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Antihypertensive Treatment in Preeclampsia

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Abstract
Hypertensive disorders affect up to 10% of pregnancy in the united state. Hypertensive disorders in pregnancy are classified in to gestational hypertension, preeclampsia, preeclampsia superimposed on chronic hypertension, and chronic hypertension. Between those disorders, preeclampsia syndrome is the most dangerous one (Cunningham, et al., 2014). Preeclampsia is clasically defined as new onset hypertension (BP ≥ 140/ 90 mmHg) and proteinuria (excrete > 300 mg/ day, or +1 dipstick test) after 20 weeks gestation (Steegers, et al., 2010). Preeclampsia is a complex multisystem disease with a still unclear etiology. It is commonly accepted that pathophysiology of preeclampsia begins with abnormal placentation, and it results in systemic dysfunction. Preeclampsia is associated with significant maternal and fetal morbidity and mortality, including eclampsia and HELLP syndrome in maternal, preterm birth, intrauterine growth restriction, and perinatal death in fetus (Hariharan, et al., 2017). Correct diagnosis and appropriate therapy are the most important factor in preventing the severity of preeclampsia. However the fetus delivery is the only definitive cure of preeclampsia (Steegers, et al., 2010). The major treatment in preeclampsia are antihypertensive treatment and anticonvulsant treatment. Antihypertensive drug therapy may be used to keep systolic blood pressure at 130-155 mmHg and diastolic blood pressure at 80-105 mmHg. First choice for antihypertensive agents in preecalmpsia are long acting nifedipine and labetalol in severe hypertension and methyldopa or hydralazine in moderate hypertension (Magee, et al., 2014).

Keyword: *Preeclampsia, Antihypertensive.*

A. INTRODUCTION

Preeclampsia is a special syndrome of pregnancy due to maternal vascular endothelial dysfunction and the effects of vasospasm that usually occur after 20 week gestation. Preeclampsia are characterised at least two clinical manifestations of hypertension and proteinuria. Hypertension is characterized by systolic blood pressure ≥ 140 mmHg and / or diastolic blood pressure ≥ 90 mmHg. Proteinuria is defined as urinary protein excretion ≥ 300 mg in 24 hours, or urine: creatinine ratio ≥ 0.3, or the presence of 30 mg / dL protein (dipstick test + 1) in a fixed urine sample. The results of dipstick test can be influenced by the urine concentration that varies between day and night. The results of the examination can show the value of +2 in a concentrated urine specimen even though the results of urine collection within 24 hours did not show the excretion of protein ≥ 300 mg. Determination of the value of urinary creatinine ratio of proteins will be preferred in determining future proteinuria status(Cunningham, et al., 2014).

B. INCIDENCE AND RISK FACTORS

In worldwide, the prevalence of preeclampsia events accounts for about 8-10% of total pregnancy rates, and it is one of the 3rd leading causes of maternal morbidity and mortality (Ghulmiyyah and Sibai, 2012; Hariharan, et al., 2017). Maternal mortality and morbidity are generally due to complications of eclampsia and HELLP syndrome, whereas the fetus is due to preterm birth, intrauterine growth restriction, and perinatal death (Hariharan, et al., 2017). The incidence of preeclampsia in the United States has increased by 25% in the last two decades (ACOG, 2013).According to WHO, preeclampsia is responsible for more than 60,000 cases of maternal deaths in developing countries, due to difficulties in achieving access to health care center in developing countries (Young, et al., 2010).

Preeclampsia is often experienced by young women, with an incidence rate of 7.5%, and is common in the first pregnancy. Women with history of preeclampsia are at greater risk for future preeclampsia (Yelumalai, et al., 2010; Young, et al., 2010). Obesity and African-American ethnic are also one of the risk factors for preeclampsia (Cunningham, et al., 2014). Some medical conditions such as chronic hypertension, diabetes mellitus, kidney disease, metabolic syndrome, and autoimmune disease are risk factors for the emergence of preeclampsia. Obstetric status may also increase the risk of preeclampsia such as multiple pregnancy (multifetal gestation) and wine pregnancy (hydatidiform mole) (Young, et al., 2010). The risk factors of preeclampsia shown in table 1.

Table 1. Risk Factors of Preeclampsia (Steegers, et al., 2010; Leeman, et al., 2016)

Risk Factor	Risk Relative
History of preeclampsia	7*
Family history	3*
Multiple gestation	3*
Increasing of body mass index	2*
Antiphospholipid antibody	9,72^
Diabetes mellitus	3,56^
Hypertension	Increasing
Renal disorder	Increasing

(*) cited from Leeman, *et al*., 2016.
(^) cited from Steegers, *et al*., 2010.

C. CLASSIFICATION OF PREECLAMPSIA

Preeclampsia is classified into severe preeclampsia and mild preeclampsia (shown in table 2), this is based on blood pressure, proteinuria values, and several other clinical manifestations. Blood pressure ≥ 160/110 mmHg, proteinuria value> 2 g / 24 h or dipstick test ≥ +3, accompanied by some clinical menifestion such as severe headache, visual impairment, abdominal pain are some criteria for severe preeclampsia. The presence of HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) also show severe preeclampsia conditions. HELLP syndrome is characterized by (1) an increase in LDH twice the upper normal limit or> 650 IU / L, (2) an increase in AST and ALT twice the upper normal limit> 70 U / L, and (3) Platelet <100,000 cells (Tranquilli, et al., 2014; Cunningham, et al., 2014).

Table 2. Classification of Preeclampsia (Cunningham, et al., 2014)

Criteria	Mild to moderate Preeclampsia	Severe Preeclampsia
Systolic blood pressure	< 160 mmHg	≥160 mmHg
Diastolic blood pressure	< 110 mmHg	≥ 110 mmHg
Proteinuria	≤ 2 g/ day or ≤ +2	>2 g/ day or ≥ +3
Headache	No	Yes
Visual impairment	No	Yes
Abdominal pain	No	Yes
Olyguria	No	Yes
Seizure	No	Yes
Creatinine serum	Normal	Increasing
Transaminase enzyme serum (AST dan ALT)	Normal	Increasing >70 U/ L
LDH	Normal	Increasing >70 U/ L
Fetal growth restriction	No	Yes
Pulmonary edema	No	Yes

D. ETHIOPATHOGENESIS

The pathogenesis of preeclampsia is not really understood, the best theorysaid there was two processes in the development of preeclampsia. Stage 1, begins with predisposing factors of preeclampsia such as immunological factors, environmental factors, and genetic factors. The presence of predisposing factors causes a person to become vulnerable to develop into preeclampsia. Followed by impairment invasion of extravilustrophoblast cells in spiral arteries. Stage 2, the emergence of maternal clinical manifestations caused by endothelial dysfunction mediated by substrates released by the placenta to the maternal circulation such as free radicals, inflammatory agents, and antiangiogenik factors (Cunningham, et al., 2014)

In preeclampsia, trophoblast invasion occurs only to the arteries in the decidual layer and does not reach the inner layer of the myometrium. This imperfect invasion causes the lumen of the spiral artery to become narrower and has a higher resistance to the vasoconstrictor than the normal placental vascular. This condition will trigger the occurrence of ischemia and tissue hypoxia around the placenta, but it will also trigger oxidative stress conditions. Hypoxic and ischemic conditions of the placenta have an adverse effect on the fetus, ie intrauterine growth retardation and fetal death in the uterus (intrauterine death). On the other hand, placental ischemia and oxidative stress conditions trigger the release of placental debris into maternal circulation such as

free radicals, oxidized lipids, proinflammatory cytokines, and antiangiogenic factors. The release of these substances may trigger injury and endothelial dysfunction, in which further process will result in clinical manifestations in maternal such as hypertension and proteinuria (Uzan, et al, 2011; Cunningham, et al., 2014). Pathogenesis of preeclampsia shown in picture 1a and 1b.

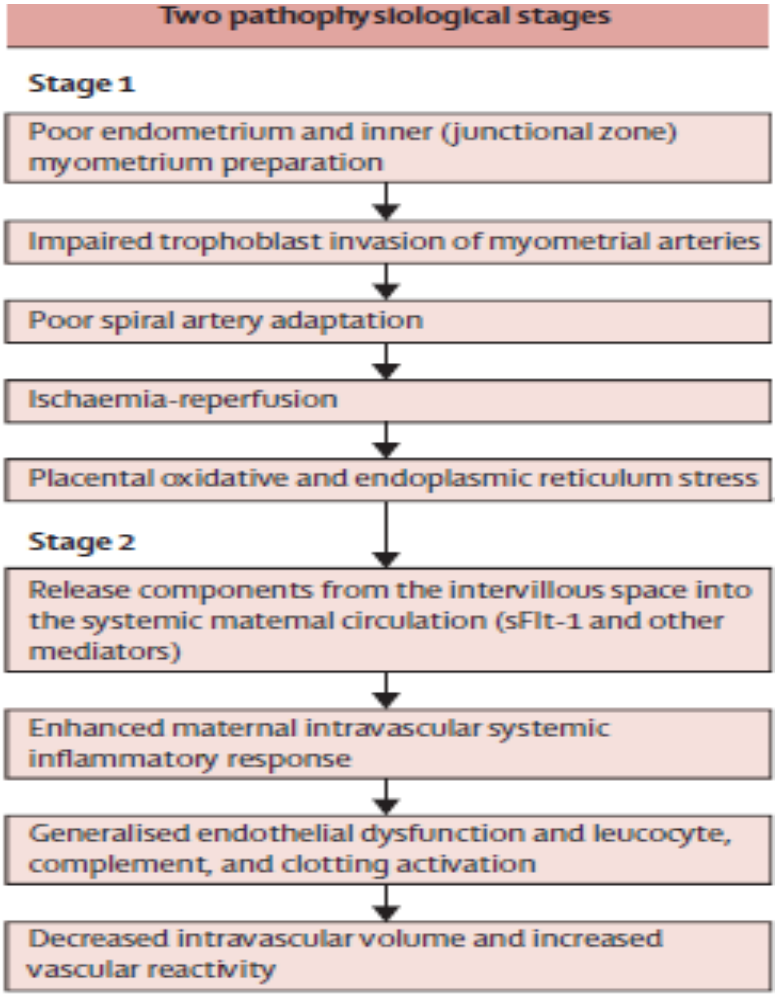

Figure 1a. Two Pathophysiology Stages of Preeclampsia (Steegers, et al., 2010).

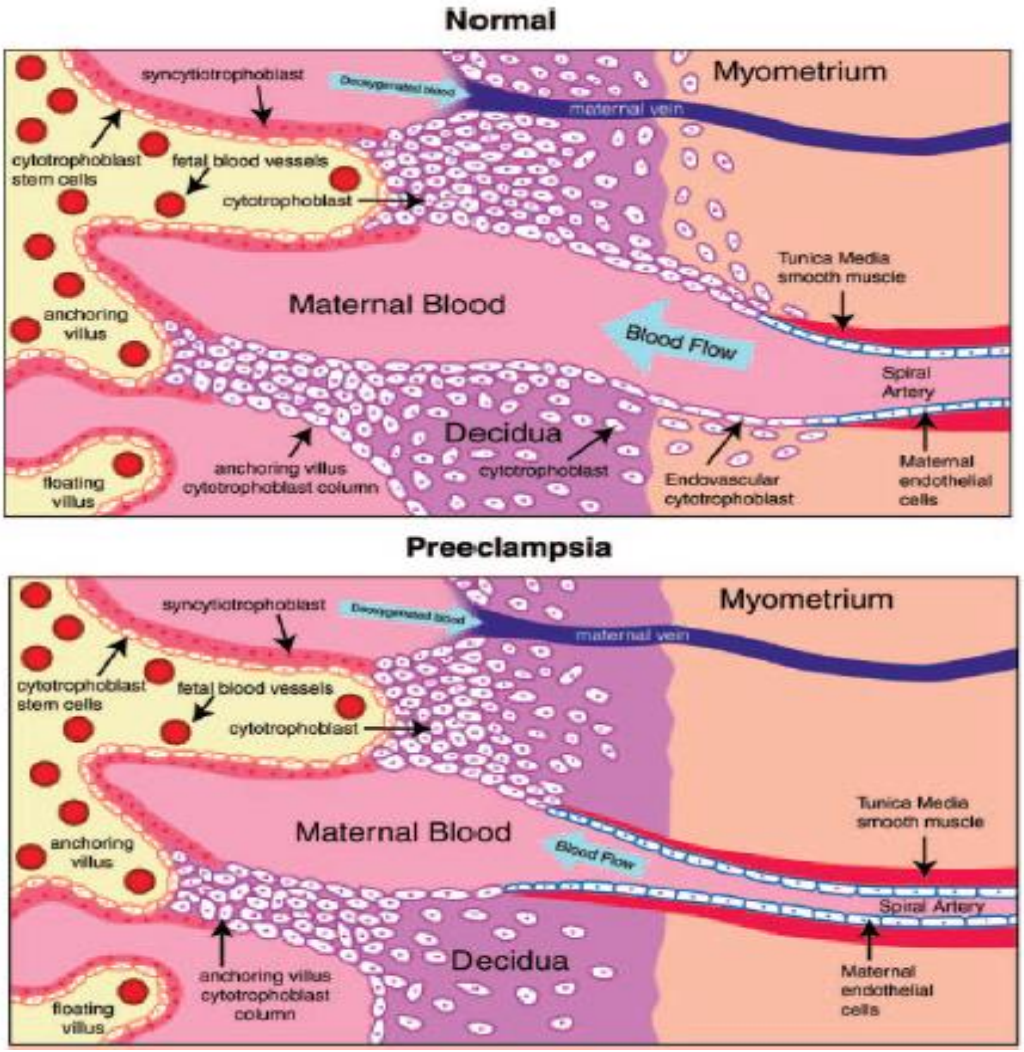

Figure 1b. Placentation in Normal Pregnancy and Preeclampsia (Wang, et al., 2009).

E. ANTI HYPERTENSEIVE IN PRE-ECLAMPSIA

Delivery is the only cure for preeclampsia. The optimal management of pre-eclampsia depends on gestational age and disease severity. Patient usually hospitalized and monitored carefully for the development of worsening preeclampsia or complications of preeclampsia, and the immature fetus is treated with expectant management with corticosteroids to accelerate lung maturity in preparation for early delivery (Magee *et al*., 2014). This review focused on 4 major antihypretensive agents use in preclampsia, such as beta blocker (labetolol), calcium channel blocker (nifedipine), methyldopa and hydralazine.

a. ***Management of Hypertension in Pregnancy***: 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 (NICE, 2011). SOGC guideline declared that pregnant woman with severe hypertension (BP >160/≥110 mmHg), BP should be lowered to <160/110 mmHg. Woman with non severe hypertension (140-159/90-109 mmHg) whitout any comorbid their BP should be lowered to 130-155/80-105 mmHg while in woman with comorbidities BP should lowered to 130-139/80-89 mmHg (Berzan, Doyle, & Brown, 2014).

   1. ***Management of mild hypertension:*** Pregnant woman with mild hypertension did not recquired pharmacologycal intervention. Drugs, bed rest and hospitaliation are not routinely recomended. Calcium supplementation may lead to reduction in arteral blood pressureand preeclampsia. Smoking and alcohol cessation should be adviced (Ghanem & Movahed, 2008).

   2. ***Management of moderate to severe hypertension:*** Several drugs commonly used to treat moderate to severe hypertension in pregnancy, ec. methyldopa 250-1000 mg three times daily, clonidine 0,1-1,2

mg two times dail, prazosin 1-10 mg two times daily, propranolol 40-120 mg two or three times daily, labetolol 100-1200 mg two times daily, Nifedipine 10-30 mg three or four times daily, and hydrochlortiazide four times daily (Ghanem & Movahed, 2008). For urgent control of severe hypertension in pregancy, several drugs can be used ec. labetolol iv 10-20 mg then to 20-80 mg maximum of 300 mg; hydralazine 5-10 mg iv or im then 5-10 mg every 20-40 minutes until BP controlled, repeat every 3 hours; nifedipine oral 10-30 mg, repeat in 45 minutes if needed; diazoxide 30-50 mg iv every 5-15 minutes; and relatively contraindicated nitroprusside in constant infusion of 0,25-5 µg/kg minutes (Podimow & August, 2008).

3. ***Management of antihypertensive post partum:*** Antihypertensive drugs should be used in woman with BP exceeds 150 mmHg in systole or 100 mmHg diastole in the first 4 days periporium. Main principle of antihypertensive drugs used post partum are to minimilized the drugs passages into milk, but in general the agents commonly used in antepartum periode can be continued post partum (Podimow & August, 2008).

b. Antihypertensive Agents in Preeclampsia

1. Beta Blocker: Beta blocker agents decrease BP in some mechanisms, ec. decrease cardiac output, influence the sensitivity of barereceptor reflex and blocking peripheral adrenoreceptor. Some beta-blocker reduce the secretion of renin in blood serum. Most of this drugs inhibit adrenoreceptor beta in cardiac, peripheral blood vessels, broncho, pancreas and liver. Beta blocker are classified as several groups: β_1 non selective (propranolol, timolol), β_1-selective (bisoprolol, metoprolol), third generation non selective (labetolol, carvedilol) and third generation selective (betaxolol, nebivolol) (Ambrosioni, Bacchelli, D.D, & Borghi, 2001).

Labetolol: Labetolol is beta blocker non selective third generation with competitive antagonist of vascular α_1-receptor has gained wide acceptance as antihypertensive in pregnancy, this drugs considered as first line therapy for antihypertensive in pregnancy. Labetolol is more potent at beta than at alpha in human, ratio are 3:1 in oral and 6,9:1 after parenteral use. Labetolol also have intrinsic symphatomimetic activity, so when given acutely, it can decreasing peripheral vascular resistance and blood pressure with little alteration in heart rate and cardiac output. But labetolol can also influence RAAS and respiratory function (Mc Carthy, 1983). Labetolol are given orally 200 to 2400 mg daily in 2-3 deviding doses. There is limited documentation of prolonged continuous infusions. Due to the prolonged duration of action, careful monitoring should be extended for the duration of the infusion and for several hours after the infusion. Excessive administration may result in prolonged hypotension and/or bradycardia. Labetolol parenterally use to treat severe hypertension, and because of a lower incidence of maternal hypotension and other adverse effect, its use now supplant that of hydralazine (Podimow & August, 2008). The most troublesome adverse effect of labetolol is posture related dizzines. Other reported side effect are GIT disturbance, tiredness, headache, scalp tingling, anaphylacti reaction, hepatic injury, hypotension/syncope (Lacy, Armstrong, Goldman, & Lance, 2008-2009).

2. ***Calcium channel blocker (CCB):*** CCB has been used to treat chronic hypertension, mild hypertension presenting late in gestation and urgent hypertension associated with preeclampsia. CCB are classified into three major groups: dihydropyridine (short acting: nifedipine, intermediate acting: nicardipine, nimodipine and long acting: amlodipine), phenylakilamine (verapamile) and non dihyropiridine (diltiazem). Major effect of dihydropiridine are vasodilatation while major effect of non dihydropyridine are cardiac contractility and conduction. Comparison of three groups of CCB are shows in table below (Sica, 2004).

Table 3. Comparison of Calcium Channel Blocker (Sica, 2004)

Effect	Phenylalkylamines (Verapamil)	Benzothiazepines (Diltiazem)	Dihydropyridines
Peripheral vasodilation	↓	↔↓	↓↓
Coronary vascular resistance	↓	↓	↓↓
Myocardial contractility	↓↓	↓	↔↓
Cardiac output	variable	variable	↔↓
Heart rate	↑ acute;↓ chronic	↓	↑ acute; ↔ chronic
Atrioventricular conduction	↓	↓	↔

↓=Decrease; ↔=neutral effect; ↑=increase

Most study has focused on using of nifedipine as first choice for severe hypertension in pregnancy because it does not seen to cause a detectable decrease in uterine blood flow. Administration of short acting nifedipine capsules, in case report, associated with maternal hypotension and fetal distress (Podimow & August, 2008). One study has shown efficacy and safety of long acting formulation of nifedipine in pregnant patient with severe hypertension (Brown, ML, T, & Davis, 2002). Long acting nifedipine (30-90 mg once daily as sustained release tablet, increase at 7-14 day interval, maximum dose of 120 mg/day) has been use in pregnant women without major problem (Auguts, 2016). Most concern related adverse event of nifedipine are angina, hypotension/syncope, peripheral edema and reflex tachicardia (Lacy, Armstrong, Goldman, & Lance, 2008-2009). Breastfeeding didnot result in measurable infant concentration of nifedipine if there was no placental exposure immediately prior or during the delivery or if mothers didnot received excessively high doses during the first week of postpartum (Anderson & Carr, 2009).

3. ***Methyldopa:*** Methyldopa is the only antihypertensive drugs with pregnacy Category of FDA is B. Methyldopa has centrally acting α_2-adrenergic agonist prodrug, which is metabolized to α-methyl norepinephrine and then replaces norepinephrine in the neurosecretory vesicles of adrenergic nerve terminals. It has indirect mechanism of action by decrease adrenal excretion from central nervous system so will decrease total periphare resistance and so will control BP gradually, over 6 to 8 hours. Methyldopa safety are based on limited data and a 40-year history of use in pregnancy. Treatment with methyldopa has been reported to prevent subsequent progression to severe hypertension in pregnancy and does not seem to have adverse effects on uteroplacental or fetal hemodynamics or on fetal well being. In a follow-up study of offspring who were exposed to methyldopa in utero, at 7.5 years of age, the children exhibited intelligence and neurocognitive development similar to control subjects (Podimow & August, 2008). Most concern adverse effet of methyldopa is hemolityc anemia, hepatic effects and sedation and in > 10% case are peripheral edema, in 1-10% case are drugs fever, mental depression, anxiety, nightmare, drowsiness, headache and dry mouth (Lacy, Armstrong, Goldman, & Lance, 2008-2009).

4. ***Hydralazine:*** Hydralazine is a direct arteriolar vasodilator, with little effet on venous capacitance vessels, that produce a rapid BP decrease with diastolic pressure reduced more than systolic (Grossman & Messerli, 2007). Hydralazine oral is first choice for chronic hypertension in pregnancy and second line antihypertensive for severe hypertension in pregnant woman who contraindicated with labetolol or labetolol therapy not adequate to control BP. For chronic hypertension, hydralazine dose are recomended in 10 mg oral every 6 hours for 2-4 days, can be increased gradually to 10-25 mg every 2-5 days, maximum doses are 50 mg every 6 hours. For severe hypertension, recomended doses for pregnant and postpartum woman are 5 mg bolus, can be repeated 5-10 mg every 20-30 minutes if BP not controlled yet until maximum doses of 20 mg in 80 minutes. If BP still not controlable, hydralazine infusion or labetolol iv bolus can be given. According to Australian Drug Evaluation Committee, hydralazine are classified as C in pregnancy woman. Most concern adverse event of hydralazine are drugs induced lupus like syndrome in larger dose and longer duration, electrolyte disturbance, photosensitivity, and sulfa allergy (Lacy, Armstrong, Goldman, & Lance, 2008-2009). Study about transplancental passage and breast milk concentration of hydralazine show that the estimated dose of hydralazine in milk feed of 75 ml are very small, would not exceeded 0,013 mg. Thus, hydralazine treatment of the pregnant woman would expose her fetus, brust feeding would not result in clincally relevant concentration in the infant (Liedholm *et al*, 1982).

F. COMPARE OF ANTI HYPERTENSIVE DRUGS IN PREGNANCY

Several study compared some antihypertensive agents used in pregnancy and preeclampsia. Cochrane review of 29 trials 3350 pregnant women with mild to moderate hypertension and compared between an antihypertensive drugs and placebo/no antihypertensive drugs showed that there is a halving risk of havig severe hypertension associated with antihypertensive drugs in 20 trials 2558 women RR 0.49 CI 95% 0.40-0.60 but little evidence of a difference in the risk of pre-eclampsia (23 trials, 2851 women RR 0.93 CI 95% 0.80-1.08). In this review also showed that in 22 trials (1723 women) comparing one antihypertensive drug with another. Alternative drugs seem better than methyldopa for reducing the risk of severe hypertension (11 trials, 638 women; RR 0.54 CI 95% 0.30-0.95; NNTH 7 (5-69). There is also a reduction in the overall risk of developing proteinuria/pre-eclampsia when beta blockers and calcium channel blockers considered together are compared with methyldopa (11 trials, 997 women; RR 0.73; 95% CI 0.54 to 0.99) (Abalos, Duley, & Steyn, 2014).

Another cochrane review on 35 trials and 3573 women to compare different different antihypertensive drugs for very high blood pressure during pregnancy showed that women with calcium channel blocker were less likely to have persistent high blood pressure compared to hydralazine (6 trials, 313 women; 8% versus 22%; RR 0.37, CI 95% 0.21 to 0.66). Labetalol was associated with a lower risk of hypotension compared to diazoxide (one trial 90 women; RR 0.06, 95% CI 0.00 to 0.99) and a lower risk of caesarean section (RR 0.43, 95% CI 0.18 to 1.02), although both were borderline for statistical significance. Both nimodipine and magnesium sulphate were associated with a high incidence of persistent high blood pressure,. Nimodipine was associated with a lower risk of respiratory difficulties (RR 0.28, 95% CI 0.08 to 0.99), fewer side-effects (RR 0.68, 95% CI 0.55 to 0.85) and less postpartum haemorrhage (RR 0.41, 95% CI 0.18 to 0.92) than magnesium sulphate (Duley, Meher, & Jones, 2013)

Study randomized clinical trial comapred the safety and efficacy of intravenous labetolol and intravenous hydralazine for acute lowering blood pressure in 200 pregnant women with severe hypertension showed that no significant difference in maternal hypotension or persistent hypertension between two groups, but palpitations (p=0.01) and maternal tachycardia (p=0.05) occur significant more often in patient treated with hydralazine (De-Gracia *et al*, 2006).

Study randomized trial compared methyldopa and labetolol in 80 patients with PIH showed that labetalol has been very effective in control BP and had lesser side effects when compared to methyldopa. Labetalol is not associated with adverse fetal 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, both the drugs were found to be safe for the neonate (Dharwadkar *et al*, 2014)..

G. CONCLUSION

Base on several study and literature we reviewed, it is known that there were no single therapy as the best choice for BP reduction of women with pre-eclampsia. Antihypertensive should be given in moderate to severe hypertension. Our review showed that labetolol and nifedipine are first choice antihypertensive for severe hypertension in preganancy while methyldopa had a better safety profile but its had gradual effect on decreasing the BP.

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