 and the median was 2.7000. In group-B (Nifedipine), the mean of birth weight (mean $\pm$ s.d.) of patients was $2.6630 \pm .2058$ with range 2.1000 - 3.2000 and the median was 2.7000. Association of birth weight in two groups was not statistically significant ($p = 0.5875$).

In group-A (Labetalol), 2(2.0%) patients had death perinatal outcome, 2(2.0%) patients had hyper bilirubinaemia, 3(3.0%) patients had IUGR perinatal outcome and 93(93.0%) patients had uneventful perinatal outcome. In group-B (Nifedipine), 1(1.0%) IUGR perinatal outcome and 99(99.0%) patients had uneventful perinatal outcome. Association of perinatal outcome in two groups was not statistically significant.

Table: Distribution of Mean Age, GESTATIONAL AGE (WKS), BMI, SBP (INITIAL), DBP (INITIAL), SBP (TARGET), DBP (TARGET) and Apgar score 5 mins in Two Groups

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Age	Group-A (Labetalol)	100	24.5400	3.7374	19.0000	34.0000	24.0000	0.9391
	Group-B (Nifedipine)	100	24.5000	3.6556	19.0000	34.0000	24.0000	
GESTATIONAL AGE (WKS)	Group-A (Labetalol)	100	37.6600	2.3835	34.0000	41.0000	37.0000	0.0647
	Group-B (Nifedipine)	100	37.0700	2.0998	34.0000	41.0000	36.0000	
BMI	Group-A (Labetalol)	100	21.5290	1.8869	18.0000	25.3000	22.0000	0.6291
	Group-B (Nifedipine)	100	21.6590	1.9131	18.0000	25.3000	22.0000	
SBP (INITIAL)	Group-A (Labetalol)	100	180.3600	9.7333	166.0000	200.0000	180.0000	0.9649
	Group-B (Nifedipine)	100	180.3000	9.5193	166.0000	200.0000	180.0000	
DBP (INITIAL)	Group-A (Labetalol)	100	126.8800	6.4843	114.0000	140.0000	128.0000	0.7938
	Group-B (Nifedipine)	100	127.1200	6.4843	114.0000	140.0000	128.0000	
SBP (TARGET)	Group-A (Labetalol)	100	134.2000	8.4734	120.0000	148.0000	134.0000	0.8061
	Group-B (Nifedipine)	100	134.5000	8.7865	120.0000	148.0000	134.0000	
DBP (TARGET)	Group-A (Labetalol)	100	94.3000	8.0120	80.0000	108.0000	94.0000	0.2837
	Group-B (Nifedipine)	100	93.0800	8.0374	80.0000	104.0000	94.0000	
Apgar score 5 mins	Group-A (Labetalol)	100	7.1700	1.2953	4.0000	9.0000	7.0000	0.0283
	Group-B (Nifedipine)	100	7.5300	.9894	4.0000	9.0000	8.0000

Figure: Distribution of Perinatal Outcome in Two Groups

CONCLUSION

A hypertensive disorder of pregnancy is one of the life threatening complication encountered in obstetrics. Management of hypertension in pregnancy is a challenging task, because drastic reduction of BP leads to uteroplacental insufficiency & that may lead to intrauterine fetal death and continuation of pregnancy with severe hypertension leads to adverse fetomaternal outcome. Therefore, there is a need for an ideal antihypertensive agent for effective control of severe hypertension in pregnancy.

significant ($p = 0.1586$).

Present study found that in group-A (Labetalol), 9(9.0%) patients had birth asphyxia. In group-B (Nifedipine), No patient had birth asphyxia. Association of birth asphyxia in two groups was statistically significant ($p = 0.0021$).

We found that in group-A (Labetalol), 9(9.0%) patients had admission to SNCU. In group-B (Nifedipine), 1(1.0%) patients had admission to SNCU. Association of admission to SNCU in two groups was statistically significant ($p = 0.0094$).

Dhali B et al¹⁵ found that on measuring and comparing the 5 mins APGAR score most of the babies having 5 mins APGAR score greater than 7 i.e. 90% in the Labetalol group & 92% in the Nifedipine. The comparison was statistically similar within 'P' value of 0.847. Hyperbilirubinaemia were 6% to 8% in the Labetalol group and Nifedipine group respectively. IUGR neonates were 20% and 30% in the Labetalol and Nifedipine group respectively. There was 1 perinatal death in each group. The comparison was statistically insignificant with P value of 0.957.

In group-A (Labetalol), the mean of Apgar score 5 (mean $\pm$ s.d.) of patients was 7.1700 ± 1.2953 min with range 4.0000 - 9.0000 min and the median was 7.0000 min. In group-B (Nifedipine), the mean of Apgar score 5 (mean $\pm$ s.d.) of patients was $7.5300 \pm .9894$ min with range 4.0000 - 9.0000 min and the median was 8.0000 min. Association of Apgar score 5 in two groups was statistically significant ($p = 0.0283$).

The fetal outcome like birth asphyxia and NICU admission was significantly higher in labetalol. APGAR score was significantly higher in nifedipine.

Although nifedipine has better efficacy a better anti-hypertensive agent is needed that overcomes all the shortcomings of others. probably this is the gist of conclusion.

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