CHAPTER - IV

MATERIALS AND METHODS
The study group consists of 300 pregnant women with pregnancy induced hypertension, according to International Society for the Study of Hypertension in Pregnancy (ISSHP) and accomplice inclusion and exclusion criteria (Brown et al., 2001).

**Inclusion criteria**

All pregnant patients with diastolic blood pressure more than 90 mm of Hg on two occasions six hours apart after 20 weeks of gestation (Liu et al., 2008), admitted to Kempegowda Institute of Medical Sciences and Research Centre hospital (KIMS), Bangalore from July 2006 to October 2010.

**Exclusion criteria**

1) Heart diseases including IHD.

2) Haematological disorders.

3) Liver diseases.

4) History of intolerance/hypersensitive to nifedipine/methyl dopa/labetalol.

5) Asthmatic patients (only for labetalol treatment group).

**Study design:** A prospective comparative clinical study in a tertiary care teaching hospital.

**Place of study:** Kempegowda Institute of Medical Sciences and Research Centre (KIMS)

Hospital, K. R. Road, Vishveshwarpuram, Bangalore -560004, Karnataka.

**Antihypertensive drugs used in the study**

Labetalol Tablets: Lobet -100 mg, (Samarth Pharma Pvt Ltd), Gravidol-100mg, (Mercury Laboratory Pvt Ltd).
Materials and Methods

Methyldopa Tablets: Alphadopa-250mg, (Wockhardt)

Nifedipine Capsules: Depin-10 mg, (Zydus Cadila), Nicardia-10 mg (J.B. Chemicals and Pharmaceuticals)

All the patients were in-patients. Ethical clearance from the Institutional Human Ethics committee of Kempegowda Institute of Medical Sciences and Research Centre hospital (KIMS), Bangalore was taken for the study. General consent was taken for administration of all drugs as deemed necessary for management. Each participant’s hospital identification number was recorded at the time of presentation, and mothers and infants data were subsequently abstracted from their hospital charts and entered into standard data collection form (Proforma) designed for the study (Annexure).

Patients were randomly allotted to three treatment groups, based on antihypertensive received. In labetalol group, 96 randomly selected patients received oral labetalol 100 to 200 mg BID, in nifedipine group, 101 randomly selected patients received oral nifedipine in the dose 10 to 20 mg TID, and in methyldopa group, 103 randomly selected patients received methyldopa orally 250 to 500 mg QID. Each group was further divided into two sub groups as mild and severe PIH patients based on severity of blood pressure at presentation. BP 140/90 to 159/109 mm Hg was considered as mild PIH, whereas BP ≥ 160/110 mm Hg was considered as severe PIH. Lower doses of antihypertensive drugs were used in mild PIH and higher doses for severe PIH.

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Mild PIH patients (number)</th>
<th>Severe PIH patients (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyldopa group (n=103)</td>
<td>59</td>
<td>44</td>
</tr>
<tr>
<td>Nifedipine group (n=101)</td>
<td>43</td>
<td>58</td>
</tr>
<tr>
<td>Labetalol group (n=96)</td>
<td>38</td>
<td>58</td>
</tr>
</tbody>
</table>
Besides complete obstetric examination, detailed history was taken, with special attention to haemorrhagic disorders, thromboembolic episode, epilepsy, hepatic or renal disorder and drug intake. Baseline characters and pre-treatment risk factors were recorded and analysed between the groups. Blood samples were taken for estimating complete blood cell count, blood sugar, blood urea, serum uric acid, serum creatinine and liver enzymes. Urine was collected for estimation of urine proteins, sugar and examination for microscopy. Foetal kick count chart, ultrasound, fundoscopy, cardiotocography (NST), and Doppler ultrasound were also done (Magee et al., 2008). Blood pressure was recorded using Mercury Sphygmomanometer with patient in 15 degrees left lateral recumbent position. Korotkoff V sound was used for determining diastolic blood pressure.

4.1. In patient history, base line characters and pre-treatment risk factors were noted in proforma before initiation of antihypertensive therapy and analysed (Brown et al., 2002; Liu et al., 2008).

- **Baseline Characters**
  - Age
  - Gravidity
  - Parity
  - Disease History: Past and family history
  - Gestational age at presentation
  - Socioeconomic status
  - Consanguinity
  - BP: Diastolic BP at presentation
  - Proteinuria
  - Fundoscopy
  - Non stress test (NST)
Materials and Methods

- **Pre-treatment risk factors:** Impending eclampsia, eclampsia, Partial HELLP syndrome, HELLP syndrome, anaemia, placenta previa, intrauterine foetal demise (IUD), intrauterine growth restriction (IUGR), oligohydramnios, acute renal failure etc.

4.2. **Following investigations were done at admission and on alternate days during treatment period for diagnosis and prognosis of PIH** (Peralta Pedrero et al., 2004; Bailey and Walton, 2005)

All women who presented with new onset hypertension, the following laboratory tests were done. Complete blood cell count, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels, serum creatinine and serum uric acid. In addition, if HELLP syndrome was suspected, a peripheral smear was performed, and serum lactate dehydrogenase (LDH) level and indirect bilirubin estimation was carried out. Coagulation profile (prothrombin time (PT), activated partial prothrombin time (aPTT) and fibrinogen) was evaluated, when platelet count was less than 1,00,000/mm³ with evidence of bleeding (Abbade et al., 2002; Magee et al., 2008). Results of above biochemical parameters were assessed for individual treatment group and compared between the groups.

4.3. **Outcome parameters after initiation of treatment**

4.3.1. **Assessment of efficacy of antihypertensive agents**

**A) Blood pressure**

Blood pressure was recorded every 6 hourly throughout the treatment period until discharge, and assessment was done at 0, 6, 24, 48 and 72 hrs of initiation of antihypertensive treatment and at the time of discharge. Antihypertensive efficacy was assessed in each treatment group separately for systolic BP, diastolic BP, mean arterial pressure (MAP) and control achieved in percentage of patients at 72 hrs and at discharge. Results of above parameters were compared between groups in mild and severe PIH.

Mean arterial pressure = Systolic pressure + (Diastolic pressure × 2) / 3
Materials and Methods

Blood pressure recording

Blood pressure was measured by sphygmomanometer with an appropriately sized cuff with the patient lying in the left recumbent position for ten minutes.

1. Bell stethoscope was used as it better amplifies the Korotkoff sounds.

2. A well maintained sphygmomanometer was used.

3. The cuff size must be correct, bladder length should encompass 80% of arm circumference and bladder width should be 40% of the arm circumference.

4. Measurement was taken with woman sitting /left lateral with arm at heart level.

5. When cuff is first inflated an approximation of systolic pressure was taken by palpation of radial pulse.

6. During auscultation, the cuff was initially inflated to a pressure 20 mm Hg higher than estimated systolic pressure determined by palpation.

7. Systolic pressure was recorded at the level where repetitive sounds were first heard (Korotkoff 1) (rounded, upward, to the nearest 2 mm Hg).

8. The diastolic pressure was recorded at the point of disappearance of these sounds (Korotkoff 1) rounded to the nearest 2 mm Hg.

9. If Korotkoff 4 and Korotkoff 5 were markedly different, it can prevent confusion if both are recorded. In this study Korotkoff 4 was used if Korotkoff 5 cannot be heard, as reference pressure for inclusion in the study of patients with preeclampsia. If diastolic blood pressure was more than 90 mm Hg, blood pressure was measured after 30 min (Johenning and Barron, 1992; Shennan et al., 1996).
B) Proteinuria

Urine proteins were estimated semi quantitatively by dipstick method at admission and daily during treatment period to assess the development of preeclampsia. Proteinuria was analysed separately for each treatment group and compared on day 0, 2, 4, 6 and 8 of treatment period. Proteinuria is described as 300mg or more urinary protein per 24 hours or persistent 30mg/dl (1+ dipstick) in random urine samples. Protein 2.0g/24 hours or ≥ 2+ dipstick increases the certainty of preeclampsia (Ray et al., 2001; Magee et al., 2008).

Semi quantitative estimation of urine proteins

Fresh mid-stream clean catch urine was collected in a wide mouthed container and sent for analysis within one hour. Estimation of urine protein was done by using multi stick reagent strip (Teco Diagnostics, Netherlands) the test area is impregnated with tetrabromophenol blue buffered to an acid pH. This area is yellow in absence of proteins, changes to shades of green to blue in presence of proteins. The change in test area depends on concentration of proteins present, and was read as traces, 1+, 2+, 3+ and 4+ depending on concentration of proteins and read against the colour code given on the multi stick box (Morikawa et al., 2008).

4.3.2. Advancement of gestational age in treatment groups

Extra days added to pregnancy after initiation of antihypertensive therapy.

4.3.3. Assessment of perinatal outcome (Ferrao et al., 2006; Grujic and Milasinovic, 2006; Fatemeh et al, 2010; Barton et al., 2011).

1. Apgar score at ‘0’ minute and 5th minute (Witilin and Sibai, 2001)
   - Low score (≤6)
   - Normal score (7-10)

2. Twin births

3. Birth weight based on gestation age (Xiong and Fraser, 2004; Zang et al., 2008)
• Appropriate for gestation age (AGA): Birth weight above 10\textsuperscript{th} percentile and below 90\textsuperscript{th} percentile for that gestational age
• Small for gestational age (SGA): Birth weight below the 10\textsuperscript{th} percentile at gestational age
• Large for gestational age (LGA): Birth weight above the 90\textsuperscript{th} percentile at gestational age

4. Birth weight
• Normal birth weight (NBW): Birth weight at term delivery is 2500g-4200g
• Low birth weight (LBW): Birth weight less than 2500g regardless of gestational age
• Very low birth weight (VLBW): Birth weight less than 1500g
• Extremely low birth weight (ELBW): Birth weight less than 1000g

5. Intra uterine growth restriction (IUGR): Is diagnosed using ultra sonography. It describes a pattern of intrauterine foetal growth that deviates from normal norms, i.e. there is restriction of height, weight, and head circumference.

6. NICU admission
7. Birth asphyxia
8. Meconium aspiration
9. Perinatal death
10. Still birth
11. Total deaths
12. Live births

13. Very preterm births: Foetus born prior to 34 weeks gestation
14. Preterm births: Foetus born prior to 37 weeks gestation
15. Term births: Foetus born 38 to 42 weeks gestation
4.3.4. Obstetric outcome

Obstetric outcome was analysed based on the mode of delivery (Abbade et al., 2002; Familoni et al., 2004; Grujic and Milasinovic, 2006).

1. Vaginal delivery: Normal delivery, operative vaginal delivery (Forceps and ventous delivery)
   - Type of labour in vaginal delivery – Induced or spontaneous
2. Caesarean section.
   - Indications for caesarean section.

4.3.5. Maternal outcome

Maternal outcome was assessed based on development complications such as eclampsia, HELLP syndrome, abruptio placentae, disseminated intravascular coagulation (DIC), acute renal failure (ARF), intra cerebral haemorrhage, maternal death etc. (Abbade et al., 2002; Yucsesoy et al., 2005; Moodley, 2011).

4.3.6. Safety of drugs

Drug safety was assessed based on side effects recorded during the treatment period in treatment groups (Vermillion et al., 1999).

4.3.7. Additional drugs used

Based on incidence of acute hypertensive episodes in treatment groups, additional drugs required apart from antihypertensive agents were analysed.

4.3.8. Follow up

After discharge, patients were called for follow up at 6 weeks and 12 weeks for assessment of BP to rule out chronic hypertension.

4.4. Statistical analysis

All continuous variables were expressed as mean ± standard error of mean (SEM) and analysed using repeated measures ANOVA (parametric) followed by Tukey Kramer
multiple comparison tests, Kruskal Wallis test (nonparametric ANOVA) followed by Dunnett’s test, Fried Man test (non parametric repeated measures ANOVA) followed by Dunnett’s test and paired ‘t’ test. Categorical data were expressed as percentage and analysed by either Fisher’s exact test, or test for proportions. All p-values were two sided. Significance was set at $P \leq 0.05$. 