JMSCR Volume||2||Issue||5||Pages 1157-1175||May 2014 2014

www.jmscr.igmpublication.org Impact Factor-1.1147
ISSN (e)-2347-176x

IGM Publication Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Comparative study of Labetalol v/s Methyl dopa in the Management of Gestational Hypertension

Authors
Dr. Mahfrid.N.Dharwadkar[1], Dr. Kanakamma MK[2], Dr. K Rajagopal[3]
[1]Post Graduate Dept of Obstetrics and Gynaecology,Yenepoya Medical University, Derlakatte Mangalore Karnataka 575 018 INDIA
[2]Prof Dept of Obstetrics and Gynaecology,Yenepoya Medical University, Derlakatte, Mangalore Karnataka 575 018 INDIA
[3]Prof and HOD Dept of Obstetrics and Gynaecology,Yenepoya Medical University, Derlakatte Mangalore Karnataka 575 018 INDIA
Email- *mndharwadkar@gmail.com[1] , kanakamma.mk@gmail.com[2] , kaipangala2002@yahoo.com[3]*
Correspondence Author
Dr. Mahfrid.N.Dharwadkar
Post Graduate
Dept of Obstetrics and Gynaecology,Yenepoya Medical University, Derlakatte
Mangalore Karnataka 575 018 INDIA
Email: *mndharwadkar@gmail.com*

Abstract
Hypertensive disorders of pregnancy are one of the most common cause of maternal and perinatal mortality and morbidity affecting between 7-15 % of all pregnancies and are associated with as much as 22% of all perinatal deaths. They represent a group of conditions associated with high blood pressure, proteinuria and in some cases convulsions. The criteria for diagnosis & classification of the hypertensive disorders of pregnancy was according to the National High Blood Pressure Education Program Working Group (NHBPEP) and the American College of Obstetricians and Gynaecologists (ACOG).
A total of 40 patients were included in this study, 20 of whom were given labetalol and 20 were given methyl dopa. During this period the maternal and foetal conditions were monitored along with control of hypertension. The outcome of therapy was based on the efficacy of the drugs in effective control of blood pressure, prolongation of pregnancy, mode of termination, requirement of additional drugs, side effects, and perinatal safety and outcome.
Labetalol was found to be safer, quicker in achieving adequate control of blood pressure with considerable prolongation of the duration of pregnancy with fewer side effects on the mother as well as the neonate when used in the management hypertensive disorders of pregnancy.
Keywords- gestational hypertension labetalol methyldopa Perinatal outcome

INTRODUCTION

Hypertensive disorders of pregnancy affect 8% of the pregnancies(1) . They form one of the deadly triad, along with haemorrhage and infection that results in a large number of maternal deaths. It has been estimated that worldwide approximately 50,000 women die each year from eclampsia. They are the second leading cause of maternal death, accounting for 20%(3) of maternal deaths and present an increased risk of complications for the foetus, including increased NICU admission, preterm delivery and low birth weight and even foetal death. In addition to the risk they present to the pregnancy, hypertensive disorders of pregnancy have been linked to future high blood pressure and cardiovascular disease in women(4,5,6,7).

In India the incidence of hypertension occurs in well over 6% to 8% of all pregnancies(19,20,21). As many as 20% of primigravidas may develop hypertension.

The criteria for diagnosis & classification of the hypertensive disorder of pregnancy was obtained according to the National High Blood Pressure Education Program Working Group (NHBPEP) and the American College of Obstetricians and Gynaecologists(2).

The management of pregnancy induced hypertension is mainly termination of pregnancy, which cannot be done in many cases due to preterm by gestational age. It is thus prudent to continue the pregnancy till the stage where in the foetal survival is good.Various antihypertensive agents have been used in the management of preeclampsia(2). usage of antihypertensive drugs in cases of severe hypertension BP≥170/110 mmHg corresponds to the level standing for a high risk of cerebrovascular incident, because of which the majority of obstetricians regard antihypertensive treatment as crucial for the mother. Identification of this specific risk made the control of acutely raised blood pressure as central point for women with severe hypertension, particularly that of preeclampsia. Coagulation disorders associated with severe preeclampsia represent additional complications and also require adequate therapy.(8,9,10)

A wide spectrum of antihypertensive agents represent the key of successful pregnancy hypertension treatment and opportunity of choice, in accordance with indications and availability of drugs provided by drug tendering (11). Methyldopa was most commonly used for treatment of hypertension during pregnancy based on its effectiveness and safety for both mother and foetus as an anti-hypertensive drug(13, 14), but it takes longer time to act and also less efficacious as hypotensive drug. It is still the most commonly used drug for long term control of blood pressure in pregnancy. This has been shown to improve the foetal outcome compared to placebo(12). Long term follow up data of 7 years shows no detrimental effects to the off springs in the Methyldopa treated group(12). At high doses the sedative and depressant effects of methyldopa are marked. Methyldopa should not be used if there is a substantial risk of maternal depression when a beta-

blocking agent or calcium antagonist may be more suitable.

Labetalol gives better control of blood pressure compared to other anti-hypertensive agents(13,14). It is a combined alpha and beta adrenergic antagonist and has become the most frequently used anti-hypertensive for acute severe hypertension. Advantage of labetalol is that, it is available as both injectable and oral and time of onset of action is earlier than methyldopa(13) . However now, it is known that b-blockers cross the placental barrier and may cause foetal bradycardia. Experimental evidence also suggests that b-blocking agents reduce foetal tolerance to hypoxic stress. Previous research has shown that babies of mothers who received labetalol when pregnant are more likely to be small-for-gestational age (SGA) due, researchers suggest, to reduced placental blood flow. Hence this study to compare and contrast the aforementioned drugs in the management of hypertension and assess their risk -benefit ratio.

METHODOLOGY

A prospective randomized study was carried out in the Department of Obstetrics & Gynaecology, Yenepoya Medical College and Hospital, Mangalore between October 2011- October 2013. All pregnant women attending the antenatal clinic were screened for and hypertensive pregnant women were included in the study after obtaining informed consent.

The criteria for diagnosis & classification of the hypertensive disorder of pregnancy was obtained according to the National High Blood Pressure Education Program Working Group (NHBPEPWG).Serial BP recordings were measured twice in a day, 12 hours apart from the time of administration of the drugs to patients who are divided into two groups based on the drug they receive.

The duration required for the drug to act was then calculated along with assessment of other parameters such as side effects, prolongation of the duration of the pregnancy & number of additional drugs required. Neonatal morbidity in terms of birth weight, 5 minute APGAR scores, NICU stay and indication of the stay were all taken into account.

Inclusion criteria: All pregnant women with BP of more than or equal to 140/90 without proteinuria were included irrespective of their gravid status, gestational age and maternal age.

Exclusion criteria: Non- consenting patients; ; Patient coming for the first time during labour; Patients with eclampsia; Platelet count < 1,00,000 / mm3; HELLP syndrome; Pulmonary oedema; Recurrent pregnancy loss; Known case of Diabetes mellitus, Renal disease, Cardiac disease, haematological disorders; Hydatidiform mole; Multiple gestation

A total number of 40 patients attending the ante-natal clinic were included after diagnosing them with hypertension. These patients were randomly assigned with either Labetalol(group A) or methyldopa(group B) in groups of 20 cases each. A detailed history was taken & patients were examined & investigated in detail. Blood pressure was recorded using mercury sphygmomanometer

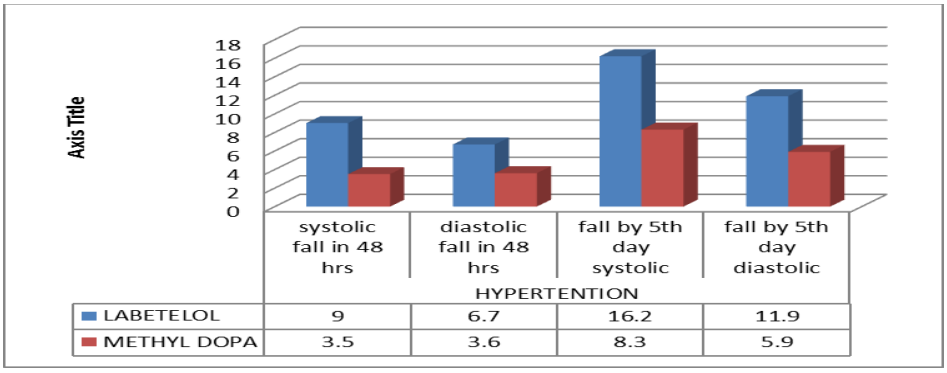
with patient in left lateral recumbent position after 20 min rest. Korotkoff I was taken as systolic and korotkoff V sound was taken as diastolic blood pressure.

Thereafter, the same parameters were recorded twelfth hourly during the period of hospital stay which depended upon the maternal response and gestational age. Patients close to term were followed up in the hospital whereas others were discharged after 7-10 days provided they had good control of BP, and did not show significant proteinuria or gross intra uterine growth retardation. On discharge, patients were advised to take the dose titrated for them based on their assessment during their hospital stay and were advised to come for weekly follow up and get re-admitted if BP control was unsatisfactory.

Patients whose BP remained uncontrolled inspite of therapy in both the groups were closely monitored in the hospital and attempt was made to continue the pregnancy with additional drugs such as nifedepine in varying doses or phenobarbital or magnesium sulphate were given. Prophylactic corticosteroids were given in patients who were less than 36 weeks period of gestation to better the neonatal outcome especially in those patients in whom the pregnancy had to be terminated early by induction of labour, and/or caesarean section done. The efficacy was measured in terms of the fall in both systolic and diastolic blood pressure by 48 hours as well as 5th day of the drug administration and the results were tabulated

RESULT- Fall in BP Table 1

	GROUP	N	Mean	S.D	t	df	P VALUE
systolic fall in 48 hrs	labetalol	20	9	2.714	6.119	38	**<0.001**
	m-dopa	20	3.5	2.965			
diastolic fall in 48 hrs	labetalol	20	6.7	2.849	3.976	38	**<0.001**
	m-dopa	20	3.6	2.01			
fall by 5th day systolic	labetalol	20	16.2	3.548	6.119	38	**<0.001**
	m-dopa	20	8.3	4.555			
fall by 5th day diastolic	labetalol	20	11.9	3.463	5.851	38	**<0.001**
	m-dopa	20	5.9	3.007			



The above table and the graph unequivocally depicts that labetalol has a better effect on control of BP added by quick onset of action which is not the case with methyl dopa. Further-more the maintenance of optimal BP levels were seen through-out the course of therapy with labetalol

SIDE EFFECTS **Table 2:**

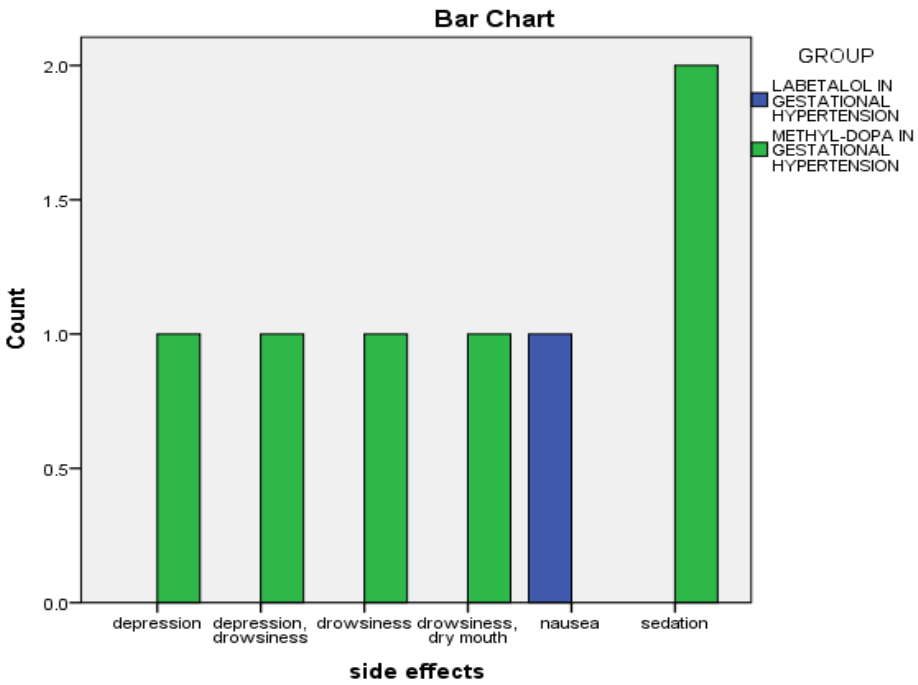
Crosstab

			group		Total
			labetalol in gestational hypertension	methyl-dopa in gestational hypertension	
side effects	Depression	Count	0	1	1
		% within side effects	0.0%	100.0%	100.0%
		% within GROUP	0.0%	16.7%	14.3%
	depression, drowsiness	Count	0	1	1
		% within side effects	0.0%	100.0%	100.0%
		% within GROUP	0.0%	16.7%	14.3%
	Drowsiness	Count	0	1	1
		% within side effects	0.0%	100.0%	100.0%
		% within GROUP	0.0%	16.7%	14.3%
	drowsiness, dry mouth	Count	0	1	1
		% within side effects	0.0%	100.0%	100.0%
		% within GROUP	0.0%	16.7%	14.3%
	Nausea	Count	1	0	1
		% within side effects	100.0%	0.0%	100.0%
		% within GROUP	100.0%	0.0%	14.3%
	Sedation	Count	0	2	2
		% within side effects	0.0%	100.0%	100.0%
		% within GROUP	0.0%	33.3%	28.6%
Total		Count	1	6	7
		% within side effects	14.3%	85.7%	100.0%
		% within GROUP	100.0%	100.0%	100.0%

Table 3

Chi-Square Tests

	Value	Exact Sig. (2-sided)
Fisher's Exact Test	6.456	.714
N of Valid Cases	7	



Though there aren't statistically significant p value the presence of side effects is slightly more with methyl dopa than with labetalol

ADDITIONAL DRUGS REQUIRED

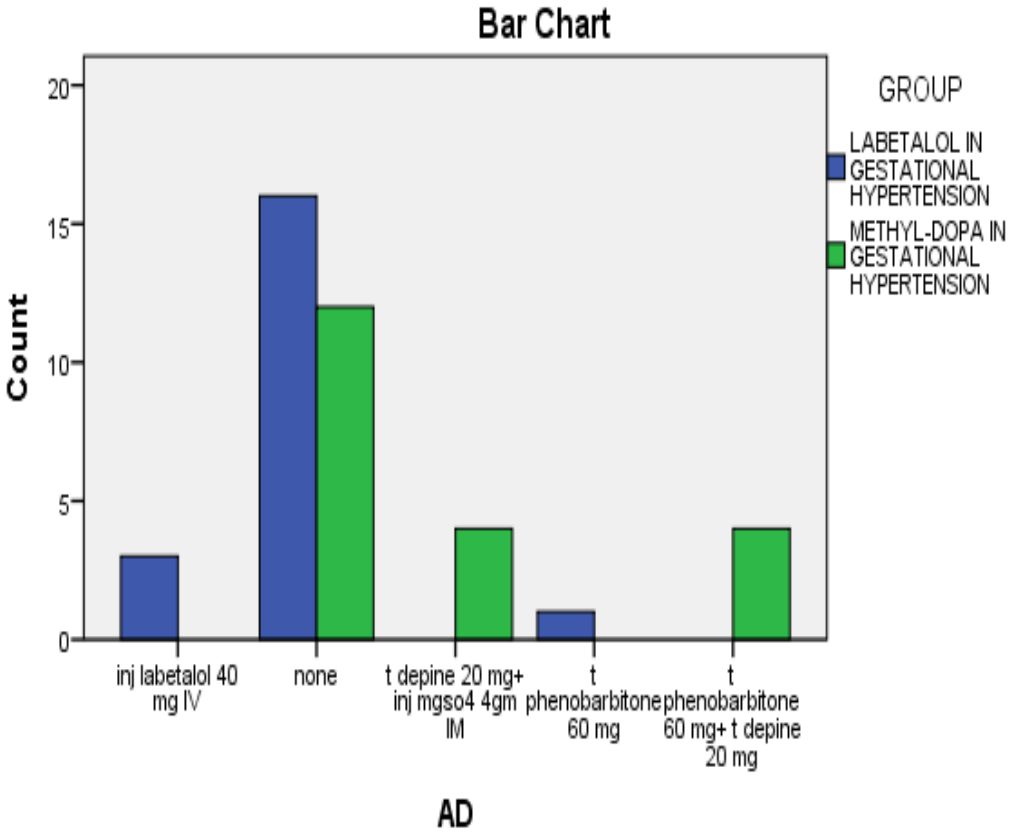
Table 4:

Crosstab

			group		Total
			labetalol in gestational hypertension	methyl-dopa in gestational hypertension	
AD	inj labetalol 40 mg IV	Count	3	0	3
		% within AD	100.0%	0.0%	100.0%
		% within GROUP	15.0%	0.0%	7.5%
	None	Count	16	12	28
		% within AD	57.1%	42.9%	100.0%
		%within GROUP	80.0%	60.0%	70.0%
	t depine 20 mg+ inj mgso4 4gm IM	Count	0	4	4
		% within AD	0.0%	100.0%	100.0%
		%within GROUP	0.0%	20.0%	10.0%
	t phenobarbitone 60 mg	Count	1	0	1
		% within AD	100.0%	0.0%	100.0%
		%within GROUP	5.0%	0.0%	2.5%
	t phenobarbitone 60 mg+ t depine 20 mg	Count	0	4	4
		% within AD	0.0%	100.0%	100.0%
		%within GROUP	0.0%	20.0%	10.0%
Total		Count	20	20	40
		% within AD	50.0%	50.0%	100.0%
		%within GROUP	100.0%	100.0%	100.0%

Table 5: Chi-Square Tests

	Value	Exact Sig. (2-sided)
Fisher's Exact Test	11.517	**.003**
N of Valid Cases	40	



In this graphical representation note that the second blue bar which signifies no use of drugs is taller which represents labetalol demonstrating yet again that the use of other additional drugs is more with methyl dopa than labetalol.

NST AFTER 48 HOURS

Table 6:

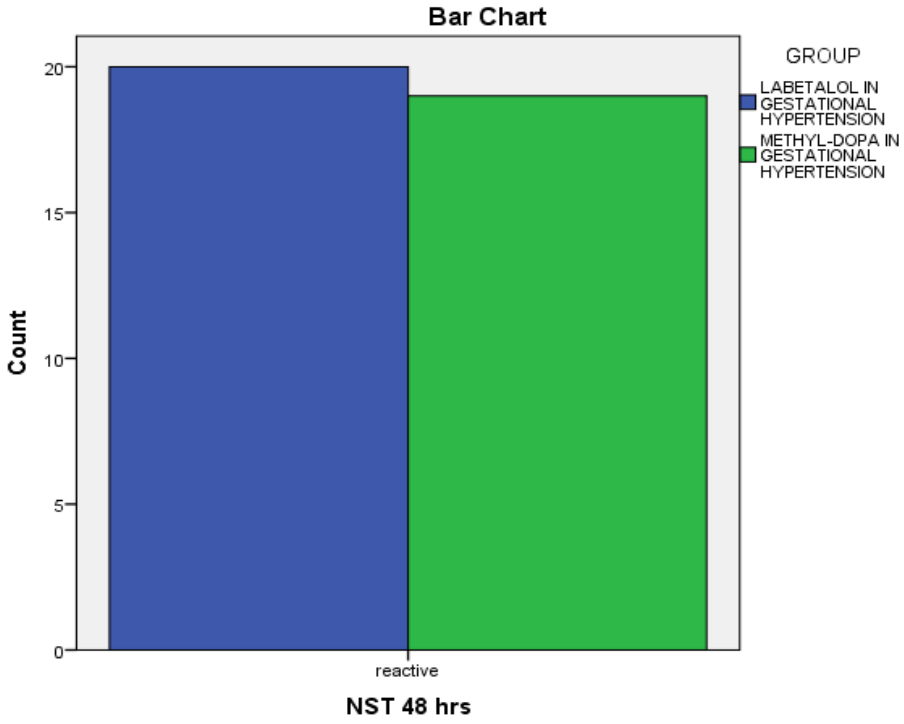
Crosstab

			GROUP		Total
			LABETALOL IN GESTATIONAL HYPERTENSION	METHYL-DOPA IN GESTATIONAL HYPERTENSION	
NST 48 hrs	reactive	Count	20	19	39
		% within NST 48 hrs	51.3%	48.7%	100.0%
		% within GROUP	100.0%	100.0%	100.0%
Total		Count	20	19	39
		% within NST 48 hrs	51.3%	48.7%	100.0%
		% within GROUP	100.0%	100.0%	100.0%

Table 7: Chi-Square Tests

	Value
Pearson Chi-Square	.[a]
N of Valid Cases	39

a. No statistics are computed because NST 48 hrs is a constant.

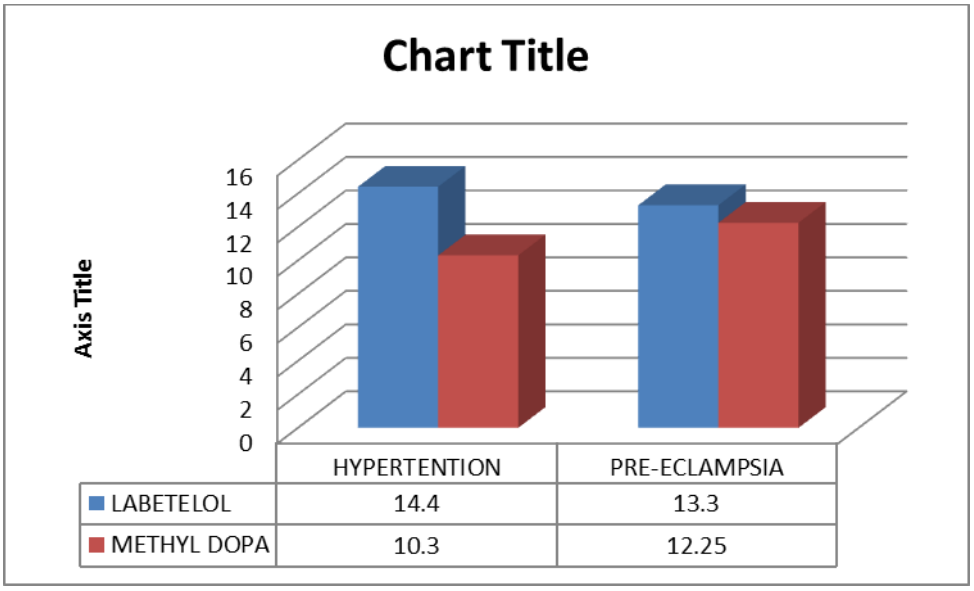


The above tables and a graph show that the NST were reactive even after administration of either drugs for 48 hrs hence showing no detrimental effect on the foetal well being by either labetalol or methyl dopa

.

Table 8: Prolongation Of Pregnancy (in days)

	CATEGORY		GROUP	N	Mean	Std. Deviation	t	df	Sig. (2-tailed)
	Hypertension	prolongation of pregnancy	LABETELOL	20	14.4days	4.489	2.977	38	**0.005**
			METHYL-DOPA	20	10.3days	4.219			



Labetalol shows a statistically significant p-value of 0.005 in gestational hypertension patients with respect to prolongation of pregnancy how-ever it is not reflected in the patients with pre-eclampsia.

MODE OF TERMINATION

Table 9: Hypertension

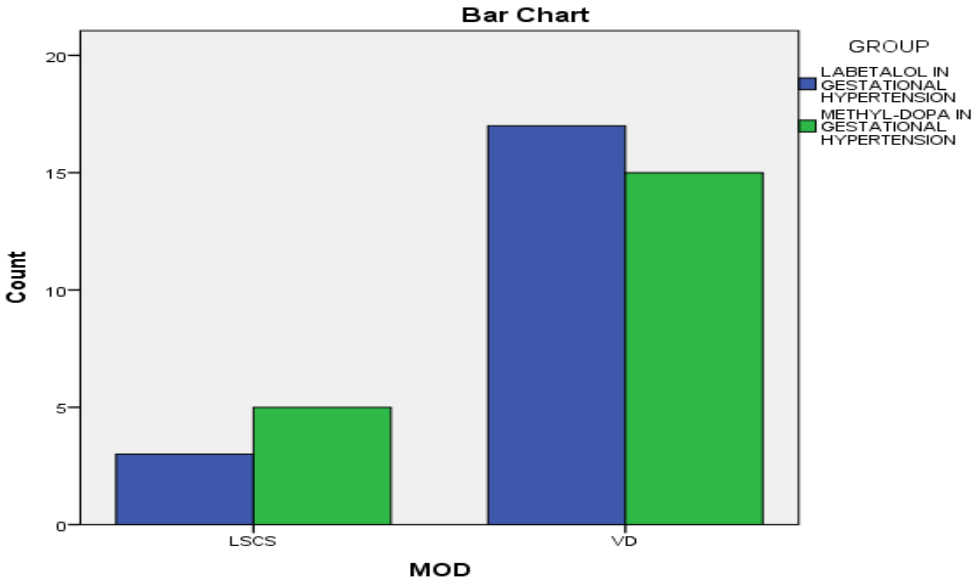
Crosstab

			group		Total
			labetalol in gestational hypertension	methyl-dopa in gestational hypertension	
MOD	LSCS	Count	3	5	8
		% within MOD	37.5%	62.5%	100.0%
		% within GROUP	15.0%	25.0%	20.0%
	VD	Count	17	15	32
		% within MOD	53.1%	46.9%	100.0%
		% within GROUP	85.0%	75.0%	80.0%
Total		Count	20	20	40
		% within MOD	50.0%	50.0%	100.0%
		% within GROUP	100.0%	100.0%	100.0%

Table 10: Chi-Square Tests

	Value	df	Exact Sig. (2-sided)
Pearson Chi-Square	.625	1	.695
N of Valid Cases	40		

b. Computed only for a 2x2 table



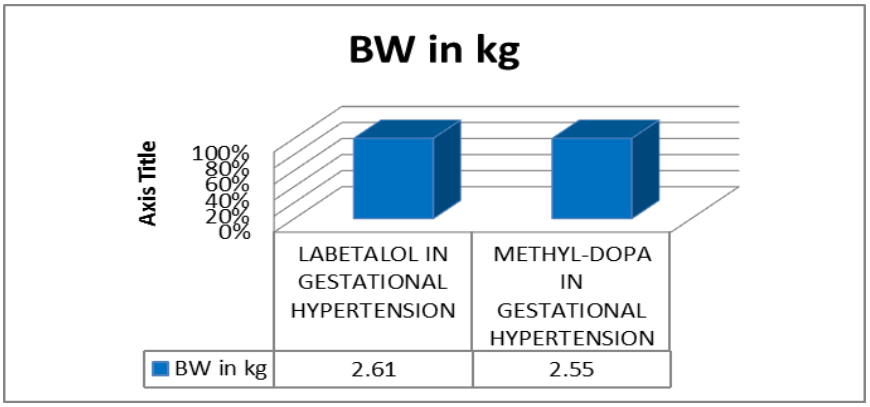
In these tabular plus graphic presentation, 15% were C- section and 85% were vaginal deliveries in labetalol group and in methyl dopa the percentages of c- section was 25% and percentage of vaginal deliveries was 75% concluding that there isn't a statistically significant value in terms of mode of termination of pregnancy in either drug groups

.

BIRTH WEIGHT

Table 11: Gestational Hypertension

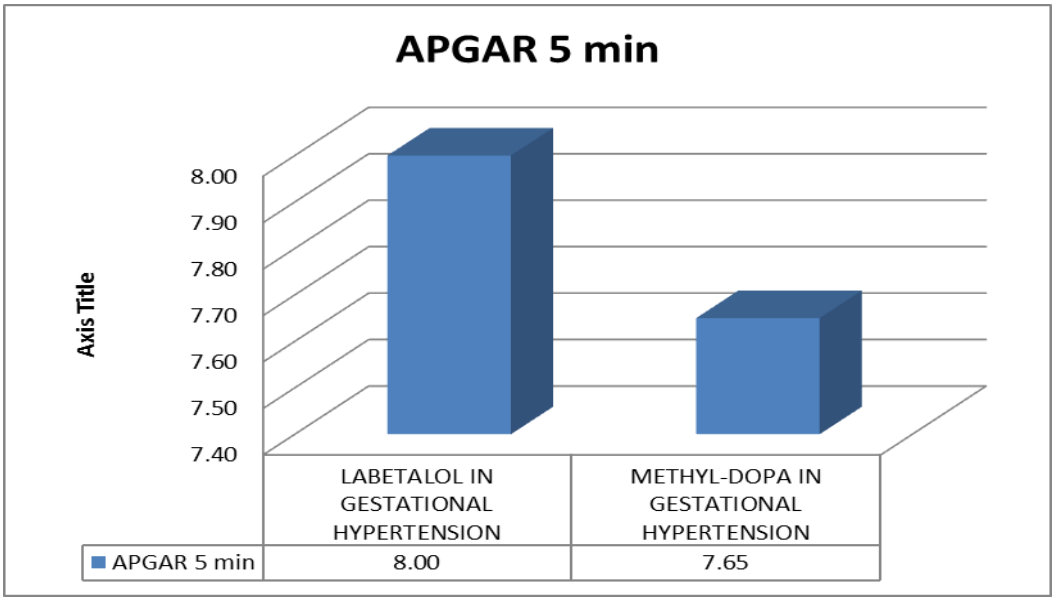
	GROUP	N	Mean	Std. Deviation	t	df	P VALUE
BW	**Labetalol in gestational hypertension**	20	2.605	0.2523	0.445	26.704	0.66
	Methyl-dopa in gestational hypertension	20	2.545	0.5482			



There was no significant difference in birth weight of the neonates in either drug groups.

Table 12: 5 MINUTE APGAR SCORES

	GROUP	N	Mean	Std. Deviation	t	df	P VALUE
APGAR 5 min	**Labetalol**	20	8	1.451	0.751	38	0.457
	Methyl-dopa	20	7.65	1.496			



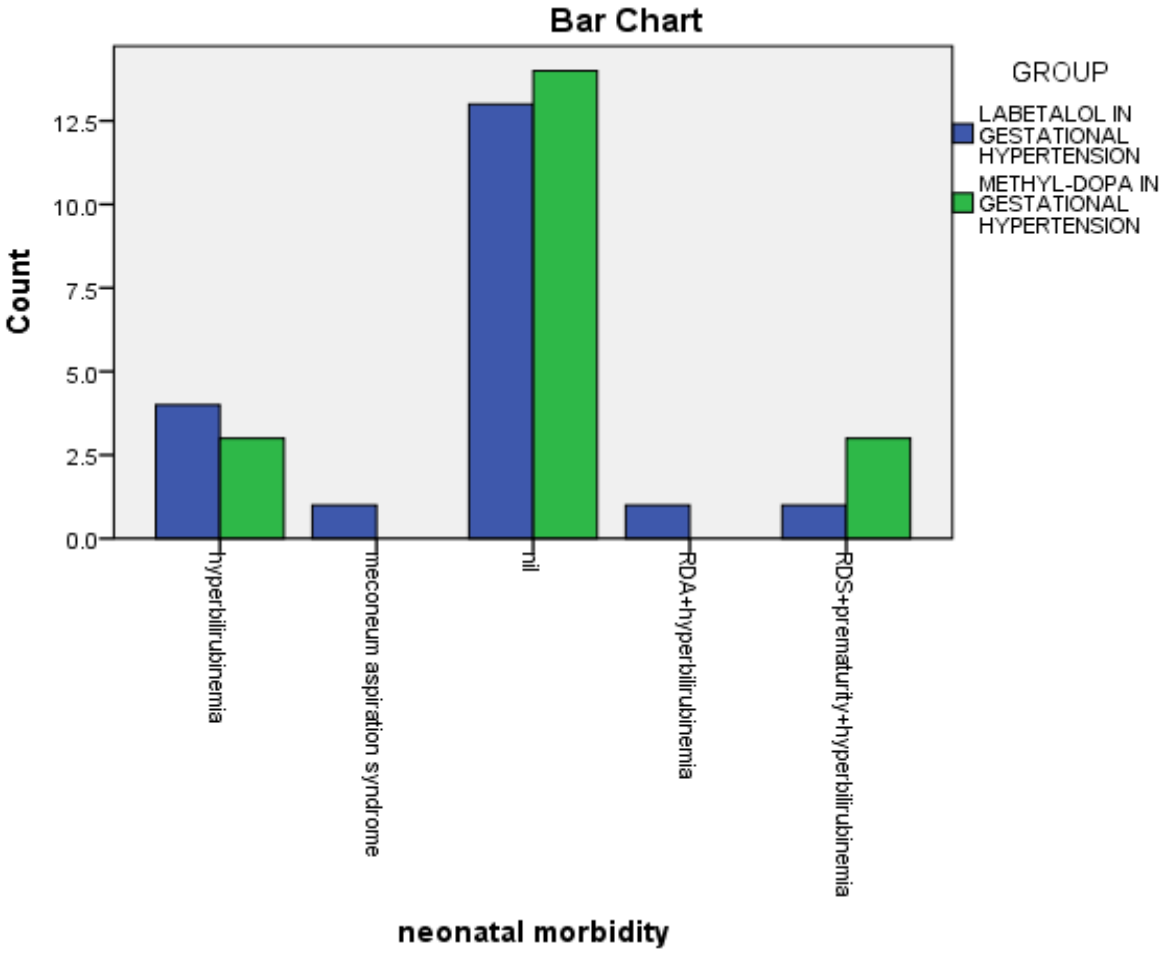
The APGAR scores(T test employed) of the neonates at 5 min were in the same range in both labetalol and methyl dopa with no significant statistical difference

Table 13: NEONATAL MORBIDITY

Crosstab					
			group		Total
			labetalol in gestational hypertension	methyl-dopa in gestational hypertension	
neonatal morbidity	hyperbilirubinemia	Count	4	3	7
		% within neonatal morbidity	57.1%	42.9%	100.0%
		% within GROUP	20.0%	15.0%	17.5%
	meconeum aspiration syndrome	Count	1	0	1
		% within neonatal morbidity	100.0%	0.0%	100.0%
		% within GROUP	5.0%	0.0%	2.5%
	nil	Count	13	14	27
		% within neonatal morbidity	48.1%	51.9%	100.0%
		% within GROUP	65.0%	70.0%	67.5%
	RDS+hyperbilirubinemia	Count	1	0	1
		% within neonatal morbidity	100.0%	0.0%	100.0%
		% within GROUP	5.0%	0.0%	2.5%
	RDS+prematurity+hyperbilirubinemia	Count	1	3	4
		% within neonatal morbidity	25.0%	75.0%	100.0%
		% within GROUP	5.0%	15.0%	10.0%
Total		Count	20	20	40
		% within neonatal morbidity	50.0%	50.0%	100.0%
		% within GROUP	100.0%	100.0%	100.0%

Table 14: Chi-Square Tests

	Value	Exact Sig. (2-sided)
Fisher's Exact Test	3.042	.764
N of Valid Cases	40	



The various causes of morbidity were hyperbilirubinemia, respiratory distress syndrome, meconeum aspiration syndrome IUGR and Pre-maturity however when compared in either drug groups there was no statistical significance.

DISCUSSION

Methyldopa was most commonly used for treatment of hypertension during pregnancy based on its effectiveness and safety for both mother and foetus(14,15), but it takes longer time to act and also less efficacious as hypotensive drug. It is still the most commonly used drug for long term control of blood pressure in pregnancy. This has been shown to improve the foetal outcome compared to placebo (13). Long term follow up data of 7 years shows no detrimental effects to the off springs in the Methyldopa treated group(13). At high doses the sedative and depressant effects of methyldopa are marked. Methyldopa should not be used if there is a substantial risk of maternal depression when a beta-blocking agent or calcium antagonist may be more suitable.

Labetalol gives better control of blood pressure compared to other anti-hypertensive agents(14,15). It is a combined alpha and beta adrenergic antagonist and has become the most frequently used anti-hypertensive for acute severe hypertension. Advantage of labetalol is that, it is available as both injectable and oral and time of onset of action is earlier than methyldopa(14).

FALL IN BP

The mean difference in the fall with labetalol of the systolic/diastolic BP by 48 hours was 9/6.7mmHg and by the 5th day it was 11.9/8.7 mmHg as compared to methyl dopa being 3.5/3.6 mmHg in the first 48 hours followed by 8.3/5.9 in the hypertension patients. Thus clearly stating that labetalol is a better drug in effectively reducing the BP of the patients and then maintain optimal BP levels. Labetalol is an effective antihypertensive which decreases both systolic and diastolic BP in pregnancy induced hypertension was proved earlier. In a few studies it was shown that the antihypertensive efficacy of either drugs is similar(15,16,17,18). However, one study says that labetalol provides more efficient control of BP than methyldopa in the treatment of mild hypertension in pregnancy(22) which was also corroborated by this study.

Side effects

Methyl dopa had side effects such as drowsiness, depression and dry mouth where as labetalol had only nausea however on comparison between the two, the numbers were statistically insignificant**.**

Additional treatment

About 40% of the methyldopa group received nifedepine and phenobarbitone where as only 20%of labetalol group received inj labetalol and phenobarbitone showing that methyl dopa requires additional drugs for BP management than labetalol.

NST after 48 hours of therapy

Out of the 40 patients in the study 1 patient's NST at admission was non-reactive hence it was not included how-ever the rest 39 patients' non-stress tests taken after 48 hours of drug administration for both the groups were reactive depicting that either

one of the drugs do not have any adverse effect on the foetus.

Prolongation of pregnancy

In patients with gestational hypertension on labetalol the mean number of days with which pregnancy was prolonged was 14.3 days whereas those on methyl dopa, it was 10.3 days as evidenced by a significant p-value of 0.005 suggesting that labetalol does prolong the duration pregnancy in women with gestational hypertension.

Mode of termination

Out of the 20 women on labetalol 3(15%) women underwent caesarean section and the rest 17(85%) underwent vaginal delivery. In the methyl dopa group 5(25%) underwent caesarean section the rest 15(75%) underwent vaginal delivery proving that neither of these drugs are directly related to the mode of delivery.

Perinatal safety

The mean birth weight in the labetalol group with gestational hypertension was 2.6kg while the mean birth weight in the methyl dopa group hypertension was 2.5kg showing that there wasn't a significant difference in terms of birth weight in either drug groups. The mean 5 minute APGAR scores for labetalol was 8 and for methyl dopa was 7.6

In the labetalol group there were 7 neonates with hyperbilirubinemia, 2 with respiratory distress syndrome(RDS) and 1 suffered from meconium aspiration syndrome(MAS).In the methyl dopa group similar numbers were seen, 5 hyperbilirubinemia, 3 RDS and 1 with MAS. There was no statistically significant difference in the neonatal morbidity between the two drug groups.

There was 1 neonatal death in methyl dopa group and none in labetalol group. These figures how-ever did not have any statistical significance but how-ever these findings were not in corroboration with study by Plouin et al[15]. He also demonstrated that there were four still births in methyldopa group. In a study by Redman et al, he found that two babies born to women assigned to labetalol died but no deaths were reported in methyldopa group.

CONCLUSION

Hypertensive disorders of pregnancy are one of the major causes of maternal and foetal mortality and morbidity and as long as its exact cause is unknown, its prophylaxis will be uncertain.

Many drugs have been used in the management of those the combined alpha+beta blocking agent labetalol has been very effective in control as well as earlier onset of action in patients. It ensures effective control of blood pressure, prevention of eclampsia and the pregnancy prolongation to achieve foetal maturity. It has lesser side effects when compared to methyldopa and is not associated with adverse foetal effects in the immediate and late neonatal period.

The chances of spontaneous onset of labor were greater in the labetalol group when compared to methyldopa group. Though there was no difference

in the groups with regard to obstetric intervention. At clinically effective doses how-ever, both the drugs were found to be safe for the neonate.

To conclude, labetalol is safer, quicker in achieving adequate control of blood pressure with considerable prolongation of the duration of pregnancy with fewer side effects on the mother as well as the neonate when used in the management gestational hypertension.

REFERENCES

1. Roberts JM, Pearson G, Cutler J, Lindheimer M, NHLBI Working Group on Research on Hypertension During Pregnancy. Summary of the NHLBI working group on research on hypertension during pregnancy. Hypertension. 2003 Mar; 41(3):437-45.
2. Cunningham FG. Leveno.K.J, Bloom SL, Hauth J.C. Hypertensive disorders of pregnancy. Chapter in Cunningham, F. Gary. III. Williams, J eds, Williams Obstetrics, 23rd edition; 34:706-709.
3. Gofton EN, Capewell V, Natale R, Gratton RJ. Obstetrical intervention rates and maternal and neonatal outcomes of women with gestational hypertension. Am J Obstet Gynecol. 2001 Oct; 185(4):798-803.
4. Berg CJ, Chang J, Callaghan WM, Whitehead SJ. Pregnancy-related mortality in the United States, 1991-1997. Obstet Gynecol. 2003 Feb; 101 (2):289-96.
5. Villar J, Carroli G, Wojdyla D, Abalos E, Giordano D, Ba'aqeel H, et al. Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? Am J Obstet Gynecol. 2006 Apr; 194(4):921-31.
6. Hannaford P, Ferry S, Hirsch S. Cardiovascular sequelae of toxemia of pregnancy. Heart. 1997 Feb; 77 (2):154-8.
7. Seely EW. Hypertension in pregnancy: A potential window into long-term cardiovascular risk in women. J Clin Endocrinol Metab. 1999: Jun; 84(6):1858-61.
8. Sutton PD, Mathews TJ. Birth and fertility rates for states by Hispanic origin subgroups: United States, 1990 and 2000. Vital Health Stat 21. 2006 May ;(57):16-95.
9. Lloyd-Jones DM, Sutton-Tyrrell K, Patel AS, Matthews KA, Pasternak RC, Everson-Rose SA, et al. Ethnic variation in hypertension among premenopausal and perimenopausal women: Study of women's health across the nation. Hypertension. 2005 Oct; 46(4):689-95.
10. Whitworth JA, Schyvens CG, Zhang Y, Mangos GJ, Kelly JJ. Glucocorticoid induced hypertension: From mouse to man. Clin Exp Pharmacol Physiol. 2001 Dec; 28(12):993-6.
11. Cochrane study group Magee L, Duley L. Oral beta-blockers for mild to moderate

hypertension during pregnancy. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD002863.

12. Goodman & Gilman's the pharmacological basis of therapeutics- 11th ed.(2006):32.
13. Heazell A, Baker PN, Hypertensive disorders of pregnancy, Chapter in Oakely C, Warnes CA (Eds), Heart diseases in pregnancy, 2nd edition, BMJI, Blackwell Publishing, Oxford, 2007, pp 264 – 280.
14. Redman CW. Foetal outcome in trial of anti-hypertensive treatment in pregnancy. Lancet 1976; 2: 753 – 6.
15. Plouin PF, Breart G, Maillard F, Papiernik E, Relier JP, the Labetalol Methyldopa Study Group. Comparison of antihypertensive efficacy and perinatal safety of labetalol and methyldopa in the treatment of hypertension in pregnancy: a randomized controlled trial. British Journal of Obstetrics and Gynaecology 1988; 95:868–76.
16. Pickles, Broughton, Symonds. A randomized placebo controlled trial of labetalol in the treatment of mild to moderate pregnancy induced hypertension. Br J Obstet Gynecol 1992; 99: 964-968.
17. Redman CWG, Gallery ED, Mitchell MD, Fall in BP in response to volume expansion in pregnancy associated hypertension (PE): Why does it occur? BMJ 1984 April; 2(2):177-82.
18. Sibai BM, Gonzalez AR, Mabie WC,Moretti M, A comparison of labetalol plus hospitalization versus hospitalization alone in the management of preeclampsia remote from term. Obstet Gynecol 1987; 70:323–7.
19. Mudaliar & Menon clinical obstetrics, 7th edition
20. Dev PK, Sultan, Sautpur SR Review of Eclampsia cases, Journal of Obstetrics Gynaecology India 1976:26-53
21. Chesley LC. History.In Chesley LC (ed): Hypertensivedisorders in pregnancy. New York, Appleton, Century, Crofts,1978:17034
22. Brunton L, Chabner B, Knollman B, Goodman and Gilman's The Pharmacological basis of Therapeutics. 12th ed. New York (USA): The McGraw Hill Companies; c2011. Chapter 12, Adrenergic agonists and antagonists; p. 328-9.