



(RESEARCH ARTICLE)



Study to analyse prescription pattern of antihypertensive drugs used in preeclampsia patients at a secondary care hospital: A Prospective observational study

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Abstract

Hypertension is one of the common medical complications of pregnancy and contributes significantly to maternal and perinatal morbidity and mortality. Once the hypertension is diagnosed starting with antihypertensive therapy help to manage the outcomes of pregnancy, for both mother and baby. The main objective of the study is to assess prescribing patterns of antihypertensive drugs in pregnant women. It was a prospective observational study that was conducted for 4 months from November 2021 to February 2022. A total of 120 prescriptions were analyzed. Through the current study, we could assess the utilization of antihypertensive drugs in pregnant women. The study reveals that most of the patients having PIH were from Primi gravida in the age group 25-28 years old. The study also shows that Labetalol an alpha-beta blocker is mostly prescribed as monotherapy followed by Nifedipine a calcium channel blocker, or a combination of Labetalol with Nifedipine. Also according to the study, 12% of patients showed co-morbidities and the other 88% were without co-morbidities. Other than antihypertensive prescribed to maximum patients were a combination of several supplements that are protein powders, iron-calcium supplements (Protex powder, Anaport powder, LG-9 sachet, bio folate, calcium supplements, Hbcare, cc250, RG-9 sachet). The current study assessed that most of the patients showed mild to moderate preeclampsia that is blood pressure between 140-160 mmHg. It will help the prescriber to pay more attention to the outcomes of B.P. during pregnancy. If PIH can be treated rationally the complication of pregnancy that affect the mother and baby can be overcome and there would be a significant reduction in maternal and perinatal morbidity and mortality.

Keywords: PIH; Preeclampsia; Antihypertensive drugs; Perinatal morbidity and mortality; Gravida; Supplementary therapy; Combination therapy

1. Introduction

The principle aim of prescription pattern analysis is to facilitate the rational use of drugs in the population. For individual patients use of rational use of drugs implies the prescription of the well-documented drug at an optimal dose, with correct information and also affordable price.

Prescription pattern analysis also provides insight into the efficacy of drug use, i.e. whether certain drug therapy provides value for money and the result of such research can be used to help to set priorities for the ration allocation of health care budgets.

High Blood pressure is defined as systolic blood pressure (BP) \geq 140mmhg/diastolic pressure \geq 90mmhg. The diastolic pressure represents the pressure during the ventricular relaxation in the diastolic and the systolic pressure represents

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the peak pressure due to ventricular contraction during systole. Either or both have specified upper limits of normal and elevated pressure and are used to define hypertension. According to Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure JNC 8th report (2004) hypertension is defined and classified as:

Table 1 Blood pressure category in adults

Blood Pressure categories in Adult		
Category	Systolic (mmHg)	Diastolic (mmHg)
Normal	<140	<80
Elevated	140-159	<80
Hypertension		
Stage 1	130-129	Or 80-89
Stage 2	≥ 140	Or ≥90

1.1. Hypertension is one of the common medical complications of pregnancy and contributes significantly to maternal and perinatal morbidity and mortality [1].

Hypertension is a sign of an underlying pathology, which may be pre-existing or appears for the first time during pregnancy. The identification of this clinical entity and effective management plays a significant role in the outcome of pregnancy, both for the mother and the baby. In developing countries, with inadequately cared for pregnancies, this entity on many occasions remains undetected till major complications supervene. Hypertension during pregnancy is defined as a diastolic blood pressure of 90 mmHg or greater on two occasions more than 4 hours apart or a single diastolic blood pressure above 110 mmHg. Hypertensive disorders during pregnancy occur in women with pre-existing primary or secondary chronic hypertension, and in women who develop new-onset hypertension in the second half of pregnancy. [2]

1.1.1. Chronic hypertension

- Hypertension is defined as elevation either of systolic BP to 140 mm Hg or higher or of diastolic BP to 90 mm Hg or higher.
- Chronic hypertension is defined as hypertension diagnosed before pregnancy or before 20 weeks gestation or elevated BP that is first diagnosed during pregnancy and persists after 42 days postpartum.

1.1.2. Preeclampsia

Preeclampsia is defined as elevated BP and proteinuria after 20 weeks gestation (except in the presence of trophoblastic disease or multiple gestations, in which cases preeclampsia may appear before 20 weeks gestation).

1.1.3. Eclampsia

Eclampsia is a convulsive condition associated with pre-eclampsia.

Table 2 Classification of hypertension in pregnancy (NHBPEP 2000 and ACOG-2013)

Disorder	Definition
Hypertension	BP>140/90 mm Hg or =140/90 mm Hg measured two times with at least 6 hour interval.
Proteinuria	Urinary excretion of > 0.3g protein/24 hour specimen or 0.1g/L.
Gestational Hypertension	BP >140/90 mm Hg or =140/90 mm Hg for the first time in pregnancy after 20 weeks, without proteinuria.
Preeclampsia	Gestational hypertension with proteinuria.
Eclampsia	Women with preeclampsia complicated with grandmal seizures and or coma.
HELLP syndrome	Hemolysis(H), Elevated liver enzymes (EL) and Low platelet count (LP).
Chronic Hypertension	Known hypertension before pregnancy or hypertension diagnosed first time before 20 weeks of pregnancy.
Superimposed preeclampsia or eclampsia.	Occurrence of new onset of proteinuria in women with chronic hypertension.
Chronic hypertension with superimposed preeclampsia and eclampsia.	The common causes of chronic hypertension- Essential hypertension Chronic renal disease(renovascular). Coarctation of aorta. Endocrine disorders (diabetes mellitus, pheochromocytoma and thyrotoxicosis.) Connective tissue disease (Lupus erythematosus). The criteria for diagnosis of super imposed preeclampsia- New onset of proteinuria>0.5g/24 hours of specimen. Aggravation of hypertension. Development of HELLP syndrome. Development of headache scotoma and epigastric pain.

1.2. Preeclampsia

1.2.1. Definition

Preeclampsia is a multisystem disorder of unknown etiology which is characterized by the development of hypertension to the extent of 140/90 mm Hg or more with proteinuria after the 20th week in a previously normotensive and non-protein uric woman. Some amount of edema is common in a normal pregnancy. Edema has been excluded from the diagnostic criteria unless it is pathological.

The preeclamptic features may appear even before the 20th week as in cases of hydatid form mole and acute polyhydramnios.

The term, "Pregnancy-induced hypertension (PIH)" is defined as hypertension that develops as a direct result of the gravid state. It includes

- gestational hypertension
- preeclampsia, and
- Eclampsia.

Mild preeclampsia

The following criteria must be met to confirm the diagnosis of mild preeclampsia:

- BP of 140/90 mm Hg or higher after 20 weeks gestation, measured on two occasions at least 6 hours apart.

- Proteinuria greater than 300 mg in a 24-hour urine collection or a score of 1+ on a random urine dipstick test.
- Edema frequently accompanies preeclampsia but is not required for diagnosis.
- Edema must be generalized for association with preeclampsia; dependent edema (e.g., low back, legs) is not sufficient.
- Fluid retention is evidenced by rapid weight gain (more than 5 lb in 1 week).^[3]

Severe preeclampsia

The following criteria are used to confirm the diagnosis of severe preeclampsia:

- BP during bed rest of 160 mm Hg systolic or 110 mm Hg diastolic, measured on two occasions at least 6 hours apart
- Proteinuria greater than 5 g in a 24-hour collection or a score of 3+ to 4+ on random urine dipstick test
- Oliguria, indicated by a 24-hour urine output of less than 400 mL or serum creatinine level higher than 1.2 mg/dl (unless known to be higher previously)
- Cerebral or visual disturbances, including altered consciousness, headache, scotomata, blurred vision, or some combination of these
- Pulmonary edema or cyanosis
- Epigastric or right upper quadrant pain
- Impaired liver function without a known cause, indicated by elevated AST level of 70 U/L or higher
- Thrombocytopenia, indicated by a platelet count lower than 100,000/mm³, or evidence of microangiopathic haemolytic anaemia, such as abnormal
- Findings on peripheral smear, increased bilirubin level (1.2 mg/dl. or higher), or elevated lactate dehydrogenase (LDH) level (600 U/L or higher).

Risk Factors in pre-eclampsia:

- **Primi gravida:** Young or elderly (first-time exposure to chorionic villi)
- **Family history:** Hypertension, preeclampsia
- **Placental abnormalities:**
- **Hyperplacentosis:** Excessive exposure to chorionic villi— (molar pregnancy twins, diabetes)
- **Placental ischemia.**
- **Obesity:** BMI >35 kg/m², Insulin resistance.
- **Pre-existing vascular disease.**
- **New paternity**
- **Thrombophilia's** [antiphospholipid syndrome, protein C, S deficiency, Factor V Leiden

Table 3 Risk factors of preeclampsia ^[4]

Pre-existing hypertension	Diabetes
Genetic factors	Paternal-specific antigens
Nulliparity	Fetal factors from donor eggs
Multiple gestations	Black race
Molar pregnancies	Increased testosterone
Older maternal age	Increased blood homocysteine
Obesity	Concentration

1.3. Medication to treat hypertension in pregnancy ^[5]

1.3.1. Centrally acting alpha-2 adrenergic agonist

Methyldopa is a centrally-acting alpha-2 agonist used in pregnancy. Methyldopa has a long history of use in pregnancy and does not appear teratogenic, it's safe as it does not impair uteroplacental circulation and consequent fetal growth. The dose of methyldopa is similar to that of the non-pregnant patient.

Clonidine is also an alpha-2 centrally acting drug having similar safety and efficacy as methyldopa and is used as a third-line agent in the control of hypertension. But according to the FDA methyldopa is a class B drug and clonidine is a class C drug. According to World Health Organization/Thomson, lactating rating methyldopa is usually more compatible with breast milk as clonidine has possible breast milk effects.

1.3.2. Peripherally acting adrenergic-receptor antagonist

Labetalol is a non-selective beta-blocking agent with vascular alpha-1 receptor blocking. The patient having fetal growth restriction and low placental weight is usually given atenolol during the second trimester, but not with a beta-blocking agent such as labetalol which is for the treatment of acute hypertension during pregnancy and has slower equivalent efficacy and better tolerability compared to hydralazine.

1.3.3. Calcium channel blocker

Oral nifedipine and verapamil are frequently seen as second-line agents used for the treatment of hypertension in pregnancy. The calcium channel blocker does not appear to be teratogenic. According to the FDA nifedipine and verapamil are class C drugs that are usually compatible with breast milk.

1.3.4. Direct Vasodilators

Hydralazine is now predominantly used intravenously for the treatment of severe hypertension in pregnancy. It does not appear teratogenic but there have been a report of neonatal thrombopenia, rare cases of pyridoxine-responsive polyneuropathy with chronic use, and drug-induced lupus. However, labetalol or oral nifedipine is preferable as first-line agents as compared to intravenous hydralazine which is a class C drug according to FDA and is compatible with breast milk. Sodium nitroprusside is rarely used in pregnancy and is reserved for life-threatening hypertension.

1.3.5. Diuretics

Diuretic therapy remains controversial, primarily due to theoretical concerns about reduced plasma volume. Thiazide are class B drugs according to FDA. They may cause volume contraction and electrolyte abnormalities but are rare with small doses. A diuretic may reduce milk production. Spironolactone is not recommended due to potential fetal antiandrogen effects.

1.3.6. Renin-angiotensin system drugs

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) are contraindicated in pregnancy due to their association with adverse fetal effects. ACE inhibitors are labeled as FDA class C drugs for the first trimester of pregnancy and class D for the third trimester.

2. Material and methods

The study was conducted according to the ICH GCP guidelines the main aim was to determine the most commonly used antihypertensive agents in preeclampsia with their dose, frequency, and route. Also, evaluate the type of drug therapy (monotherapy/combination therapy) and find out the average number of drugs per prescription.

2.1. Study Duration

This study estimates a total duration of 3 months.

2.2. Study Population

The total enrolment of patients is estimated to be 120.

2.3. Study design

It was a prospective observational study.

2.4. Study criteria

Pregnant women were enrolled in the study by considering the following criteria:

2.5. Inclusion criteria

- Pregnant women diagnosed with preeclampsia with or without comorbidities
- Pregnant women with a history of preeclampsia with or without comorbidities.
- Pregnant women above the age of 18 years.

2.6. Exclusion criteria

- Pregnant women having age below 18 years.

2.7. Source of data

Pregnant women visiting the Obstetrics and Gynecology Department of SDA Diamond Hospital and MRC, Surat.

2.8. Ethical Clearance

The study protocol was submitted to the Shree Dhanvantary Pharmacy College ethics committee on human subject research and applied for clearance. The study is approved by the institutional ethics committee and issued an ethical clearance certificate.

2.9. Study materials

The following study materials were prepared and used during the study period.

2.10. Patient data collection form

A suitably designed data collection form was prepared in consultation with the physician and clinical pharmacist, also referring to standard textbooks and journals, which include information on patient details such as age, weight, gravida, BP, comorbidities, and prescribing patterns of antihypertensive drugs. Type of therapy, mode of therapy, category of the drugs used in the treatment of hypertension in pregnancy.

2.11. Prescribing pattern analysis

Prescriptions of pregnant women containing at least one drug were analyzed and the drugs prescribed were classified according to their pharmacological class. The pregnant women were divided according to their Gravida, age, and BP, and the prescriptions were analyzed for different classes of drugs.

3. Results

Table 4 No. of pt. v/s age ;(n=120)

Age	No of patient	%
20-22	8	6.67%
22-25	28	23.4%
25-28	34	28.4%
28-31	26	21.7%
31-34	13	10.8%
34-37	10	8.34%
37-40	1	0.83%

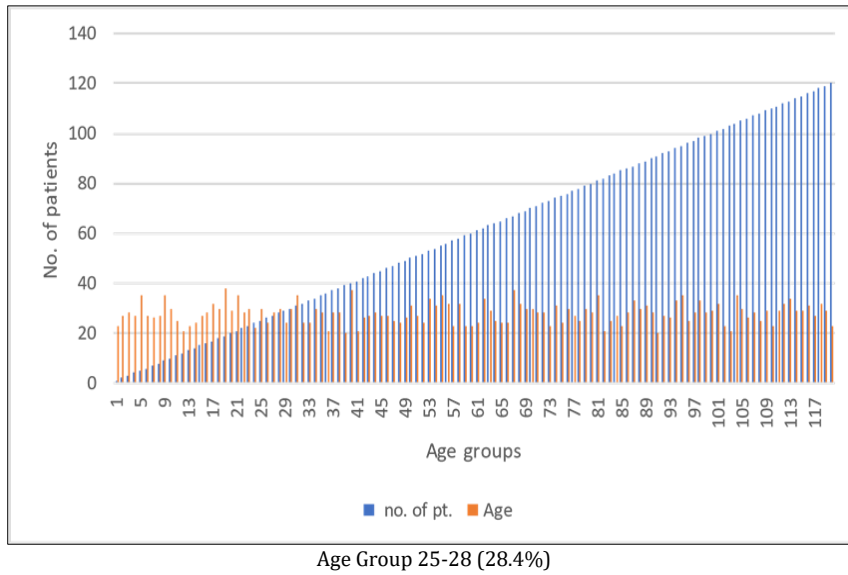


Figure 1 No. of pt. v/s age ;(n=120)

According to the study maximum, pregnancy-induced hypertension cases were seen in Age Group 25-28 (28.4%).

Table 5 No. of patient v/s comorbidities

Comorbidities	% of the patient has comorbidities
No comorbidities	88%
Comorbidities	12%

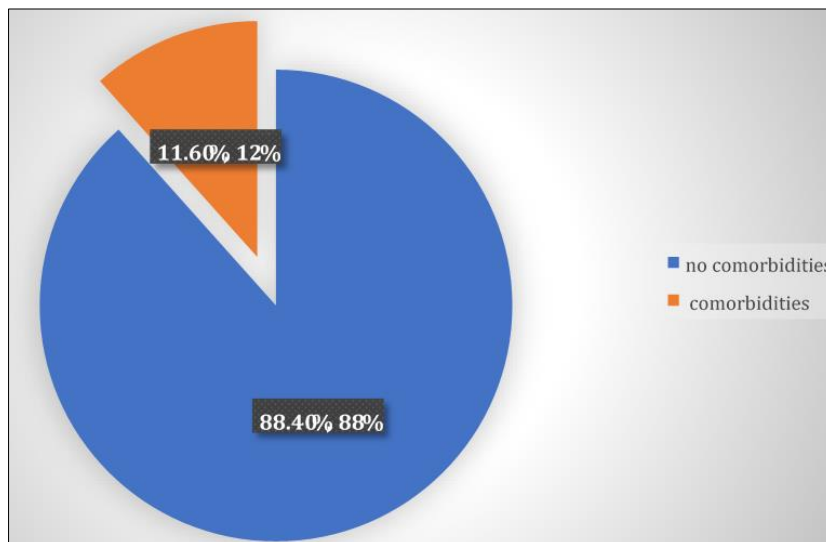


Figure 2 No. of patient v/s comorbidities

The study reveals that 12% of females were found to have PIH with comorbidities other 88% of females had PIH without comorbidities.

Table 6 Types of comorbidities observed in study

Comorbidities	No of patient	% of patient
Diabetes Mellitus	8	6.67%
Hypothyroidism	5	4.17%

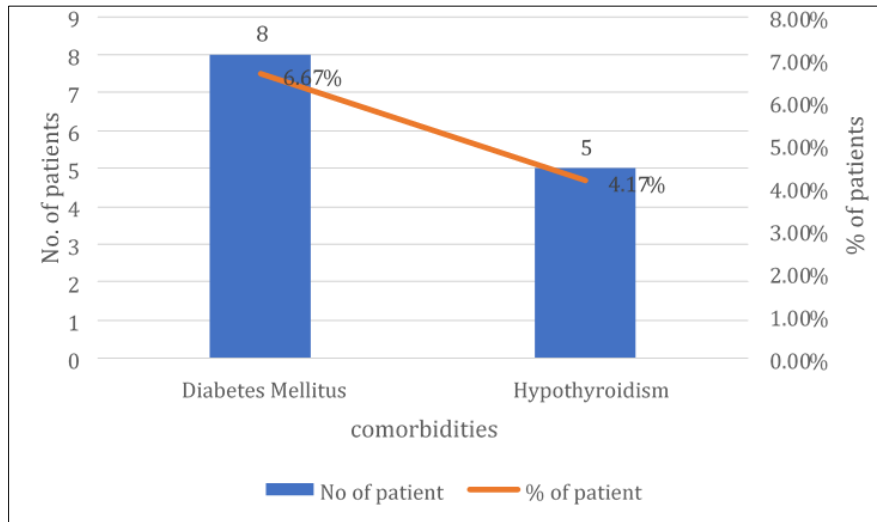


Figure 3 No. of patient v/s % types of comorbidities

Among 12% having comorbidities 61.50% of patients had diabetes mellitus (gestational diabetes) and 38.46% patients had hypothyroidism.

3.1.1. Gravida

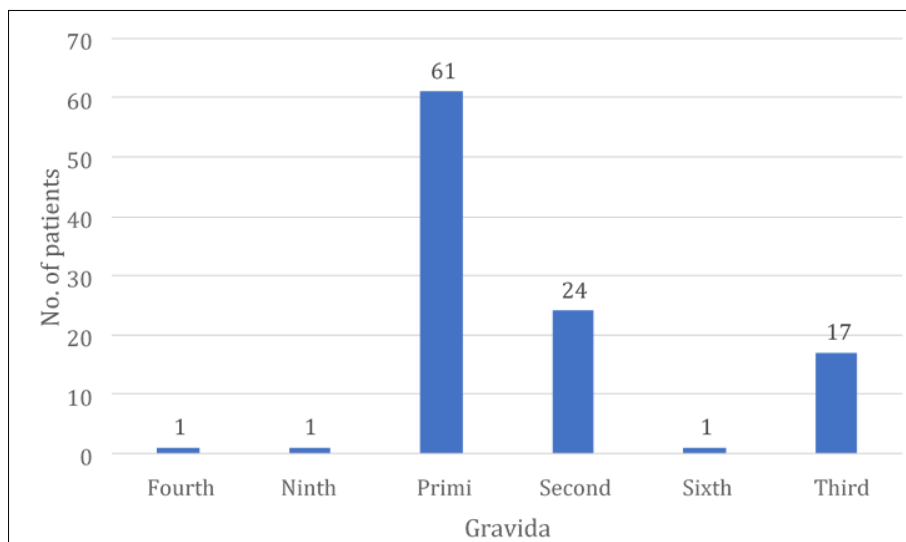


Figure 4 No. of patients v/s Gravida

According to the study maximum, PIH cases were seen in Primi gravida (50.8%) which is the first pregnancy.

3.1.2. Other than antihypertensive

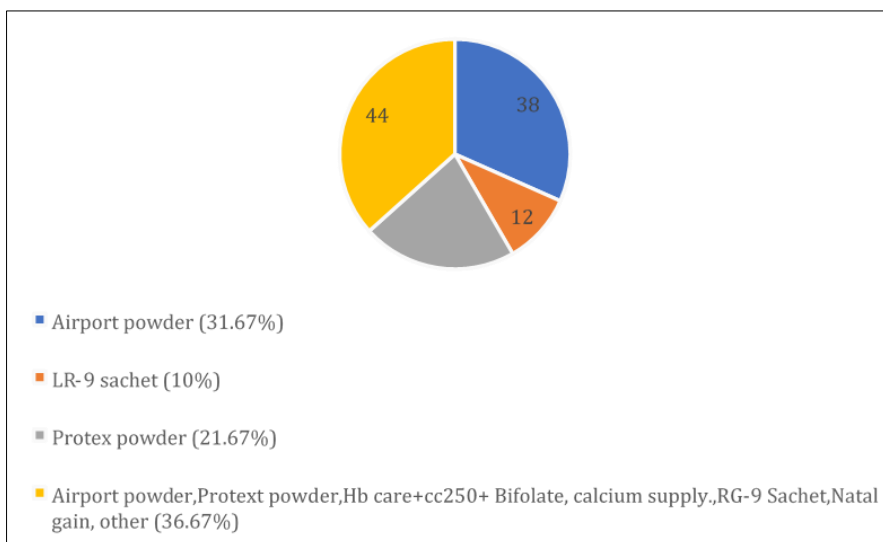


Figure 5 Other than antihypertensives

Study reveals that supplements such as Anaport powder (31.67%), LR-9 Sachet (10%), Protex powder (21.67%), and more than one supplement (36.67%). In maximum PIH patients, more than one supplement (other than antihypertensive) was preferred.

3.1.3. Type of therapy

Table 7 Type of therapy

Therapy	No. of patients
Combination (5.83%)	7
Monotherapy (94.2%)	113

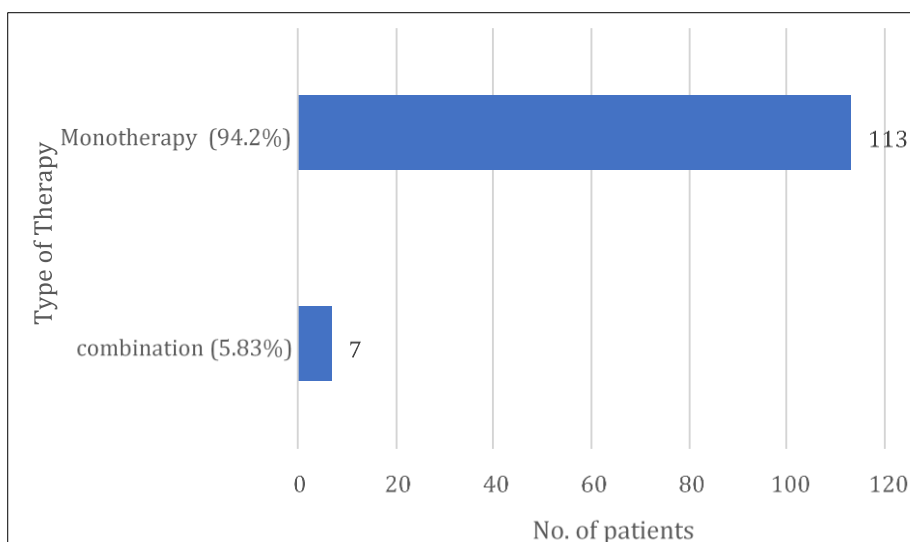


Figure 6 No. of patients v/s type of therapy

The study says that (94.2%) of PIH patients were prescribed monotherapy therapy and only (5.83%) were prescribed combination therapy.

3.1.4. Class of antihypertensive ;(n=120)

Table 8 Types of antihypertensive drugs.

Class of drug	Name of drug	No. of drugs	% of drugs
Alpha-beta blocker	Labetalol	91	75.8
Calcium channel blocker	Nifedipine	21	17.5
Angiotensin receptor Blocker	Telmisartan	2	1.67
CCB+ Alpha-Beta Blocker	Nifedipine +Labetalol	6	5

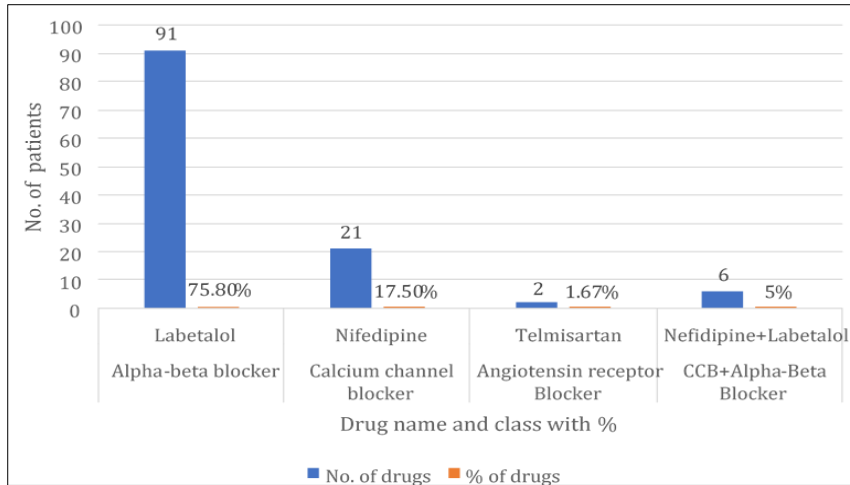


Figure 7 No. of patients v/s no. and % of drugs

The study says that the maximum drug prescribed was from the alpha-beta blocker class (Labetalol 75.8%). Other drugs were calcium channel blockers (Nifedipine – 17.5%), combination (Labetalol+Nifedipine-5%), and ARB (Telmisartan-1.67%).

3.1.5. Stages of preeclampsia

Table 9 Stage-wise classification of preeclampsia

Stages Of preeclampsia	B.P
Stage-1 mild (130-140 mmhg) (59.2%)	71
Stage-2 moderate (140-160 mmhg) (25.8%)	31
Sever (≥ 160) (15%)	18

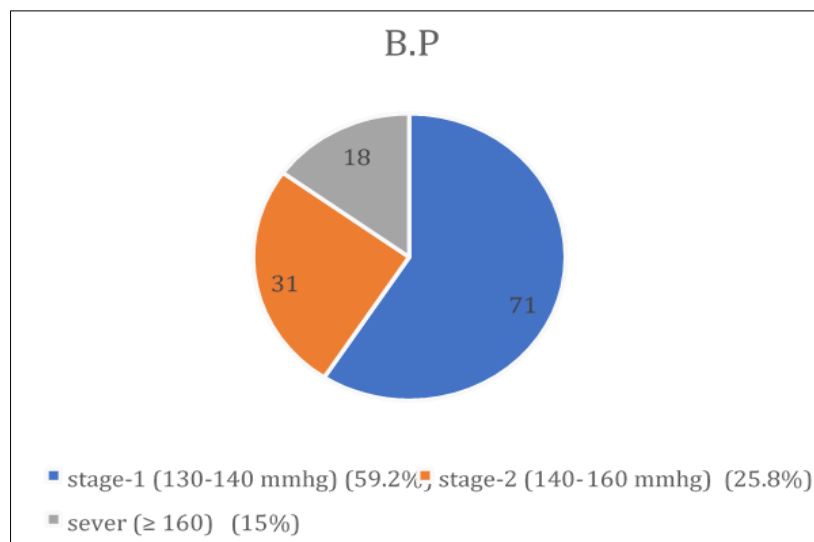


Figure 8 Stages of Preeclampsia

According to the study, 59.2% of patients had mild preeclampsia (stage-1 1130-140 mmHg), 25.8% had moderate (stage-2 140-160 mmHg), and 15% had severe (≥ 160 mmHg).

4. Discussion

Hypertension in pregnancy is considered to be a major worldwide health problem leading to an increased risk of perinatal and maternal mortality^[6]. Preeclampsia is more frequent in patients under 21 years of age than in older than 35 years.⁽⁹⁾ In our study 96 (80%) patient lies in the age group 20-30 and 24 (20%) patients lie above the 30 age group. The main antihypertensive given to the patient was Labetalol 75.8% (Alpha-beta blocker), followed by Nifedipine 17.5% (Calcium channel blocker), Telmisartan 1.67% (ARBs), a combination of Labetalol +Nifedipine (CCB + Alpha-beta blocker). In our study, only 12% of PIH patients had comorbidities other 88% were with no comorbidities.

There is an increased chance of in young Primi gravida under 20 years and all over 30 years.⁽¹⁰⁾ According to our study maximum PIH cases were seen in Primi gravida 50.8%.

Our study was performed among 120 patients where the most commonly prescribed drug was from class Alpha-Beta Blocker that is Labetalol as monotherapy. The second common drug was from the class calcium channel Blocker which is Nifedipine, followed by the rare was from class ARBs which is Telmisartan. Sometimes the combination of CCB and Alpha-Beta blocker was also given that is Labetalol + Nifedipine.

Other than antihypertensive was also prescribed that is supplemental therapy is required in pregnancy. In our study maximum number of patients that is 36.67% patient more than one supplement preferred (that is Anaport powder+ Protex powder + LR 9 -sachets + RG 9sachet + HB care + CC250 + calcium supplements + Bifolate), followed by Anaport powder in 31.67% pt., Protex powder in 21.67% pt., and LG-9 sachets in 10% pt.

Similarly, in a study done by IJBCP (international journal of basics and clinical pharmacology) the most commonly used drug was Labetalol given to 75 patients followed by Methyldopa given to 42 patients followed by other drugs like nifedipine, and amlodipine. 33.33% of patients belonging to the second gravida constitute the majority of patients i.e. 50 patients while 30% belong to the third gravida. Also, most of the patients were of the moderate and mild type corresponding to 48% and 32% respectively and only 20% of patients belong to severe cases.⁽¹¹⁾

5. Conclusion

Hypertension in pregnancy has become one of the major alarming situations in a pregnant women's life. Our study concluded that Labetalol was most commonly prescribed for preeclampsia in secondary care hospitals due to its benefits followed by Nifedipine, Telmisartan, or a combination of Labetalol + Nifedipine. To conclude our study gave an overall idea regarding prescribing pattern of antihypertensive during pregnancy and we should focus on ratio drug prescribing, in our study most of the PIH patient (59.2%) belongs to stage-1 that is mild preeclampsia having B.P

between 130-140 mmHg. A similar study should be done to promote the rational prescribing pattern which will ultimately reduce the chances of further complications of PIH in pregnant women and lead to healthy mothers and reduce the infant mortality rate.

Abbreviations

ACEI	Angiotensin Converting Enzyme Inhibitors
ARB	Angiotensin Receptors Blockers
BP	Blood Pressure
CCB	Calcium channel Blockers
CKD	Chronic Kidney Disease
PE	Pre-eclampsia
DM	Diabetes Mellitus
HTN	Hypertension
OPD	Out Patient Department
IPD	In patient department
SVR	Systemic vascular resistance
GFR	Glomerular filtration rate
IV	Intravenous
DBP	Diastolic blood pressure
SBP	Systolic blood pressure
JNC	Joint national committee
BUN	Blood urea nitrogen
Mg	Magnesium
MAP	Mean arterial pressure
Chr	Chronic
HDP	Hypertensive disorder of pregnancy
NHBPEP	National high blood pressure education programme
TOD	Target organ damage
ACOG	American college of gynaecology
DM	Diabetes mellitus

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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