A COMPARATIVE STUDY OF INTRAVENOUS LABETALOL WITH ORAL ANTIHYPERTENSIVE COMBINATION NIFEDIPINE AND ALPHA-METHYLDOPA IN THE ACUTE MANAGEMENT OF HIGH BLOOD PRESSURE IN SEVERE PREGNANCY-INDUCED HYPERTENSION PATIENTS

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ABSTRACT

Normal pregnancy is characterised by unique physiological changes. It is mandatory for an anaesthesiologist to understand these changes and their anaesthetic implications. Pregnancy-Induced Hypertension (PIH) is a disorder of unknown aetiology affecting 5-10% of all pregnancies characterised by the development of hypertension with proteinuria after 20 weeks of gestation. Hypertension is defined as sustained systolic pressure of at least 140 mmHg or a sustained diastolic pressure of at least 90 mmHg that occurs after 20 weeks of gestation in a woman with previously normal blood pressure. Maternal complications of severe pregnancy-induced hypertension include pulmonary oedema, intracerebral haemorrhage, and renal failure. Foetal complications include Intrauterine Growth Retardation (IUGR), perinatal mortality. Management of severe pregnancy-induced hypertension requires multidisciplinary approach. Definitive treatment consists of termination of pregnancy along with prevention of seizures and control of blood pressure. The drugs used in the control of blood pressure are oral anti-hypertensives like alpha-methyldopa and intravenous agents like hydralazine, labetalol, nitroglycerin, etc. Intravenous labetalol injection is a unique drug with both alpha and beta-adrenergic receptor blocking properties. It has both blood pressure and heart rate reducing properties. This makes it a good choice in treating high blood pressure in severe pregnancy-induced hypertension patients.

AIM OF THE STUDY

The aim of this study is to find out and compare the efficacy of intravenous labetalol injection with the routinely used regimen of oral antihypertensives combination of tablet alpha-methyldopa and tablet nifedipine in the acute management of high blood pressure in severe pregnancy-induced hypertension patients.

METHODS

Forty patients with severe PIH were randomly allocated to receive either inj. labetalol (Group L) (n=20) or oral anti-hypertensives combination namely Tab. nifedipine 10 mg and Tab. alpha-methyldopa 500 mg (Group A) (n=20). Administration of drugs with respect to Age, Gravid Status, Blood Pressure, Urine Albumin Levels, Side Effects, Drug Dosage, Additional Treatment, Prolongation of Pregnancy, Foetal monitoring, mode of termination, Indication of Caesarean Section, and APGAR Scores were studied. The statistical level of significance was taken at $P < 0.05$.

RESULTS

Oral antihypertensive combination of tablets alpha-methyldopa and nifedipine achieved blood pressure control that often necessitated intravenous nitroglycerin as rescue drug. Intravenous labetalol achieves adequate and faster blood pressure control with better heart rate maintenance than the routinely used oral antihypertensive combination. There was no difference in the groups with regard to obstetric intervention. Neonatal outcomes were same in both groups.

CONCLUSION

In conclusion, intravenous labetalol achieves adequate and faster blood pressure control with better heart rate maintenance than the routinely used oral antihypertensive combination of tablets alpha-methyldopa and nifedipine in the control of blood pressure in severe pregnancy-induced hypertension patients.

KEYWORDS

Severe PIH; Labetalol; Nifedipine; Alpha-Methyldopa; Blood Pressure Control.

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INTRODUCTION

Normal pregnancy is characterised by unique physiological changes. It is mandatory for an anaesthesiologist to understand these changes and their anaesthetic implications. Pregnancy-Induced Hypertension (PIH) is a disorder of unknown aetiology affecting 5-10% of all pregnancies characterised by the development of hypertension with proteinuria after 20 weeks of gestation.

Hypertension-sustained systolic pressure of at least 140 mmHg or a sustained diastolic pressure of at least 90 mmHg that occurs after 20 weeks of gestation in a woman with previously normal blood pressure.

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FACTORS	MILD	SEVERE
Systolic Blood Pressure	<160 mmHg	>160 mmHg
Diastolic Blood Pressure	<110 mmHg	>110 mmHg
Urinary Protein	<5 gm/24 hrs. Dipstick 1+ or 2+	>5 gm/24 hrs. Dipstick 3+ or 4+
Headache	No	Yes
Visual Disturbance	No	Yes
Epigastric Pain	No	Yes
Right Upper Quadrant Pain	No	Yes
Pulmonary Oedema	No	Yes
Cyanosis	No	Yes
HELLP	No	Yes
Platelet Count	>1,00,000/cumm	<1,00,000/cumm

Features of Pregnancy-Induced Hypertension

Maternal complications of severe pregnancy-induced hypertension include pulmonary oedema, intracerebral haemorrhage, and renal failure. Foetal complications include Intrauterine Growth Retardation (IUGR), perinatal mortality. Management of severe pregnancy-induced hypertension requires multidisciplinary approach.

Prophylaxis

- Aspirin 60-100 mg/day. Not well established.
- Oral calcium 2 gm/day. Not well established.
- Definitive treatment consists of termination of pregnancy along with prevention of seizures and control of blood pressure.

OBSTETRIC MANAGEMENT

Regardless of Gestational Age Immediate Delivery is Advocated in

1. Persistent severe hypertension for 24-48 hrs.
2. Progressive thrombocytopenia (<1,00,000).
3. Progressive renal dysfunction (urine output <0.5 mL/kg/mt., serum creatinine 1 mg% above baseline).
4. Premonitory signs of eclampsia.
5. Foetal jeopardy.
6. Pulmonary oedema.
7. Elevated liver enzymes ALT/AST >2 times normal with abdominal pain.
8. AF index <2.

Drug Therapy

Magnesium sulphate for seizure prophylaxis.

Antihypertensives-to bring diastolic blood pressure between 90-105 mmHg and mean arterial blood pressure 105-125 mmHg.

The drugs used in the control of blood pressure are oral antihypertensives, alpha-methyldopa, nifedipine, labetalol, intravenous agents like hydralazine, labetalol, nitroglycerin, etc.

Intravenous labetalol[1] injection is a unique drug with both alpha and beta-adrenergic receptor blocking properties. It has both blood pressure and heart rate reducing properties.

This makes it a good choice in treating high blood pressure in severe pregnancy-induced hypertension patients.

Our study is to find out the efficacy of intravenous labetalol injection in the acute control of high blood pressure in severe Pregnancy-Induced Hypertension (PIH) patients.

MATERIALS AND METHODS

After obtaining the necessary institutional and ethical committee clearance following study was conducted in Intensive Care Unit of Dept. of Obstetrics and Gynaecology, Govt. Vellore Medical College, Adukkamparai, Vellore. All antenatal mothers were screened for severe Pregnancy-Induced Hypertension (PIH). Forty (40) patients with severe PIH were selected. Informed consent was obtained from them and randomly divided into 2 groups namely Group A and Group L of 20 each.

Inclusion Criteria: (Any One of the Following)

1. Systolic blood pressure > 160 mmHg.
2. Diastolic blood pressure >110 mmHg.
3. Proteinuria (Dipsticks) >+3 or+4.
4. History of oliguria or urine output <500 mL in 24 hours.
5. Presenting with imminent features-blurring of vision, epigastric pain, hyperreflexia, HELLP.

Exclusion Criteria: (Any One of the Following)

1. Secondary hypertension.
2. Cardiac arrhythmia.
3. Bronchial asthma.
4. Diabetes mellitus.
5. Complications due to severe pregnancy-induced hypertension like intracerebral haemorrhage, acute left ventricular failure, coagulopathy, bleeding disorders.
6. Patients already on oral antihypertensives are not included in group L.

Selected patients were examined and the nature of disease and its treatment explained to them. They were made to lie down in supine position with a 15-25 degree lateral tilt by placing a wedge below the right hip to avoid supine hypotension syndrome/aortocaval compression. All patients were maintained on nil per status since admission. Baseline parameters like weight, height, blood pressure, heart rate, respiratory rate, temperature, SpO2, jugular venous pulse, and foetal heart rate were recorded. A 16G intravenous line was started in the dorsum of left hand and Ringer lactate was administered at 85 mL per hour. Urinary bladder was catheterised and urine output monitored. Blood sample was collected and sent for following investigations: Blood grouping/typing, Hb, PCV, urea, creatinine, electrolytes, sugar, uric acid, fibrinogen, platelet count, bleeding time, and clotting time.

Group A patients were administered two tablets of alpha-methyldopa 250[2] mg and one tablet of nifedipine[3][4] 10 mg each with a sip of water. In the Intensive Care Unit (ICU), they were monitored for control of blood pressure/progress of pregnancy/seizures. If 3 hours after starting oral antihypertensive combination either the Mean Arterial Pressure (MAP)/Diastolic Blood Pressure (DBP) is found to be more than 125 mmHg/105 mmHg, then injection nitroglycerin infusion[5] is administered at 5 microgram/kg/min. as a rescue drug.

Group L patients, injection labetalol 20 mg was administered by intravenous route slowly and repeated every 10 minutes if necessary.

The aim in both groups of patients is to achieve a target blood pressure of mean arterial pressure 105-125 mmHg and diastolic blood pressure 90-105 mmHg.[6]

Both group of patients were administered 4 gm of magnesium sulphate intravenously over 30 minutes in 100 mL of normal saline followed by administration of 1 gm/hr magnesium sulphate IV for the next 24 hrs. The patients were monitored for evidence of magnesium toxicity like absence of tendon reflexes, diminished respiration, and urine output. If evidence of magnesium toxicity is found, the administration of magnesium sulfate is stopped and calcium gluconate 1 gm IV is administered slowly with ECG monitoring.

The Following Parameters were Recorded Every 5 Minutes During the Study.

1. Systolic Blood Pressure (SBP).
2. Diastolic Blood Pressure (DBP).
3. Mean Arterial Pressure (MAP).
4. Heart rate.
5. Foetal heart rate.
6. SpO2 - room air.
7. Urine output (Hourly).

The Administration of Either Nitroglycerin or Labetalol is Tapered[7]/Stopped Respectively if

1. Diastolic blood pressure < or = 105 mmHg and mean arterial pressure < or = 125 mmHg.
2. Heart rate <60/min.
3. Total labetalol dose administered >2 mg/kg body weight.
4. Foetal heart rate <120/min or >160/min.[8]

If any patient developed diastolic blood pressure <90 mmHg or mean arterial pressure <105 mmHg even after stopping all antihypertensives,[9] patient is administered humidified 100% oxygen by face mask, adequately ventilated, and fluid infused rapidly until diastolic blood pressure more than 90 mmHg/mean arterial pressure >105 mmHg with caution to avoid pulmonary oedema.

If any patient developed heart rate <60/min and features of symptomatic bradycardia (shortness of breath, light headedness, angina, ischaemic changes, cool peripheries, diastolic blood pressure/mean arterial pressure <90/105 mmHg), injection labetalol is stopped, patient is administered humidified 100% oxygen by facemask, adequately ventilated, and fluid infused rapidly until diastolic blood pressure more than 90 mmHg/mean arterial pressure >105 mmHg, injection atropine 0.3-0.5 bolus repeated if necessary at 5 min intervals (maximum 3 mg) with caution to avoid pulmonary oedema.

In our study, pregnancy was terminated for obstetric reasons in all patients of both groups. After premedication with 0.2 mg glycopyrrolate intramuscular, 10 mg injection metoclopramide intramuscular, and injection ranitidine 50 mg intravenous, emergency termination of pregnancy is accomplished by

1. Induction of labour and normal vaginal delivery (only one patient in group L who failed to achieve target blood pressure).
2. Emergency LSCS under general anaesthesia[10] (4 patients in group A who failed to achieve target blood pressure).
3. Emergency Lower Segment Caesarean Section (LSCS) under regional anaesthesia (All patient in both groups who achieved target blood pressure).

RESULTS

Mean Values	Group A (n=20)	Group L (n=20)
Age (Years)	25.2	25
Weight (kg)	63.1	64.8
Height (cms)	143.5	148.5

Table 1: Demographic Profile

Table no. 1 shows the patient characteristics, age, height, and weight observed in both groups.

	Group A (n=20)	Group L (n=20)	p Value
Mean	32.8	33.5	0.28 (not significant)
S.D.	1.92	2.11	
Median	32	33.5	
Range	30-37	30-37	

Table 2: Gestational Age (Weeks)

Table no. 2 shows the distribution range and mean gestational ages observed in both groups. In Group A, the mean gestational age is 32.8 weeks. In Group L, the mean gestational age is 33.5 weeks. Both groups are comparable with p value (0.28) not significant.

	Group A (n=20)	Group L (n=20)	p Value
Failure	20% (n=4)	5% (n=1)	0.34 (not significant)

Table 3: Failure Rate to Achieve Blood Pressure Control

Table no. 3 shows the failure rate to achieve blood pressure control in both groups. In Group A, out of 20 patients, 4 patients (20%) failed to achieve blood pressure control despite using injection nitroglycerin as rescue drug. In Group L patients, only one patient (5%) failed to achieve blood pressure control. The failure rate between the 2 groups is not statistically significant with p value (0.34).

Time	Group A (n=16)	Group L (n=19)	p Value
Mean	185.9	46.8	<0.001 (significant)
S.D.	20.75	11.57	

Table 4: Time to Achieve Target Blood Pressure (in Minutes)

Table no. 4 shows the mean, standard deviation of the time taken to achieve target blood pressure in both groups. In Group A patients, (n=16) the mean time taken to achieve target blood pressure is 185.9 minutes. In Group L patients, (n=19) the mean time taken to achieve target blood pressure is 46.8 minutes. The time difference to achieve target blood pressure between the 2 groups is statistically significant (p value <0.001).

	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	Mat HR (/min.)	R.R. (/min.)	Fet. HR (/min.)	U.O. (mL)	TIME (min.)
Before Treatment	178.1 +/- 14.34	118.7+ /- 12.16	140.8+ /- 12.35	81.2+/ -7.29	24.6+ /- 2.01	135.2+ /-4.87	175.0+ /- 59.60	185.9+ /- 20.75
After Treatment	151.8 +/- 5.34	100.4+ /-4.15	118.1+ /-4.57	104.2+ /- 11.48	24.2+ /- 1.09	135.7+ /-5.91		

Table 5: Group A Mean Values + Standard deviation

	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	Mat. HR (/min.)	R.R. (/min.)	Fet. HR (/min.)	U.O. (mL)	Time (min.)
Before Treatment	184.7 +/- 19.16	122.7 +/- 8.43	143.4+/ -11.63	95.2+/- 6.68	25.1+ /-2.7	137.8 +/- 6.15	137.5 +/- 65.60	46.8+ /- 11.57
After Treatment	146.2 +/-4.5	100.6 +/- 3.42	115.8+/ -3.01	76.5+/- 7.89	25.8+ /- 2.71	135.7 +/- 5.13		

Table 6: Group L Mean Values + Standard Deviation

APGAR Score	Group A (n=20)	Group L (n=19)	p Value
1 min.			
Mean	6.45	6.53	0.70 (not significant)
S.D.	0.61	0.61	
Median	6	6	
Range	6-8	6-8	
5 min.			
Mean	8.5	8.6	0.42 (not significant)
S.D.	0.51	0.50	
Median	8.5	9	
Range	8-9	8-9	

Table 7: APGAR Scores-1 Min. and 5 Min.-Distribution

Table No. 7 shows the Distribution of APGAR Scores of both Group Neonates at 1 Min. and 5 Min. Intervals.

- In group A neonates, the mean Apgar at 1 min. is 6.45.
- In group L neonates, the mean Apgar at 1 min. is 6.53.
- Both groups are comparable with a p value of 0.70.
- In group A neonates, the mean Apgar at 5 min. is 8.5.
- In group L neonates, the mean Apgar at 5 min. is 8.6.
- Both groups are comparable with a p value of 0.42.

DISCUSSION

In severe pregnancy-induced hypertension patients, it is of vital importance to control high blood pressure preoperatively to reduce the incidence of maternal complications like pulmonary oedema, intracerebral haemorrhage, and renal failure. Foetal complications include Intrauterine Growth Retardation (IUGR), perinatal mortality.[11]

Various drugs like methyldopa, ketanserin, hydralazine, labetalol, nifedipine have been used to control high blood pressure.

In our study, group A patients were administered a combination of oral alpha-methyldopa and nifedipine. Only 16 out of 20 patients achieved blood pressure control and 4 patients failed to achieve target blood pressure despite using intravenous nitroglycerin as rescue drug. Also, out of the 16 patients who achieved blood pressure control, 13 patients necessitated the use of rescue drug namely intravenous nitroglycerin. Only 3 patients achieved blood pressure control within 3 hours after starting oral antihypertensive combination without use of rescue drug nitroglycerin. The maternal mean arterial blood pressure was reduced 22.7 mmHg from 140.8+/-12.35 mmHg to 118.1+/- mmHg, but mean maternal heart rate increased 23/min. from 81.2+/-7.29/min. to 104.2+/-11.48/min. due to nitroglycerin-induced reflex tachycardia.

In our study group, L patients were administered intravenous labetalol, 19 out of 20 patients achieved blood pressure control with one patient failing to do so. In that patient, the dose was restricted to a maximum of 2 mg/kg, though a maximum of 140 mg per episode has been recommended.[6] The maternal mean arterial blood pressure was reduced 27.4 mmHg from 143.4+/-11.63 mmHg to 115.8+/-3.01 mmHg while the mean maternal heart rate was reduced 18.7/min. from 95.2+/-6.68/min. to 76.5+/-7.89/min. Since injection labetalol 20 mg was administered intravenously and repeated every 10 minutes if necessary with careful monitoring, there was not any case of hypotension or haemodynamic collapse.[12] Though, there was a reduction in the maternal heart rate after administration of labetalol injection, none of the patients developed symptomatic bradycardia because of careful titration of the drug and the fact that none of our patient received the maximum dose of 140 mg. One patient delivered a dead born baby. One of the known foetal complications of severe pregnancy-induced hypertension is perinatal mortality due to uncontrolled hypertension.

In our study, Group L patients target blood pressure was achieved in a shorter time of 46.8+/-11.57 min. when compared to group A patients who took a longer time of 185.9+/-20.75 min.

In our study, group L patients who received intravenous labetalol for acute management of high blood pressure in severe Pregnancy-Induced Hypertension (PIH) achieved more rapid blood pressure control with better heart rate control than Group A patients who received oral antihypertensives.

CONCLUSION

In conclusion, intravenous labetalol achieves adequate and faster blood pressure control with better heart rate maintenance than the routinely used oral antihypertensive combination of tablets alpha-methyldopa and nifedipine in the control of blood pressure in severe pregnancy-induced hypertension patients.

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