

Antihypertensive Drugs used during Pregnancy: an Evaluation

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ABSTRACT

BACKGROUND & OBJECTIVES: Hypertensive disorders during pregnancy are a leading cause of maternal mortality occurring in 5-10 percent of pregnancies. While the goal of treatment is to reduce maternal risk, the agents selected must be efficacious and safe for the foetus. Thus, the present study was carried out with objectives to assess the prevalence of hypertensive disorders during pregnancy, the prescribing pattern to treat these conditions and to monitor adverse drug reactions. **METHODOLOGY:** A six months prospective study was carried out at a tertiary care hospital, after obtaining Ethical clearance. Data was collected from the antenatal cards and case sheets of all pregnant women diagnosed with elevated BP and admitted to the wards. Classification of hypertensive disorders of the patients were performed according to the criteria by Davey and Mac Gillivray, American College of Obstetrics & Gynecology (ACOG) and endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP). **RESULTS & CONCLUSION:** 152 patients met inclusion criteria. Prevalence of hypertensive disorders during pregnancy was found to be 12.2%. Based on the classification, 65% of patients had Gestational Hypertension, 26% had Pre-eclampsia/Eclampsia and 9% had Chronic Hypertension. The most commonly prescribed medicines to treat the hypertensive disorders during pregnancy were Nifedipine, Methyldopa, MgSO₄, Atenolol, Furosemide and their combinations. Nifedipine was widely used in patients with Gestational Hypertension (14.1%) and Pre-eclampsia/Eclampsia (22.5%). For Chronic Hypertension, a combination of Nifedipine and Methyldopa (38.5%) were prescribed. The treatment given for the management of hypertensive disorders during pregnancy was found to be at par with the guidelines.

Keywords: Antihypertensive drugs, eclampsia, gestational hypertension, pre-eclampsia, pregnancy

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INTRODUCTION

Hypertension is a frequently encountered complication of pregnancy which presents several challenges to the clinicians' right from diagnosis to treatment. Hypertensive disorders complicate 5-10% of pregnancies and are a leading cause of maternal mortality in both the developed and developing world [1]. In pregnant women, hypertension – blood pressure (BP) levels higher than 140/90 mmHg can be detrimental and even life threatening to the mother and fetus if untreated.

Maternal and foetal outcomes depend upon the nature of the hypertension affecting the pregnancy, which can range from mild gestational hypertension to severe

preeclampsia with its associated multi-systemic complications. Pregnant women with hypertension are at higher risk of severe complications such as abruption placentae, cerebrovascular accident, organ failure and disseminated intravascular coagulation. The fetus is at risk for intrauterine growth retardation, preterm delivery and intrauterine death. While for some, hypertension during pregnancy is easily resolved, for others, it can result in a high risk pregnancy with increased risk for premature labor, delivery and maternal complications [2]. Most women who will develop hypertension during pregnancy

will not do so until after the 24th week of pregnancy.

DEFINITION

Hypertension in pregnancy is defined by Australian Society for the study of hypertension in pregnancy as a sitting systolic blood pressure (sBP) greater than 140mmHg and / or a diastolic blood pressure (dBP) greater than 90mm Hg.

Readings should be confirmed several hours apart, to exclude stress related elevations in BP. The widely accepted classification is based on the system proposed by Davey and Mac Gillivray, American College of Obstetrics & Gynecology and endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP)) (Table 1) [3-5].

Table 1: Classification & Definition of Hypertensive Disorders during Pregnancy

Pre-eclampsia / Eclampsia	SBP \geq 140, DBP \geq 90mmHg and proteinuria $>$ 300 mg/L in 24hrs after 20 weeks of gestation.
Gestational Hypertension (Transient)	Same as above but no proteinuria.
Chronic Hypertension	Hypertension antedating pregnancy Chronic Hypertension with superimposed preeclampsia; worsening blood pressure with proteinuria $>$ 300mg/L in 24hrs.

Goals of treatment of Hypertension in pregnancy differ from those for the general Hypertensive population. The benefit of treatment of mild diastolic hypertension has been clearly established and documented for general population, while in Pregnancy it remains an area of controversy. The choice of antihypertensive medication in pregnancy is limited by concerns for fetal safety. Care must be taken to avoid rapid and profound changes in maternal blood pressure to prevent maternal cerebral vascular accident.

Methyldopa is the first choice agent that is recommended for treatment of non-severe hypertension in pregnancy. For acute management of severe hypertension, the dBP should be reduced by 10mmHg in the

first instance and maintain the blood pressure at or below that level with Nifedipine as first choice agent. Anticonvulsant therapy with MgSO₄ (4g IV stat, then 1g/hr) should be initiated as prophylaxis. For management of eclampsia, MgSO₄ (4g IV stat, then 1g/hr) and for management of recurrent seizures MgSO₄ (2g IV stat, then increase to 1.5g/hr) can be used. There is controversy over whether use of short-acting nifedipine should be relatively contraindicated in women who are on MgSO₄, due to concerns about maternal neuromuscular blockade [1, 6-9]. Treatment for women with acute hypertension (Diastolic BP $>$ 105mmHg), antihypertensive agents as suggested in Table 2 can be used [10].

Table 2: Antihypertensive Agents used during Pregnancy

Agent	Dose	Comment
Methyldopa	250 – 1,000 mg bid	Best safety record
Labetalol	100 – 600 mg bid	Potent, easy to titrate
Hydrochlorothiazide	12.5 – 50 mg qd	Not indicated for preeclampsia
Nifedipine XL	30 – 90 mg qd	May increase phenytoin toxicity
Hydralazine	25 – 100 mg bid	Can cause tachycardia
MgSO ₄	(4g IV stat, then 1g/hr)	Potential synergism with Nifedipine may induce hypotension

Considering the importance of the safety of the pregnant mother and the foetus, it is important to treat hypertensive disorders in pregnancy judiciously. Hence, the present

study was carried out with the main objective to study the prescribing pattern of antihypertensive drugs in pregnant women and also to estimate the prevalence of

hypertensive disorders in pregnancy in a tertiary care hospital at Bangalore.

MATERIALS & METHODS

STUDY DESIGN & DURATION

This is a prospective study carried out for a period of six months at the gynecology & obstetrics wards of a tertiary care hospital.

STUDY PROTOCOL

All pregnant women diagnosed with elevated BP, attending the antenatal clinic and those admitted to the in-patient department of Obstetrics and Gynecology wards for delivery were included in the study. Pregnant women with chronic conditions such as asthma, epilepsy, thyroid disorders, renal or hepatic failure were not considered for inclusion.

Institutional Ethical Committee clearance was obtained before commencing the study. Data was collected from a prospective series of 152 patients by scrutinizing the antenatal cards and case sheets of those who were admitted to Gynecology & Obstetrics wards of the hospital. Total number of deliveries during the study period was obtained from the delivery registers of Obstetrics & Gynecology wards of St. Martha's Hospital, Bangalore.

METHOD OF DATA COLLECTION

Data for the present study were collected by scrutinizing the antenatal cards and case sheets of the patients. Classifications of hypertensive disorders were performed according to the criteria by Davey and Mac Gillivray, American College of Obstetrics & Gynecology (ACOG) and endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP). The data collected was analyzed for the following:

- Prevalence of hypertensive disorders during pregnancy
- Demographic details of the patients
- Patient history
- Maternal Characteristics
- Delivery & Neonatal outcome
- Treatment of hypertensive disorders during pregnancy

The treatment given for the management of hypertensive disorders of pregnancy were assessed based on various international standard treatment guidelines such as JNC

VIII, Australian Society for the Study of Hypertension in Pregnancy etc.

RESULTS

During the study period, there were a total number of 1242 deliveries in OB & Gynecology department of which 152 patients were identified to be having hypertensive disorders during pregnancy. The prevalence of hypertensive disorders of pregnancy was found to be 12.2%. Based on the classifications of hypertensive disorders during pregnancy, 65% of patients had Gestational Hypertension, 26% had Pre-eclampsia/Eclampsia and 9% had Chronic Hypertension. Their demographic details are listed in (**Table 3**).

Demographic details of the patient's showed that the patients in the study group were between the ages of 18 to 37 yrs of which majority were 20-29 years. Analysis of the educational status revealed that only 4% of the patients were uneducated. Majority of the patients included in the study were housewives. A family history of hypertension was observed in 32.9% of the study population, of which 84.6% were in the group of Chronic Hypertension. History of hypertensive disorders during pregnancy were observed in 6.8% of the study population of which 30.8% belonged to the group of chronic hypertension. No significant differences were observed in the incidences of hypertensive disorders during pregnancy in primigravidae and multigravidae.

It was observed that, 29.6% of the patients had premature delivery, 32.9% had cesarean delivery, 16.4% had intra uterine growth retardation (IUGR) and 5.9% reported intra uterine death (IUD).

The most commonly prescribed medicines to treat the hypertensive disorders during pregnancy are listed in (**Table 4**).

Atenolol and Furosemide were prescribed postpartum. Nifedipine was widely used in patients with Gestational Hypertension (14.1%) and Pre-eclampsia/Eclampsia (22.5%). For the treatment of Chronic Hypertension, a combination of Nifedipine and Methyldopa (38.5%) were widely prescribed, these results are depicted in (**Table 5**).

Table 3: Demographic Detail of the Patients

Characteristics	Gestational Hypertension n*(%)	Chronic Hypertension n (%)	Pre-eclampsia / Eclampsia n (%)
AGE			
20-24	35 (35.4)	2 (15.4)	19 (47.5)
25-29	35 (35.4)	2 (15.4)	9 (22.5)
Occupation			
House Wives	90 (90.9)	10 (76.9)	37 (92.5)
Education			
Grade 2 SSLC, PUC	58 (58.6)	5 (38.5)	7 (17.5)
Patient History			
Family history of hypertension	28 (28.3)	11 (27.5)	11 (84.6)
History of Gestational hypertension in previous pregnancy	4 (4.04)	2 (5)	4 (30.8)
Maternal Characteristics			
Primigravidae	50 (50.5)	19 (47.5)	8 (61.5)
Multigravidae	49 (49.5)	21 (52.5)	5 (38.5)
Delivery Outcome			
Preterm Delivery (< 37weeks)	22 (30)	22 (61.1)	1 (20)
Mode of delivery: Cesarean	28 (36.8)	20 (55.6)	2 (40)
Neonatal Outcome			
Intrauterine growth retardation (IUGR)	14 (18.4)	10 (25)	2 (15.4)
Intrauterine Death (IUD)	4 (5.2)	4 (1)	1 (7.7)

*n= Number of patients

Table 4: List of Various Antihypertensive Drugs Prescribed during Pregnancy

Antihypertensive Drugs Prescribed (Monotherapy / Combination)	Number of Patients (n)	Percentage (%)
Oral Methyl dopa 250/500mg (upto 1000mg/day in divided doses)	53	34.9
Oral Nifedipine 10/20mg BID	100	65.8
IV MgSO ₄ (Zuspan regimen) LD: 4g IV MgSO ₄ infusion 1gm / hr	19	12.4
Oral Atenolol 25/50mg / OD	6	4.6
Oral Furosemide 20mg / day	3	1.96

MgSO₄ – Magnesium Sulphate**DISCUSSION**

Hypertensive disorders during pregnancy are the second leading cause, after embolism, of maternal mortality. Hypertensive disorders occur in 5-10 percent of pregnancies and contribute significantly to still-births and neonatal

morbidity and mortality. Expectant mothers with hypertension are predisposed to the development of potentially lethal complications. While the goal of treatment is to reduce maternal risk, the agents selected must be efficacious and safe for the

foetus. There are very few antihypertensive agents that fit into these requirements.

Due to the complexity of the disease, it poses various challenges to the clinician right from diagnosis to the choice of treatment that is most appropriate for the patient. Therefore, the present study was

carried out to assess various objectives like the prevalence of hypertensive disorders during pregnancy, the prescribing pattern to treat these conditions and to monitor adverse drug reactions of antihypertensive drugs used in pregnancy.

Table 5: Treatment of Hypertensive Disorders during Pregnancy in the Study Population

Treatment	Gestational Hypertension n (%)	Chronic Hypertension n (%)	Pre-Eclampsia/ Eclampsia n (%)
Methyldopa + Nifedipine	14 (14.1)	5 (38.5)	5 (12.5)
Nifedipine	42 (42.4)	-	9 (22.5)
Methyldopa	13 (13.1)	2 (15.4)	3 (7.5)
Methyldopa + Nifedipine + Atenolol	2 (2.0)	-	-
Nifedipine + Atenolol	1 (1.0)	1 (7.7)	-
MgSO₄ + Nifedipine	-	1 (7.7)	7 (17.5)
MgSO₄ + Nifedipine + Methyldopa	-	-	10 (25)
MgSO₄ + Nifedipine + Atenolol + Furosemide	-	1 (7.7)	7 (17.5)
Nifedipine + Atenolol + Furosemide	-	-	1(2.5)
Nifedipine + Methyldopa + Furosemide	-	1 (7.7)	-

*n=no.of patients

N=Total number of patients (Gestational Hypertension = 99; Chronic Hypertension = 13; Pre-eclampsia/eclampsia = 40)

It was observed during the study that the prevalence of hypertensive disorders of pregnancy was 12.2%, which is slightly higher than the earlier reported studies of 5-10% [10]. Among the patients suffering from Gestational Hypertension, 70.8% of the patients were in the age group of 20-29yrs posing a higher risk to fetus. Most of the patients were housewives and their educational status was about grade 2, stating that they would be unaware of the potential complications that can occur due to elevated blood pressure. This fact accounts for the huge responsibility on physician to rightly prescribe the medication and prevent any damage to mother and fetus [11].

History of hypertension in the family of the patients played an important role in the prevalence of hypertensive disorders of pregnancy. The relationship was found to be more in case of Chronic Hypertension [12]. Family histories of hypertension were

positive in 28.3% of the patients in Gestational Hypertension, 27.5% in Preeclampsia/Eclampsia and 84.7% in Chronic Hypertension. It was observed that, patients who had suffered from hypertensive disorders during their previous pregnancies had more chances of developing Chronic Hypertension in their subsequent pregnancies. This was supported by the fact that 30.8% of patients with Chronic Hypertension had a history of Gestational Hypertension during their previous pregnancies, whereas only 4% of the patients with Gestational Hypertension and 5% of the patients with Pre-eclampsia/Eclampsia had a positive history during previous pregnancies and 2.5 % of the patients had a history of Gestational hypertension in their families. It was also observed that 5% of the patients with Gestational Hypertension were conceived by infertility treatment.

The study revealed that the possibility of the patient having Gestational Hypertension & Pre-eclampsia/Eclampsia during pregnancy does not have any relation with the number of earlier pregnancies [13]. It was also observed that among the patients 33% of the patients suffering from Gestational Hypertension, 30.8% from Chronic Hypertension and 30% from Pre-eclampsia/Eclampsia had a history of miscarriage in their previous pregnancies. Pregnancy induced hypertensive disorders have been one of the causes of preterm deliveries (<37 wks of gestational age) and intra uterine growth retardation (IUGR) [14]. In line with these observations reported in the earlier studies, it was observed that 30% of the patients were suffering from Gestational Hypertension, 61.1% of the patients suffering were from Pre-eclampsia/Eclampsia and 20% of patients were suffering from Chronic Hypertension had pre-term deliveries. Also, 36.8% of patients suffering from Gestational Hypertension and 55.6% of patients suffering from Pre-eclampsia/Eclampsia had to undergo cesarean section because of the complications due to hypertensive disorders of pregnancy. The present observation reveals that preterm deliveries were more with patients suffering from Pre-eclampsia/Eclampsia.

The basis of classification was according to *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VIII)* and results demonstrated that, 4% of the patients belonged to the group of Pre-hypertension. Under Stage-1 hypertension, 62% of the patients had Gestational Hypertension, 37.5% of the patients had Pre-eclampsia/Eclampsia and 30.8% had Chronic Hypertension. Under Stage-2 hypertension, 33.3% of patients had Gestational Hypertension, 62.5% of the patients had Pre-eclampsia/Eclampsia and 69.2% had Chronic Hypertension. All the patients suffering from the above mentioned conditions required treatment with antihypertensive drugs to achieve their target blood pressure.

Analysis of the antihypertensive drugs used in the treatment of various types of

hypertensive disorders during pregnancy revealed that, in Gestational Hypertension 55.5% of the patients were treated with a single antihypertensive agent. Nifedipine and Methyldopa were the drugs used in monotherapy. Among these drugs, Nifedipine was widely used (42.4%). In combination therapy, it was observed that Nifedipine remained a common drug in all the stages and was used in combination with other antihypertensive agents like Methyldopa, MgSO₄ and Atenolol. Among the combinations used, Nifedipine with Methyldopa was used in maximum number of patients (14.1%).

Among the patients with Pre-hypertension (4%), 2% of the patients were treated with Methyldopa, 1% with Nifedipine and 1% of the patients with the combinations of Methyldopa and Nifedipine. As per the JNC VIII guidelines, patients with Pre-hypertension need to be treated only with lifestyle modifications. However, considering the maternal and foetal well being, treatment with antihypertensive drugs may be imperative in a pregnant woman [15].

Treatment of the patients with Stage-1 hypertension (40.3%) was done with Nifedipine (25.3%), Methyldopa (9%), combination of Methyldopa and Nifedipine (5%) and combination of Atenolol and Nifedipine (1%). The results show that, 34.3% of the patients were treated with a single antihypertensive agent while 6% of the patients required combination therapy. As per the JNC VII guidelines Stage-1 hypertension needs to be treated only with monotherapy. However, considering the maternal and foetal wellbeing, combinations of antihypertensive drugs were required to be used. Even in Stage-2 hypertension, Nifedipine remained the drug of choice, which was used in 25.3% of patients.

The patients (30.2%) with Stage-2 hypertension, were treated with Nifedipine (15.2%), Methyldopa (4%), combination of Methyldopa and Nifedipine (7%), combination of Methyldopa, Nifedipine and Atenolol (3%) and MgSO₄ and Nifedipine (1%). The results reveal that 19.2% of the patients were given monotherapy and 11%

of the patients required combination therapy.

In patients with Stage-1 hypertension (35%) in the group of Pre-eclampsia/Eclampsia, 10% were treated with Nifedipine, 5% with Methyldopa, 7.5% were treated with the combination of Nifedipine and MgSO₄, 7.5% of the patients were treated with combination of Nifedipine, Methyldopa and MgSO₄. 2.5% with Nifedipine, MgSO₄, Atenolol and Furosemide and 2.5% with Nifedipine, Atenolol and Furosemide. The results reveal that 15% of the patients were treated with monotherapy and 20% of the patients needed combination therapy.

Treatment in this group of hypertensive disorders during pregnancy included a combination of more than two drugs in 12.5% of patients. MgSO₄ was used in 17.5% of the patients. It is observed that the use of MgSO₄ is essential to prevent the occurrence of seizures in the patients suffering from Pre-eclampsia and also to lower acutely elevated mean arterial BP by approximately 25% over hours without causing maternal hypotension or non-reassuring fetal heart rate that would precipitate Caesarean section [1].

Similarly, patients with Stage-2 hypertension (42.5%) in the group of Pre-eclampsia/Eclampsia were treated with Nifedipine and MgSO₄ (15%). Nifedipine alone was used in 12.5% and combination of MgSO₄, Nifedipine and Methyldopa in 12.5% and Methyldopa alone in 2.5%. Patients (23.1%) with Stage-1 hypertension in the group of Chronic Hypertension were treated with Methyldopa (7.7%), Methyldopa and Nifedipine (7.7%) and Nifedipine and Atenolol (7.7%). 7.7% of the patients received monotherapy whereas, 15.4% of the patients were treated with combination of antihypertensive drugs.

Patients (53.9%) with Stage-2 hypertension in the group of chronic hypertension were treated with Methyldopa, Nifedipine, MgSO₄ and Furosemide. 7.7% of the patients received monotherapy with Methyldopa alone, 30.8% of the patients were treated with Methyldopa and Nifedipine, & 7.7% of the patients were treated with Methyldopa, Nifedipine and MgSO₄ and 7.7% of the patients were

treated with Methyldopa, Nifedipine and Furosemide.

CONCLUSION

Looking at the findings of study it can be stated that hypertensive disorders during pregnancy are becoming very common in the present world and lack of knowledge of this fact can lead to high mortality rates of mother and fetus. Thus prompt treatment and prevention of complications can be the corner stone to achieve better health outcomes. In our study it was found that the most commonly prescribed medicines to treat the hypertensive disorders during pregnancy were, Nifedipine, Methyldopa, MgSO₄, Atenolol, Furosemide and their combinations. The treatment given was comparable with various international standard treatment guidelines such as JNC VIII, Australian Society for the Study of Hypertension in Pregnancy etc. and was found to be appropriate.

REFERENCES

1. Magee LA, Dadelszen PV; Treatment of Hypertension in Pregnancy, *Can J Clin Pharmacol*, 2004; 11(2):e199-e201.
2. Magee LA, Ornstein MP, Dadelszen PV, Management of hypertension in pregnancy. *BMJ* 1999;318:1332-1336.
3. Duckett RA, Kenny L, Baker PN; Hypertension in pregnancy. *Current Obstetrics and Gynecology* (2001)II, 7-14.
4. Soydemir F, Kenny L; Hypertension in pregnancy ; www.sciencedirect.com; Available online 7 November 2006.
5. Al-Ghamdi SMG, Al-Harbi AS, Khalil. A, El-Yahya AR Hypertensive Disorders of Pregnancy: Prevalence, Classification and Adverse Outcomes in NorthWestern Saudi Arabia. *Annals of Saudi Medicine*: 1999;19(6): 557-560.
6. Moser M, Working Group Report on High Blood Pressure in Pregnancy *J Clin Hypertens* 3(2):75-88, 2001.
7. Ben Ami M, Giladi Y, Shalev E. The combination of magnesium sulphate and nifedipine: a cause of neuromuscular blockade. *Br J Obstet Gynaecol* 1994; 101(3):262-263.
8. Snyder SW, Cardwell MS. Neuromuscular Blockade with Magnesium-Sulfate and Nifedipine. *American Journal of Obstetrics and Gynecology* 1989; 161(1):35-36.
9. Rey E, LeLorier J, Burgess E, Lange IR, Leduc L. Report of the Canadian Hypertension Society Consensus Conference:3. Pharmacologic treatment of hypertensive

- disorders in pregnancy. CMAJ 1997; 157(9): 1245-1254.
10. Reif MC, Managing Hypertension during Pregnancy. Women's health in primary care: 2003;4(6) 194-200.
 11. Al-Ghamdi SMG, Al-Harbi AS, Khalil. A, El-Yahya AR Hypertensive Disorders of Pregnancy: Prevalence, Classification and Adverse Outcomes in NorthWestern Saudi Arabia. Annals of Saudi Medicine: 1999;19(6): 557-560.
 12. Vigil-De GP, Lasso M, Ruiz E, Vega-Malek JC, de Mena FT, López JC;et al Severe hypertension in pregnancy: hydralazine or labetalol. A randomized clinical trial. PMID: 16621226 Eur J Obstet Gynecol Reprod Biol. 2006 Sep-Oct;128(1-2):157-62.
 13. Sahin G, Incidence, morbidity and mortality of pre-eclampsia and eclampsia; review prepared for the 12th Post graduate course in reproductive medicine and biology, Geneva, Switzerland;2003
 14. Carr DB, Gavrila D, Brateng D, Easterling TR. Maternal hemodynamic changes associated with furosemide treatment. Hypertens Pregnancy. Pubmed: 2007;26(2):173-8.
 15. Cifkova R. Hypertension in pregnancy: Recommendations for diagnosis and treatment. ESH Scientific Newsletter : Update on Hypertension Management: 2004(5):2.