

# Comparing Efficacy and Safety of Labetalol Over Methyldopa in Preeclampsia and Gestational Hypertension

Ratnam Andallu<sup>1</sup>, Yerraguntla Madhavi<sup>2</sup>

## ABSTRACT

**Background:** Pre eclampsia is still ill understood and complications of hypertension are the leading cause which contributes greatly to maternal morbidity and mortality.

**Material and methods:** Study is conducted for a period of 1 year, total 200 patients diagnosed as preeclampsia or Gestational Hypertension with Blood pressure levels  $\geq 140/90$  mm hg is included in the study. 100 patients are treated by oral Labetalol and 100 patients are treated by oral methyldopa with or without nifedipine.

**Results:** In patients with labetalol group 47% and in methyldopa group 54% women belonged to 21-25 yrs of age belong to low socio economic status in which early marriages are common, there is reduced the blood pressure significantly (P value  $<0.01$ ) at 1 hr and 2 hrs, very significantly (p value  $<0.01$ ) at 6 hrs and 12 hrs where as no significant reduction in blood pressure at 1 hr and 2 hrs with methyldopa. Present study patients with labetalol group 74% had term deliveries where as in methyldopa group 60% had term deliveries. 2 patients had imminent eclampsia in labetalol group whereas 8 patients had imminent eclampsia in methyldopa group. 1 of the patient developed HELLP in methyldopa group whereas none of the patients developed HELLP in labetalol group, 7% had IUGR fetuses in labetalol group where as 10% had IUGR fetuses in methyldopa group, Present study need of NICU admission in the labetalol group was 5% compared to 8% in methyldopa group.

**Conclusion:** Labetalol has good perinatal outcome compared to methyldopa group. The results revealed that labetalol is safer, quicker in action and more efficient in controlling and sustained effect on blood pressure.

**Keywords:** Pre eclampsia, Labetalol, Methyldopa, Nifedipine.

## INTRODUCTION

Hypertensive disorders complicating pregnancy are common and form one of the deadly triad, along with hemorrhage and infection, which contributes greatly to maternal morbidity and mortality. This disorder affects approximately 5 to 10% of pregnancies and is significant in causing of maternal and fetal morbidity and mortality.<sup>1</sup> Although preeclampsia is not preventable, maternal deaths from the disorder can be prevented. According to national centre for health statistics, gestational hypertension was identified in 3.7% of pregnancies<sup>1</sup> reported that almost 16% of pregnancy related deaths were due to complications of pregnancy related hypertension.<sup>2</sup> Half the maternal deaths resulting from complications of pregnancy related hypertension were preventable.

Etiology of pre eclampsia is still ill understood and hence management is necessarily symptomatic complications of hypertension are the third leading cause of pregnancy related deaths, superseded only by hemorrhage and embolism.

Preeclampsia is associated with increased risks of placental abruption, acute renal failure, cerebrovascular and cardiovascular complications, disseminated intravascular coagulation and maternal death. Consequently, early diagnosis of preeclampsia and close observation are needed.

The only definitive “cure” of preeclampsia is “delivery”,<sup>3</sup> either vaginal or caesarean (C – section). Inducing labour is the treatment of choice for women who have reached a gestational age of atleast 37 weeks. In all cases the consensus is that all women with preeclampsia should be delivered by 40 weeks, and the use of induction drugs and cervical ripening agents is common. For women who have not reached 37 weeks, treatment focuses on allowing the baby to mature as much as possible before inducing labour. The goal of preeclampsia treatment is to avoid progression of disease and complications.

There is no single reliable, cost effective screening test for preeclampsia and there are no well established measures for primary prevention. The basic management objectives for any pregnancy complicated by preeclampsia are Termination of pregnancy with least possible trauma to mother and fetus, Birth of an infant who subsequently thrives and Complete restoration of health to the mother.

Fetal and maternal morbidity is not increased for those with mild hypertension (DBP  $< 100$  mm Hg) irrespective of the use of antihypertensive medication.<sup>4</sup> Delaying the treatment of hypertension in pregnancy till diastolic blood pressure of 100 mmhg is not associated with additional maternal or fetal risk. Therefore mild hypertension do not require anti hypertensive therapy, if they are closely observed during pregnancy and delivery, especially if there has been no hypertension before pregnancy and no proteinuria develops (Hjertberg et al).<sup>5</sup> The treatment goal is to lower systolic pressure to 140 to 150 mmhg and diastolic pressure to 90 to 100 mmhg. To avoid hypotension, blood pressure should be lowered gradually.

All the drugs used to treat hypertension in pregnancy cross the placenta may effect the fetus directly by means of their action within the fetal circulation, or indirectly by their effect on uteroplacental perfusion. Use of antihypertensive

<sup>1</sup>Associate Professor, <sup>2</sup>Professor, Department of Gynaecology and Obstetrics, Government Maternity Hospital and Osmania Medical College, Hyderabad, Telangana, India

**Corresponding author:** Dr. Madhavi, Associate Professor, Department of Gynaecology and Obstetrics, Osmania Medical College, Hyderabad, Telangana.

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agents should aim at avoiding vascular damage due to Blood pressure elevation without marked fall in blood pressure that would critically affect uteroplacental insufficiency<sup>6</sup>

An ideal anti hypertensive is one that has

1. Predictable reduction in blood pressure, in supine as well as in erect position.
2. Rapid action with sufficient duration
3. Free from toxic effects, not reducing circulation to vital organs.
4. No tolerance on long term use
5. Synergistic with other anti-hypertensive agents.

Nifedipine and labetalol are now the first line alternatives to hydralazine in the management of severe preeclampsia. ACOG currently recommends labetalol as one of the first line antihypertensive medications in preeclampsia.<sup>7</sup>

Present study is done to compare the efficacy and safety of oral Labetalol over oral methyldopa with or without Nifedipine in Preeclampsia and gestational Hypertension and maternal and fetal outcome in preeclampsia is noted.

**MATERIAL AND METHODS**

This study is conducted in Gandhi Hospital from 2010 may to 2012 may. A total number of 200 patients diagnosed as preeclampsia or Gestational Hypertension with Blood pressure levels  $\geq 140/90$  mm hg is included in the study. 100 patients are treated by oral Labetalol and 100 patients are treated by oral methyldopa with or without nifedipine. In both groups patients are selected according to the following criteria.

**Inclusion criteria**

1. Preeclampsia with blood pressure  $\geq 140/90$  mmhg and

Number of patients with	Labetelol	Methyldopa
Gestational Hypertension	32	40
Mild Pre-Eclampsia	38	36
Severe Pre-Eclampsia	30	24
Age Group		
$\leq 20$ Yrs	21	21
21-25 Yrs	47	55
26-30 Yrs	29	21
$\geq 31$ Yrs	3	3
Parity Distribution		
Primi	54	59
Multi	46	41
Gestational Age(Weeks)		
28-32weeks	12	13
33-36 Weeks	19	27
37-40 Weeks	69	60

**Table-1:** Distribution of Hypertensive disorders of pregnancy in patients studied.

Mean reduction in:	Labetalol	DBP	Methyl DOPA	DBP
	SBP		SBP	
1 <sup>st</sup> hour	Significant	Significant	Not Significant	Not Significant
2 <sup>nd</sup> hour	Significant	Significant	Not Significant	Not Significant
6 <sup>th</sup> hour	Significant	Significant	Significant	Significant
12 <sup>th</sup> hour	Significant	significant	Significant	Significant

P value is significant when it is less than 0.01

**Table-2:** P value of mean reduction in Systolic and diastolic blood pressures

- urine albumin  $\geq 1+$  dips tick.
2. Gestational Hypertension with Blood pressure  $\geq 140/90$  mmhg.
3. Primi and multigravida
4. Gestational age  $\geq 28$  weeks

**Exclusion criteria**

1. Patients having asthma, h/o Congestive heart failure, diabetics, heart block, severe liver disease and peripheral vascular disease.
2. Patients with h/o eclampsia
3. Patients with chronic Hypertension due to secondary causes.

**RESULTS**

In study group with labetalol 32 patients had gestational hypertension,38 patients had mild preeclampsia and 40 patients with severe preeclampsia. In study group with methyldopa 40 patients had gestational hypertension,36 patients had mild preeclampsia and 24 patients with severe preeclampsia.

Majority of the women included in this study belonged to the age group of 21-25years. Majority of the women in both groups are primigravidae

Most of the women delivered at term in both groups. Out of 100 patients in labetalol group in 89 patients blood pressure was controlled with 200mg per day, 10 patients required 400mg per day and one patient required 600mg per day. In patients with methyldopa group 78 patients required 750mg per day and 22 patients required 1500mg per day.

Reduction in mean systolic blood pressure after 1<sup>st</sup> hour was 5.6 and 1, after 2<sup>nd</sup> hour was 14.7 and 0.9, after 6<sup>th</sup> hour was 21.1 and 12, after 12<sup>th</sup> hour was 22.3 and 13.6 in Labetalol and Methyl dopa group respectively.

Reduction in mean diastolic blood pressure after 1<sup>st</sup> hour was 8.1 and 0.3, after 2<sup>nd</sup> hour was 14.8 and 0.8, after 6<sup>th</sup> hour was 20.2 and 13, after 12<sup>th</sup> hour was 20.4 and 16.7 in Labetalol and Methyldopa group respectively.

P value was found to be significant all the time in Labetalol group whereas it was not significant in 1<sup>st</sup> and 2<sup>nd</sup> hour in Methyldopa group. P value was found to be very significant in Labetalol group after 6<sup>th</sup> and 12<sup>th</sup> hour whereas it was found to be significant after 6<sup>th</sup> and 12<sup>th</sup> hour in Methyldopa group.

No. of vaginal deliveries were 57 in Labetalol group whereas 41 in Methyldopa group. No. of LSCS were 43 in Labetalol group whereas 58 in Methyldopa group.

In patients with labetalol 2 had imminent eclampsia and in methyldopa group 8 had imminent eclampsia. In patients with methyldopa 4 had abruption where as patients with labetalol 3 had abruption. In patients with methyldopa 1 patient developed HELLP syndrome. In labetalol group no 0ne

	Labetalol No. of Patients	Methyl Dopa No. of Patients
<b>Mode of delivery</b>		
Vaginal Spontaneous delivery	32	20
Vaginal Induced delivery	25	21
LSCS Elective	13	20
LSCS Emergency	30	38
<b>Maternal Complications</b>		
Imminent Eclampsia	2	8
Abruption	3	4
Eclampsia	0	0
HELLP	0	1
DIC	0	0
ARF/Oliguria	0	0
Pulmonary Oedema	0	0
Others	0	0

**Table-3:** Mode of delivery and Maternal Complications

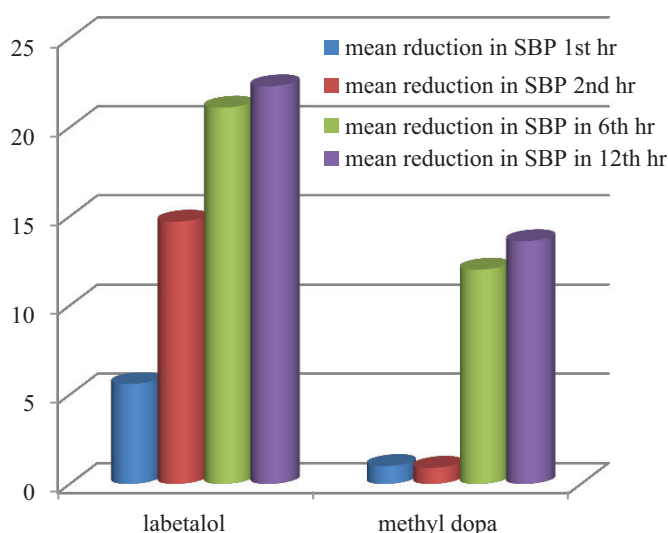
Delivery	Labetalol		Methyl Dopa	
	No. Of Patients	%	No. Of Patients	%
Preterm	39	39	33	33
Term	61	61	67	67
<b>Fetal Outcome</b>				
Live Babies				
Without NICU	89	89	85	85
With NICU	5	5	8	8
IUDs	3	3	4	4
IUGR	7	7	10	10
Still Born	2	2	2	2
Neonatal Death	1	1	1	1

**Table-4:** Fetal Outcome

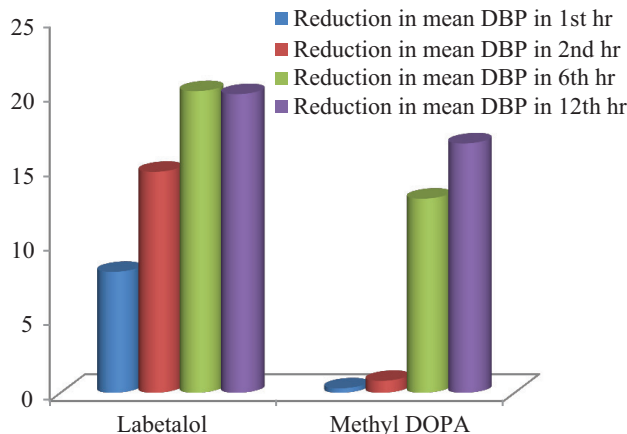
developed HELLP syndrome. No of preterm deliveries in Labetalol group were 39. No of preterm deliveries in Methyldopa group were 33. No of term deliveries in Labetalol group were 61. No of term deliveries in Methyl Dopa group were 67. No of preterm deliveries in Labetalol group were 39. No of preterm deliveries in Methyldopa group were 33. No of term deliveries in Labetalol group were 61. No of term deliveries in Methyl Dopa group were 67. No of live babies in Labetalol group were 94 and in Methyl dopa group 93, but no. babies requiring NICU admission in labetalol group were 5 as compared to 8 in Methyldopa group. 7 babies were born with IUGR in labetalol group as compared to 10 babies being born with IUGR in Methyldopa group. No. of Still births and neonatal deaths were same in both the groups.

**DISCUSSION**

Study is done on 200 patients with pre-eclampsia and gestational hypertension. In both the study groups majority of the women were primigravidae, as pre-eclampsia is more common in them. In patients with labetalol group 47% and in methyldopa group



**Figure-1:** Reduction in mean systolic blood pressure



**Figure-2:** Reduction in mean diastolic blood pressure

54% women belonged to 21-25 yrs of age as the patients seeking care in government hospitals belong to low socio economic status in which early marriages are common, therefore early conceptions. Need of additional anti-hypertensives in patients treated with labetalol is 6% compared to 21% with methyldopa group in study. In the cochrane database 2007, Abulos et al<sup>8</sup> studied the effect of antihypertensive drug treatment for mild to moderate hypertensive during pregnancy and concluded, Beta blocker seem better than methyldopa for reducing the risk of sever hypertension and need for additional anti-hypertension's. The present study correlates with authors study. Lamming et al<sup>9</sup> conducted a trial comparing labetalol with methyldopa. They reported that BP was more satisfactorily controlled with labetalol. In present study reduced the blood pressure significantly (P value <0.01 ) at 1 hr and 2 hrs, very significantly (p value <0.01 ) at 6 hrs and 12 hrs where as no significant reduction in blood pressure at 1 hr and 2 hrs with methyldopa. Labetalol reduces blood pressure rapidly and effectively in hypertensive emergencies as reported by Elatrous S et al.<sup>10</sup> Present study patients with labetalol group 74% had term deliveries where as in methyldopa group 60% had term deliveries. A study by A.M.E.I-Qarnalaw et al<sup>11</sup>, reported that prolongation of pregnancy was more common in the labetalol

group than in the methyldopa group. The present study correlates with the authors study. This finding is explained by the mild tocolytic effect of labetalol on the myometrium (Thulesius et al)<sup>12</sup>

2 patients had imminent eclampsia in labetalol group whereas 8 patients had imminent eclampsia in methyldopa group. 1 of the patient developed HELLP in methyldopa group whereas none of the patients developed HELLP in labetalol group.

In present study, 7% had IUGR fetuses in labetalol group where as 10% had IUGR fetuses in methyldopa group, Redman et al<sup>14</sup> compared labetalol and methyldopa in severe pregnancy induced hypertension. Higher incidence of IUGR was observed in methyldopa group and less perinatal mortality in labetalol group. Present study need of NICU admission in the labetalol group was 5% compared to 8% in methyldopa group Michael et al<sup>15</sup> reported that labetalol has a direct action on the fetal lung maturation, thereby significantly reducing respiratory distress syndrome.

There has been many anecdotal and retrospective studies reported literature on use of anti-hypertensive drugs in women with hypertension of pregnancy. A large study by Redman et al in 243 patients indicated a significant difference in the antihypertensive group as improving fetal salvage.

Mabie et al<sup>16</sup>, compared intravenous hydralazine in the acute treatment of severe hypertension. Labetalol is found to lower blood pressure more gradually without reflex tachycardia which accompanies the use of dihydralazine and diazoxide. Thulesius et al<sup>12</sup>, studied the effect of labetalol on the contractility of human myometrial preparations and reported a mild tocolytic effect of labetalol on myometrium. Sibai et al<sup>13</sup>, analysed data from 200 patients given labetalol and could discern no difference in fetal growth and birth weights of infants whose mother received labetalol. It is also noticed that labetalol decreased the incidence of induction of labour. Walker et al<sup>17</sup>, reported reversal of thrombocytopenia with labetalol by stimulation of prostacyclin like substances. Studies have compared the fetal effects, with labetalol and methyldopa and found to have no difference regarding the incidence of preterm births, rate of fetal growth retardation, Birth weight, perinatal and neonatal hypoglycemia (Walker et al<sup>17</sup>). Cruickshank DJ et al<sup>18</sup>, reported that Labetalol decreases the incidence of proteinuria in patients who have already developed proteinuric preeclampsia.

Tomoko Saotome<sup>19</sup>, studied the hypotensive effects, kinetics and concentration-relationship of labetalol in women with severe hypertension during the third trimester of pregnancy. Labetalol significantly reduced blood pressure without any side effects with a peak concentration at one hour post-dose. Elatrous et al<sup>10</sup>, compared nicardipine and labetalol in the management of severe hypertension. Concluded that both drugs are effective and safe in the treatment of severe hypertension of pregnancy.

Magee LA et al<sup>20</sup> (Cochrane Database 2003) assessed the effects of beta blockers on mild to moderate hypertension during pregnancy. It is reported that oral beta blockers reduces the risk of severe hypertension and the need for additional anti hypertensives. Beta blockers are well tolerated with very few side effects. Incidence of respiratory distress syndrome

was decreased. Beta blockers compared with any other anti-hypertensive drug is associated with lower risk of small for gestational infants and this effect is borderline for statistical significance. When compared with methyldopa, they appear to be equally safe and effective.

Duley L et al<sup>21</sup> (Cochrane Database 2006) compared different antihypertensive drugs for hypertension in pregnancy. He reported that labetalol is associated with lower risk of hypotension and caesarean section).

Number of oral antihypertensives are used for lowering blood pressure, but not proven to be safe during pregnancy. Methyldopa is the oldest drug used, it is said to be safe and effective both for mother and fetus. The main disadvantage with methyldopa is delayed onset of action. Labetalol, an alpha -beta adrenergic blocking drug has a rapid onset of action without serious side effects on both mother and fetus.

## CONCLUSION

The results revealed that labetalol is safer, quicker in action and more efficient in controlling and sustained effect on blood pressure. Therapy must be tailored to the clinical entity and the patient. Number of patients that could reach term, with reduced complications and ending in spontaneous normal deliveries are more with labetalol group. Labetalol group had lesser number of cases of imminent eclampsia, and no case landed in HELLP syndrome. Labetalol has good perinatal outcome compared to methyldopa group. However this being a pilot study, of only 100 patients, long term study with larger number of patients is needed to get a better understanding of the efficacy of the drug and its safety.

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