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Labetalol Versus Alpha Methyldopa for Control of Pregnancy Induced Hypertention RANDOMIZED CONTROLLED TRIAL

Protocol of thesis
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ABSTRACT

Background: Pregnancy-induced hypertension is associated with various adverse fetal and maternal outcomes. The use of anti-hypertensive drugs in pregnancy is controversial. We conducted a prospective study to evaluate the comparative effectiveness and safety of methyldopa and labetalol monotherapy in patients with pregnancy-induced hypertension.

Objective: To compare the efficacy & safety of Methyldopa and Labetalol on Blood pressure in Pregnancy-induced hypertension (PIH) patients.

Methods: Patients n= 88 pregnant women with blood pressure of 140/90 mm Hg or more with ≥1+ proteinuria and gestational age between 22-40 weeks were included in this randomized controlled trial study. Cases were randomly divided into two groups of 44 each. Group –I received labetalol (n=44) and Group II received methyldopa (n=44). Blood pressure was measured at 48 h of initiation of antihypertensive drugs. Patients were also followed up for development of adverse drug effects during this period.

Results: both Methyl Dopa & labetalol are effective in controlling blood pressure among participants but not reached a significant value .As the mean arterial pressure in patients treated with labetalol group on admission was 113.90. mm Hg while on day 7 it reduced to 91.21mmHg, With methyldopa group, the mean arterial pressure on admission was 112.61mmHg which reduced to 90.15mmHg on day 7.

Conclusions: labetalol is an effective and safe drug for use in the control of blood pressure in pregnancy-induced hypertension with less maternal and fetal side effects than methyldopa treated group and proved to be drug of choice in pregnancy induced hypertension

KEYWORDS: Antihypertensive, Pregnancy-induced hypertension (PIH), Pre- eclampsia Methyldopa, Labetalol.

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List of Abbreviations

Abbreviations	Meaning
ABPM	ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme.
ACOG	American College of Obstetricians and Gynecologists
APS	Anti-phospholipid syndrome.
BMI	body mass index.
BP	Blood pressure
CCBs	Calcium channel blockers.
CHIPS	Control of Hypertension in Pregnancy Study.
CKD	Chronic kidney disease.
CMACE	Centre for Maternal and Child Enquiries
DBH	dopaminebeta-hydroxylase.
DBP	diastolic blood Pressure.
DIC	disseminated intravascular coagulation.
ESRD	end stage renal disease.
FDA	Food and Drug Administration.
HELLP	hemolysis elevated liver enzymes and low platelets
HUS	hemolytic uremic syndrome
ISSHP	International Society For The Study of Hypertension In Pregnancy's
IUGR	intrauterine growth restriction.
IV	intravenously.
NHBPEP	National High Blood Pressure Education Program
NICE	National Institute for Health and Clinical Excellence
NK cell	Natural killer cell.
PE	Preeclampsia
PIGF	Placental growth factor.
PIH	Pregnancy induced hypertension.
PRES	Posterior reversible encephalopathy syndrome.
RCTs	Randomized controlled trial
RLS	Restless legs syndrome .
SBP	systolic blood pressure
sEng	solubleendoglin
sFlt1	soluble Flt1 (fms-like tyrosine kinase 1)
SGA	small for gestational age
SNPs	single nucleotide polymorphisms
SOGC	Society of Obstetricians and Gynaecologists of Canada
TTP	thrombocytopenia purpura
VEGF	vascular endothelial growth factor.
WCH	white coat hypertension
Who	World Health Organization

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PROTOCOL

Introduction

Hypertensive disorders seem to complicate approximately 10 per cent of pregnancies and are important causes of maternal and fetal mortality **(Chauhan et al., 2007).**

Hypertension is the most common medical problem encountered during pregnancy **(Arias et al., 2008).**

It is estimated that globally 6-8% of pregnancies are complicated by hypertention (**Magee et al., 1999**).

It is said that preeclampsia and eclampsia contribute to death of a woman every 3 minutes worldwide (**Shah et al., 2007**).

There are four major hypertensive disorders that occur in pregnant women.

Chronic hypertension (preexisting)

Chronic hypertension is defined as blood pressure elevation that predates pregnancy. If blood pressure is unknown prior to pregnancy and elevation is discovered prior to 20 weeks of gestation, the presumed diagnosis is chronic hypertension or if it persists beyond 6 months postpartum. **(Seely et al., 2014)**

1- Gestational hypertension (GH)

GH is diagnosed in women whose blood pressure reaches≥140/90 mmhg for the first time during pregnancy (after 20 weeks of gestation),but without proteinuria. Blood pressure normalizes by 12 weeks postpartum **(Melamed et al., 2014).**

2- Preeclampsia(PE)

Hypertention (blood pressure ≥140/90mmhg) accompanied with proteinuria exceeding 300mg/24 hours emerges for the first time after 20 weeks geststion, but both symptoms normalize by 12 weeks postpartum **(Hutcheon et al., 2011)**.

3- Superimposed preeclampsia(S-PE)

Superimposed preeclampsia is diagnosed in the following three cases.

- New onset proteinuria(≥300mg/24 hours) in hypertensive women who exhibit no proteinuria before 20 weeks gestation.
- Hypertension and proteinuria documented antecedent to pregnancy and/or detected before 20 weeks gestation, one or both of which progressing after 20 weeks gestation.
- Renal disease with proteinuria documented antecedent to pregnancy and/or detected before 20 weeks gestation, which is accompanied with new onset hypertension after 20 weeks gestation (**Viera et al., 2010)**.

4- Eclampsia (E)

Eclampsia is defined as the onset of convulsions in a woman with PIH that cannot be attributed to other causes. The seizures are generalized and may appear before, during, or after labor.

Pregnancy induced hypertension is a temporary diagnosis for hypertensive pregnant women who do not meet criteria for preeclampsia (both

hypertension and proteinuria) or chronic hypertension (hypertension first detected before the 20th week of pregnancy) **(Roberts et al., 2013).**

The diagnosis is changed to:

- Preeclampsia if proteinuria develops.
- Chronic hypertension if blood pressure elevation persists ≥ 12 weeks postpartum.
- Transient hypertension of pregnancy if blood pressure returns to normal by 12 weeks postpartum.

Thus reassessment up to 12 weeks postpartum is necessary to establish a final definitive diagnosis **(Cruz et al., 2011).**

The pathophysiology of pregnancy induced hypertension is unknown.

It is not clear whether pregnancy induced hypertension and preeclampsia are different diseases with a similar phenotype (hypertension) or if pregnancy induced hypertension is an early or mild stage of preeclampsia **(Melamed et al., 2014)**.

There are some data to suggest preeclampsia and pregnancy induced hypertension are different diseases:

- Primiparity is a strong risk factor for preeclampsia, but not for Pregnancy induced hypertension **(Villar et al., 2006).**
- The recurrence risk for pregnancy induced hypertension is several-fold higher than that for preeclampsia (20 to 47 percent versus about 5 percent for preeclampsia at term) **(Brown et al., 2007).**
- Total blood and plasma volumes are significantly lower in women with preeclampsia (mean 2660 mL/m2 and 1790 mL/m2 respectively) than in

women with pregnancy induced hypertension (3139/m2 and 2132 mL/m2, respectively) **(Silver et al., 1998).**

The diagnosis of pregnancy induced hypertension is clinical as defined above: Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg in a previously normotensive pregnant woman who is ≥ 20 weeks of gestation and has no proteinuria.

The main goals in the initial evaluation of pregnant women with newly developed hypertension are to distinguish pregnancy induced hypertension from preeclampsia, which has a different course and prognosis and to determine whether hypertension is mild or severe, which affects management and outcome **(Anumba et al., 2010).**

The major goal of antihypertensive medication in PIH is to prevent or treat severe hypertension (generally defined as Blood Pressure (BP)of ≥ 160/110 mmHg) and its associated complications to the mother and the fetus and to prolong pregnancy for as long as possible **(Magee et al., 2014).**

The risk of developing sever hypertension is reduced to half by using antihypertensive medications **(Duley et al ., 2013).**

In the past pregnancy induced hypertension was managed as follow:

A trial of bed rest preferably in the lateral position is attempted. Sedation in the form of phenobarbitone is recommended as an adjunct to bed rest to reduce the patient's anxiety and her mental and physical activity **(Gant et al ., 1974).**

In addition to lowering the blood pressure bed rest may also reduce extravascular fluid volume by its natriuretic and saluretic effects **(Menon et al .,**

1961). and increase uteroplacental blood flow by decreasing the demands of activity related organs and structures.

The objective of therapy is to keep the diastolic blood pressure from rising above 90-100 mmHg.Aftera trial of bed rest, a hypotensive agent is indicated if the diastolic blood pressure remains above 100 mmHg **(Moore et al., 1982).**

Commonly Used Drugs in The Past For Hypertensive Pregnancy drugs as:

- Methyldopa
- Clonidine(Catapres).
- Reserpine.
- Dihydrallazine.
- Diazoxide(Hyperstat).
- Magnesiumsulphate (MgSO.).

(Sibai et al., 1986).

Now days methyl dopa is commonly used for control pregnancy induced hypertension. In the future labetalol may be superior to alpha methyldopa in the control of BP.

The following drugs are effective antihypertensive agents with an acceptable safety profile in pregnancy. The choice of drug depends on the acuity and severity of hypertension and whether or not parental or oral therapy is used.

Methyldopa has been widely used in pregnant women and its long-term safety for the fetus has been demonstrated but it is only a mild antihypertensive agent and has a slow onset of action(three to six hours). Many women will not achieve blood pressure goals on this oral agent or are bothered by its sedative effectn ***(Arulkumaran et al., 2013)***.

Labetalol has both alpha and beta adrenergic blocking activity, and may preserve uteroplacental blood flow to a greater extent than traditional beta-blockers. It has a more rapid onset of action than methyldopa within (two hours versus three to six hours) (**Bateman et al., 2012).**