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A Study of Intravenous Labetalol In Severe Hypertension In 90 Cases of Preeclampsia From February 2013 to March 2014 At Government Maternity Hospital, Osmania Medical College, Hyderabad

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Abstract:
Aim: *Is to study the safety and effectiveness of IV Labetalol in severe hypertension in pregnancy.*
Background*: Hypertensive disorders of pregnancy, including preeclampsia, complicate up to 10% of pregnancies worldwide, constituting one of the greatest causes of maternal and perinatal morbidity and mortality worldwide[1].*
Analysis of Maternal Mortality from Jan'09 to Jun'12 in 3 and1/2yrs showed 125 maternal deaths,18 [14.4%] due to Eclampsia - of which 11 were due to cerebrovascular accident, 2 due to PPH, 2 due to pulmonary edema ,2 due to aspiration pneumonia and 1 due to pulmonary embolism. There were many more cases of severe maternal and perinatal morbidity. Magnesium Sulphate is a safe and effective anticonvulsant and successful induction of labor is achieved with Prostaglandins. We are left with the problem of immediate control of HTN as CVA is found to be the leading cause of maternal mortality in eclampsia .This shows the scope for use of IV Labetalol.
Material and Methods *:During one year period from February 2013 to March 2014 - 90 Women with severe HTN, imminent eclampsia and eclampsia with a Diastolic pressure >110mmhg are selected. Intermittent Intravenous Labetalol is given either alone or with other antihypertensive drugs with the aim to reduce the severity of diastolic pressure to <110 mmhg .Blood pressure and pulse rate are monitored before and after giving the dose. Control of Blood pressure, Side effects of the drug and perinatal outcome are analyzed.*
Results: *None of the patients had any symptoms suggestive of side effects. There is considerable variation in dose.20mg of IV Labetalol was sufficient in 30% cases. Maximum dose required was 110mg,smaller doses were required when used with oral nefidipine. Duration of action was 6hrs in 91% cases.Perinatal Survival is 92.1%*
Conclusion: *IV Labetalol is both effective and safe in severe HTN in pregnancy. ACOG recommends labetalol as an appropriate first line treatment in severe HTN in pregnancy.*
Keywords*: Hypertension in Pregnancy, Severe hypertension, Intravenous Labetalol.*

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I Introduction

Hypertensive disorders are the most common medical complications of pregnancy and are an important cause of maternal and perinatal morbidity and mortality worldwide [1]. Hypertension in pregnancy is still a leading cause of maternal and perinatal morbidity and mortality. Incidence is as high as 10-15% with estimated 50,000-60,000 preeclampsia-related deaths per year worldwide. For every preeclampsia-related death that occurs in there are probably 50-100 other women who experience "near miss" significant maternal morbidity. Early diagnosis and timely intervention prevents grave complications. Hypertension is considered severe if there is sustained elevation of systolic pressure to 160mmhg and diastolic pressure to 110mmhg for at least 6hrs .Severe hypertension in pregnancy should be treated promptly to prevent eclampsia, cerebrovascular accident, congestive cardiac failure, pulmonary edema and placental abruption and to decrease maternal and perinatal morbidity and mortality [2 3 4]. Controlling blood pressure is the optimal intervention to prevent deaths due to stroke in women with preeclampsia[5] Acute-onset, severe systolic hypertension (greater than or equal to 160 mm Hg); severe diastolic hypertension (greater than or equal to 110 mm Hg); or both can occur in the antepartum, intrapartum or postpartum period. Intravenous (IV) labetalol, oral nefidipine and hydralazine have long been considered first-line medications for the management of acute-onset, severe hypertension in pregnant women and women in the postpartum period[2].

Labetalol is a nonselective Beta-Blocker and Postsynaptic alpha1 adrenergic Blocker. The ratio of Alpha to Beta blockage is 1:3&1:7 with oral and IV administration respectively. It slows heart rate and decreases systemic vascular resistance. Shows dose related fall in blood pressure without reflex tachycardia. Increase in exercise induced BP and heart rate are blunted. Elevated levels of plasma renins are reduced. Metabolism is mainly through conjugation to glucuronide metabolites. Excreted in urine and via bile in faeces.55%-60% appears in urine unchanged or as a conjugate within 1st 24hrs.Crosses placental barrier in humans. Negligible amounts crossed BBB in animal studies. As 50% is protein bound, <1% is removed by either peritoneal or hemodialysis. It is available as100mg tab, given as100mg bid to a max of 2,400mg/day.

Injectable preparation is available as 2ml ampoule (5mg/ml).It is given intermittently as 0.25mg/kg slowly over 2min as IV bolus repeated at 10-15 min intervals at 0.5mg/kg till baseline blood pressure is achieved and upto a maximum of 300mg.

Can also be given as slow continuous infusion diluted with any of the IV fluids -40ml in 160ml such that 200ml contains 200mg or 1mg/ml administered at a rate of 2ml/2mg/min or 40ml/250ml fluid=200mg in250ml=2mg/3ml given at a rate of 3ml/2mg / min. Woman should be hospitalized and kept in supine position for 3hrs.Rate of infusion is adjusted according to

response using a graduated burette or an infusion pump till satisfactory response is achieved and then switched over to oral preparation. Half life of IV preparation is 5-6hrs and of oral is 6-8hrs.Total body clearance is 33ml/min/kg and not altered with impaired hepatic or renal function. Bioavailability is increased in hepatic impairment due to decreased first pass metabolism.

Blood pressure and pulse rate are monitored before and after giving the dose. Look for any symptoms suggestive of side effects. Common side effects are postural hypotension, fatigue, headache dizziness nausea, vomiting, nasal stuffiness, flushing of skin and tingling of scalp etc. Use with caution in patients with asthma , bronchitis, diabetes mellitus, hepatic or renal impairment and in hyperthyroidism .Routine laboratory tests are not required before or after IV Labetalol .It can be used with other antihypertensive drugs like calcium channel blockers. Should be used with caution with frusemide[1].

B-blockade further depresses myocardial contractility and precipitates severe failure but can be used with caution in patients with history of CCF.It does not interfere with inotropic effect of digitalis. Abrupt cessation of B-blockers may cause angina and myocardial infarction. Safety not established in nonallergic bronchospasm .B-blockage may prevent the appearance of signs and symptoms of hypoglycemia e.g. tachycardia and reduces the release of insulin requiring dosage adjustment. Protracted severe fall in blood pressure may cause problems during surgery. Short term use of labetalol does not impair cardiac function or peripheral vascular resistance.

Glucagon is an antidote for labetalol toxicity; it corrects hypoglycemia and hypotension with IV dose of 300-600 micrograms/kg.

Hydrallazine is not available in our country and the side effects such as headache, nausea, and vomiting were found to be common and mimic symptoms of deteriorating pre-eclampsia[6]. A metaanalysis of randomized clinical trials using Hydralazine for the treatment of severe hypertension in pregnancy concluded that the evidence does not support the use of these agents as first line drug when compared with Labetalol and Nifedipine [7]. Oral nefidipine as a single drug is not found to be effective in all the cases. Nifedipine has been associated with an increase in maternal heart rate, and with overshoot hypotension (12.). . Hence, the aim is to study IV Labetalol in terms of efficacy, doses required to achieve desired level of blood pressure, safety profile and also to observe the fetomaternal outcomes.

Material and Methods: This hospital based prospective study was carried out in the department of Obstetrics from February 2013 to March 2014 in one year period in 90 pregnant women with severe hypertension. The study protocol was approved by ethical committee of the institution and the written informed consent was taken from all the study participants.

Inclusion criteria for the study were pregnant women with severe hypertension ,systolic BP ≥ 160mm of Hg and diastolic BP ≥ 110mm of Hg, imminent eclampsia and eclampsia with a diastolic pressure >110mmhg are selected. Intermittent Intravenous Labetalol is given either alone or with other antihypertensive drugs .Initial dose is 0.25mg/kg wt (10mg/40kgs) weight diluted with distilled water is given slow IV.Repeated every 10-15min in a dose of 0.5mg/kg weight (20mg/40kgs) with the aim to reduce the severity of diastolic pressure <100 mmhg .Blood pressure and Pulse rate are monitored before and after giving the dose. After the successful control of BP further antihypertensive was given orally. Adverse effect of the drug if any was noted carefully and treated accordingly. It was also noted if any additional drugs or crossover of drug was required if the BP was not controlled. Perinatal outcome is also analyzed.

Table no. 1

OBSERVATION AND ANALYSIS

Parity And Clinical Presentation

N 90

Parity	No	SV HTN	IE	ECLM
Primi	48	32	6	10
Multi	42	28	6	8

The incidence of Severe HTN, IE and Eclampsia is almost the same in both Primipara and multipara

Table no .2

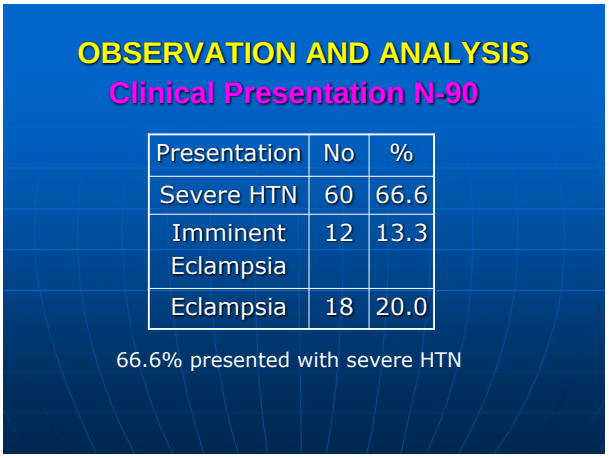
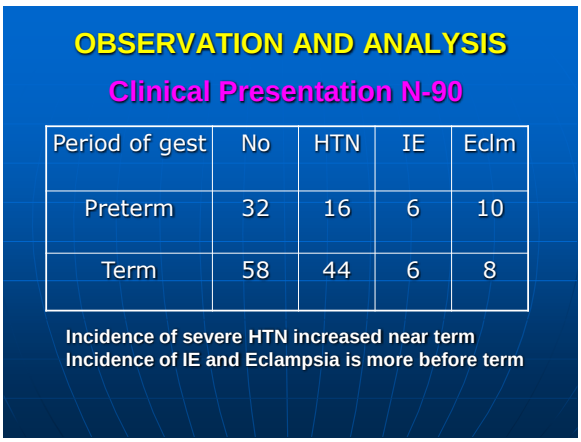


Table 3



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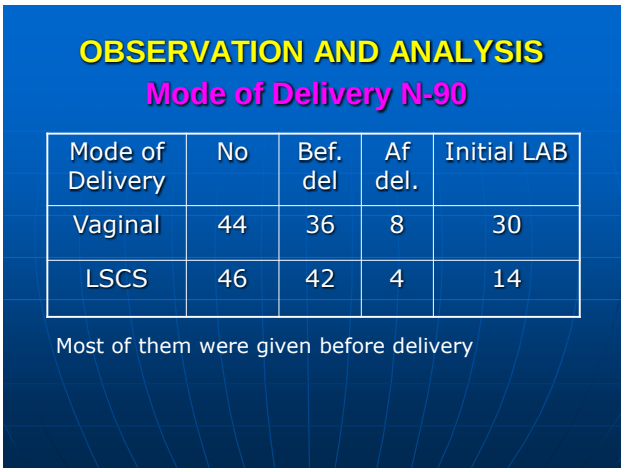


Table 5

OBSERVATION AND ANALYSIS
Birth WT And Perinatal Outcome N 90

Wt in Kg	<1	1-2	2.1-3	>3	Total
Live on Admn	_	26	40	10	76
IUD	_	10	4	_	14
Abortion		_	_	_	
Stillbirth	_			_	
Neonatal death	_		_	_	

Of the 76 babies alive at birth, 5 were stillbirth's .1 twin baby of 1.25kg had neonatal death. The perinatal survival was 92.1%.One patient with severe hypertension at term and on Nefidepine ,received 30mg of IV Labetalol but BP was not well controlled and we lost the baby due to antepartum haemarrhage.Four babies with fetal distress in labor had stillbirth**.**

Table 6

OBSERVATION AND ANALYSIS
Mode of Delivery And Dose N-90

Mode of Delivery	No	10 mg	20 mg	30 mg	40 mg	70 mg	110 mg
Vaginal	44	4	20	8	4	8	---
LSCS	46	12	14	6	2	10	2
Total	90	16	34	14	6	18	2

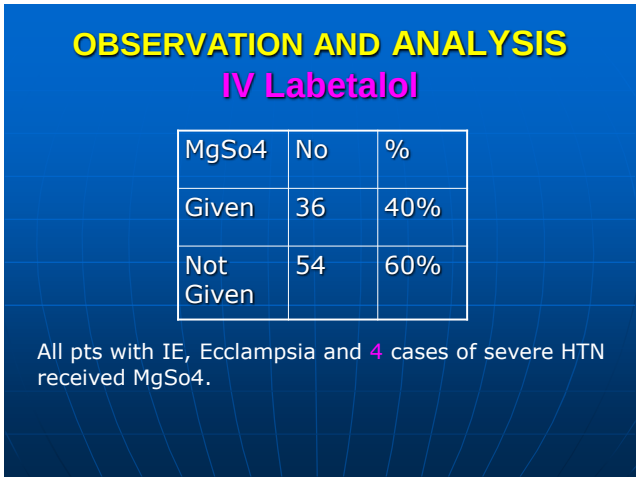
There is considerable variation in dose in both the groups

Table 7

OBSERVATION AND ANALYSIS
IV Labetalol

Time of Admn	No	Initial LAB	VD/CS	Other drugs	VD/CS
Before Del	78	38	24/14	40	12/28
After Del	12	6	4/2	6	2/4

Table 8



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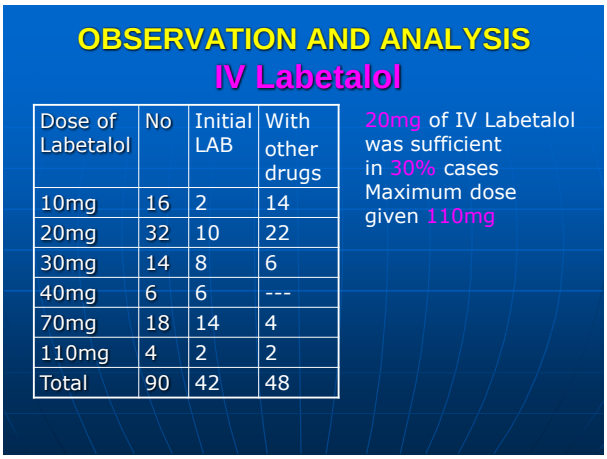

Table 10

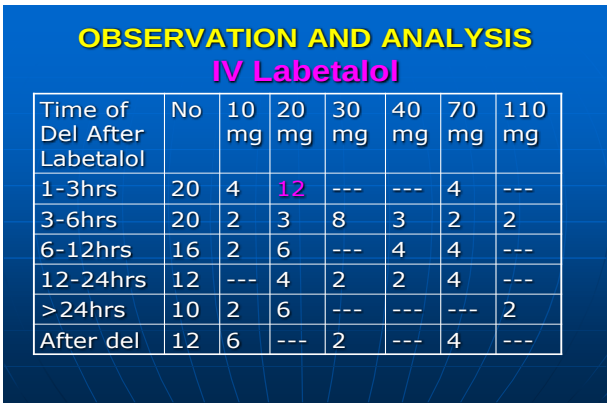

Table 11

MONITORING
IV Labetalol N- 90

DP > 110	Initial LAB	Other drugs	No	%
1hr	12	6	18	20
3hrs	6	6	12	13
6hrs	4	4	8	8.8

In one case Labetalol was stopped due to bradycardia. Nefidepine was added in others.
Duration of action was 6hrs in 91% cases

Table 12

COMPARATIVE STUDY
IV Labetalol

Study Grp	Yr	DP	Rx failure	%	FD
Mabie etal	1987	>110	4/40	10	0
Garden etal	1982	115-130	2/6	33	0
Micheal etal	1986	105-140	3/45	7	0
Ashe etal	1987	>118	6/10	60	1
Our study	2013-14	>110	18/90	20	0

Mabie etal concluded that there is considerable variation in dose with short duration of action in those requiring highest dose
Ashe etal- concluded that there are no harmful effects on fetus/neonate.
Michael etal-concluded that BP is better controlled, which may influence perinatal outcome

Results

The incidence of Severe HTN, imminent eclampsia, and ecclampsia is almost the same in both Primipara and multipara. 66.6% presented with severe HTN.None of the patients had any symptoms suggestive of side effects. In 5/6pts with pulse rate 100 and above it has come down to 80-100. One patient developed bradycardia after 20mg of Labetalol and it was stopped. Incidence of severe HTN increased near term and incidence of IE and Eclampsia is more before term.
There is considerable variation in dose and smaller doses are required when used with oral nefidipine as seen in Mabie etal study who concluded that there is considerable variation in dose with short duration of action in those requiring highest dose.
All patients with imminent eclampsia, ecclampsia and 4 cases of severe HTN received MgSo4 with no untoward effects.20mg of IV Labetalol was sufficient in 30% cases. Maximum dose required was 110mg.
One patient had APH and stillbirth due to severe HTN .One patient with oliguria, and tachycardia was given Labetalol without any untoward effects. Duration of action was 6hrs in 91% cases.Perinatal Survival is 92.1%. It is found to be safe and effective antihypertensive for emergency use, especially useful to control BP before emergency LSCS.Was useful in patients with tachycardia with decrease in the pulse rate. None of cases with severe HTN developed imminent eclampsia or eclampsia.There were no cases of CVA, PPH, Aspiration Pneumonia or Pulmonary edema in the study group. There was no Maternal Mortality in 90 cases studied.

Discussion

Two thirds of the maternal deaths in the most recent Confidential Enquiries report from the United Kingdom for 2003–2005 resulted from either cerebral hemorrhage or infarction. The degree of systolic hypertension (as opposed to the level of diastolic hypertension or relative increase or rate of increase of mean arterial pressure from baseline levels) may be the most important predictor of cerebral injury and infarction. Thus, systolic blood pressure (BP) of 160 mm Hg or greater widely is

included as part of the definition of severe hypertension in pregnant women or women in the postpartum period. Pregnant women or women in the postpartum period with acute-onset, severe systolic hypertension; severe diastolic hypertension; or both require antihypertensive therapy. The goal is not to normalize BP, but to achieve a range of 140–150/90–100 mm Hg in order to prevent repeated, prolonged exposure of the patient to severe systolic hypertension, with subsequent loss of cerebral vasculature autoregulation. When this happens, maternal stabilization should occur before delivery, even in urgent circumstances[9]. As per NICE clinical guideline 107 - Hypertension in Pregnancy[8] the first line antihypertensive which can be used in severe pregnancy induced Hypertension are Labetalol (Oral / intravenous), Hydralezine (intravenous) or Nefidipine (oral). Of those we had chosen intravenous Labetalol for controlling the blood pressure in severe pre-eclampsia.

Labetalol effectively reduced BP in those women with severe hypertension complicating pregnancy. The results of the use of labetalol in the treatment of severe hypertension arising in pregnancy are encouraging[14]. The freedom from maternal and fetal side-effects, the efficient hypotensive action and consequent improved perinatal mortality in a condition usually accompanied by high fetal loss, indicate that labetalol is suitable for use during pregnancy. There was considerable interpatient variability in the dose of labetalol required to control BP, which could not be predicted by any clinical characteristic before therapy. The duration of action also varied in the labetalol, with the shortest duration occurring in those patients who required the highest dosage for BP control.

Conclusion

Risk reduction and successful, safe clinical outcomes for women with preeclampsia, eclampsia, or chronic hypertension with superimposed preeclampsia require avoidance and management of severe systolic and severe diastolic hypertension. Increasing evidence indicates that standardization of care improves patient outcomes. Systolic BP ≥ 160 mm Hg or diastolic BP ≥ 110 mm Hg warrant prompt evaluation at the bedside and treatment to decrease maternal morbidity and mortality. We conclude that labetalol appears to be a safe and effective alternative to hydralazine for treating hypertension in the peripartum period, but serious rare side effects have not yet been quantified.(4) Labetalol is both effective and safe in severe HTN.ACOG recommends labetalol as an appropriate first line treatment in severe HTN in pregnancy. All pregnant women with pre-eclampsia and a systolic blood pressure of 150–160 mmHg or more require urgent and effective anti-hypertensive treatment in line with the recent guidelines from the National Institute for Health and Clinical Excellence (NICE) .

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