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 the antihypertensive therapy help to manage the outcomes of pregnancy, for both mother and baby. The main objective of the study was to assess prescribing patterns of antihypertensive drugs in pregnant women. It was prospective observational study, which was conducted for 4 months from November 2021 to February 2022. A total 120 prescriptions were analysed. Through the current study, we could assess the utilization of antihypertensive drugs in pregnant women. The study reveals that most of the patients having preeclampsia were from primi gravida in 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 combination of Labetalol with Nifedipine. Also according to study 12% of patients, showed co morbidities and other 88% were without co morbidities. Other than antihypertensive prescribed to maximum patients were combination of several supplements that are protein powders, iron- calcium supplement (protex powder, Anaport powder, LG-9 sachet, bio folate, calcium supplements, hicare, 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 has provided the insight into the prescription pattern of drugs in pregnant women with respect to B.P control. It will help the prescriber to pay more attention on outcomes of B.P during pregnancy. If preeclampsia can be treated rationally, the complication of pregnancy that affect mother and baby can be overcome and there would be significant reduction in maternal and perinatal morbidity and mortality.

Keywords: Pregnancy induced Hypertension, Pre-eclampsia, Antihypertensives, Alpha+beta blocker, CCB

1. Introduction

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;140</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Elevated</td>
<td>140-159</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>130-129</td>
<td>Or ≥80-89</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥ 140</td>
<td>Or ≥90</td>
</tr>
</tbody>
</table>

2. Preeclampsia

Definition:
Preeclampsia is a multisystem disorder of unknown etiologic characterized by 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 anormal pregnancy. Edema has been excluded from the diagnostic criteria unless it is pathological. The preeclampsia 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 the
hypertension that develops as a direct result of the gravid state. It includes—(i) gestational hypertension, (ii) preeclampsia and (iii) Eclampsia.

**Medication to treat hypertension in pregnancy:**

**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 foetal growth. The dose of methyldopa is similar to that of non-pregnant patient.

Clonidine is also and alpha-2 centrally acting drug having similar safety and efficacy as methyldopa and used as a third line agent in control of hypertension. However, according to 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.

**Peripherally acting adrenergic-receptor antagonist:**
Labetalol a non-selective beta-blocking agent with vascular alpha-1 receptor blocking in patient having foetal growth restriction and low placental weight were usually given atenolol during second trimester, but not with 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.

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

**Direct Vasodilators:**
Hydralazine is now predominantly used intravenously for treatment of severe hypertension in pregnancy. It does not appear teratogenic but there have been report of neonatal thrombocypenia, rare cases of a pyridoxine-responsive polyneuropathy with chronic use, and drug induce lupus. However, labetalol or oral nifedipine are more preferable as first line agents as compared to intravenous hydralazine, which is 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.

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

**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 foetal effects. ACE inhibitors is labelled as FDA class C drugs for the first trimester of pregnancy and class D for third trimesters.

### 3. Methodology

The study was conducted according to the ICH GCP guidelines. The study was conducted once institute ethics committee granted the permission.

The study was designed as prospective observational. This is single site study, which was conducted in SDA diamond hospital, Surat. For patients who have been diagnosed with preeclampsia. The main aim was to determine the most commonly used antihypertensive agents in preeclampsia with its dose, frequency and route. Also, evaluated types of drug therapy (monotherapy/combination therapy) and to find out the average number of drugs per prescription. The number of patients in the study was 120. The primary criteria were the patient should have preeclampsia.

**Study Duration and Population:**
This study estimates a total duration of 3 months. The total enrolment of patients was 120.

**Study design and criteria:**
It was a prospective observational study. Pregnant women were enrolled into the study by considering the following criteria:

**Inclusion criteria:**
- Pregnant women diagnosed with preeclampsia with or without comorbidities
- Pregnant women with history of preeclampsia with or without comorbidities.
- Pregnant women above the age of 18 years.

**Exclusion criteria:**
- Pregnant women having age below 18 years.

**Source of data:** 26

**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 was approved by institutional ethics committee and issued ethical clearance certificate.

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

**Patient data collection form:**
Prescriptions of the pregnant women containing at least one drug were analysed and the drugs prescribed were classified according to their pharmacological class. The pregnant women were divided according to their Gravida, age, BP and the prescriptions were analysed for different classes of drugs.
4. Result

1) No. of patient v/s Age:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No of patient</th>
<th>% of patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-22</td>
<td>8</td>
<td>6.67%</td>
</tr>
<tr>
<td>22-25</td>
<td>28</td>
<td>23.4%</td>
</tr>
<tr>
<td>25-28</td>
<td>34</td>
<td>28.4%</td>
</tr>
<tr>
<td>28-31</td>
<td>26</td>
<td>21.7%</td>
</tr>
<tr>
<td>31-34</td>
<td>13</td>
<td>10.8%</td>
</tr>
<tr>
<td>34-37</td>
<td>10</td>
<td>8.34%</td>
</tr>
<tr>
<td>37-40</td>
<td>1</td>
<td>0.83%</td>
</tr>
</tbody>
</table>

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

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>
<thead>
<tr>
<th>Comorbidities</th>
<th>No. of patient</th>
<th>% of patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>8</td>
<td>6.67%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>5</td>
<td>4.17%</td>
</tr>
</tbody>
</table>

% of patient having comorbidities

- No comorbidities: 88%
- Comorbidities: 12%

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

3) Gravida

According to study maximum PIH cases were seen in primi gravida (50.8%) that is first pregnancy.

4) Other than antihypertensive

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

5) Type of therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination</td>
<td>7</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>113</td>
</tr>
</tbody>
</table>

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

6) Class of antihypertensive (n=120)
The study says that maximum drug prescribed was from alpha-beta blocker class (Labetalol -75.8 percentage). Other drugs were from calcium channel blocker (Nifedipine – 17.5%), combination (Labetalol+Nifedipine -5 percentage), and ARB (Telmisartan -1, 67%).

7) Stages of preeclampsia:

<table>
<thead>
<tr>
<th>Stages of preeclampsia</th>
<th>B.P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage-1 mild (130-140 mmHg) (59.2%)</td>
<td>71</td>
</tr>
<tr>
<td>Stage-2 moderate (140-160 mmHg) (23.8%)</td>
<td>31</td>
</tr>
<tr>
<td>Sever (≥ 160) (15%)</td>
<td>18</td>
</tr>
</tbody>
</table>

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

5. Discussion

Hypertension in pregnancy is considered a major worldwide health problem leading to an increased risk of perinatal and maternal mortality. Preeclampsia is more frequent in patients under 21 years of age than in older than 35 years. In our study 96 (80%) patient lies in age group, 20-30 and 24 (20%) patients lie above 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), Combination of Labetalol +Nifedipine (CCB + Alpha-beta blocker). In our study, only 12% of preeclampsia patient had comorbidities other 88% were with no comorbidities.

There is an increase chance of in young primi gravida under 20 years and all over 30 years. According to our study, maximum preeclampsia cases were seen in primi gravida 50.8%.

Our study was performed on 120 patients where most commonly prescribed drugs was labetalol (Alpha-Beta Blocker) as monotherapy. Second common drug was nifedipine (Calcium channel blocker) followed by combination of labetalol and nifedipine (CCB+ alpha beta-blocker) and rarely telmisartan (ARB). Other than antihypertensive were also prescribed that is supplemental therapy, which is required in pregnancy. In our study maximum number of patient that is 36.67% patient more than one supplements were preferred (that is Anaport powder+ Protex powder + LR 9 -sachets + RG 9sachet + HB care + CC250 + calcium supplements + Bifolates), followed by Anaport powder in 31.67% pt., Protex powder in 21.67% pt., and LG-9 sachets in 10% pts.

Similarly, in a study done by IJBCP (international journal of basics and clinical pharmacology) that most commonly used drug was Labetalol given to 75 patients followed by Methyldopa given to 42 patients followed by other drugs like nifedipine, amloidipine. 33.33% patients belonging to second gravida constitute the majority of patients i.e. 50 patients while 30%belong to third gravida. In addition, most of the patients were of moderate and mild type corresponding to 48% and 32% respectively and only 20% of patients belong to severe cases.
6. 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 in preeclampsia in secondary care hospital due to its benefits followed by Nifedipine, Telmisartan or combination of Labetalol + Nifedipine. To conclude our study gave an overall idea regarding prescribing pattern of antihypertensive during pregnancy and we should focus on ration 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. Similar study should be done to promote the rational prescribing pattern, which will ultimately reduce the chances of further complication of PIH in pregnant women, lead to healthy mother, and reduce infant mortality rate.

7. Summary

The study provides an insight to the drug utilization patterns of antihypertensive drugs in pregnant women with respect to the level of B.P control. It will help the prescribers to pay more attention to the specific factors that affect the B.P and also help prevent further complication related to hypertension in pregnant women and reduce infant mortality. In the study where 120 patients were employed, maximum preeclampsia cases were seen in age group 25-28 (28.4%). In Pregnancy, there are several comorbid condition to occur like DM, Hyperthyroidism, hypertension, kidney functional disturbances etc. The study also reveals that among 120 PIH patients only 12% seems to have comorbidities where other 88% patients were without comorbidities. In 12% of patients with comorbidities, maximum patients had DM (that is 6.67%) and remaining had hypothyroidism (that is 4.17%).

According to the study, maximum PIH cases were seen in primi gravida (first pregnancy) that is 50.8%. Study of drug utilization patterns include type of drug therapy, choice of drugs, also other drugs such as supplemental therapy etc. According to the study, performed maximum patients were on monotherapy 94.2% and only 5.83% patients were on combination therapy. The most common drug that was prescribed was labetalol (100mg OD) an alpha-beta blocker that is 75.80%, followed by Nifedipine (20mg OD) a calcium channel blocker that is 17.50%, and combination of labetalol + Nifedipine (CCB+ Alpha-beta blocker) that is 5%. Other than antihypertensive drugs that is supplemental therapy is must in pregnant women. Several supplements such as protein powders, calcium supplements, iron supplements are prescribed. According to our study maximum patient that is 36.67% were given raising patient trust in their physician may improve patient motivation to take prescribed medicines.

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