Original Article

Pre-operative Preparation of Pre-eclamptic Patients Undergoing Cesarean Section: A Prospective Randomized Comparative Study Between The Effect of Labetalol Versus Nifedipine in Controlling Elevation of Blood Pressure

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ABSTRACT

Background: Pre-eclampsia is a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks' gestation.

Aim: This work aimed to compare the anti-hypertensive efficacy of oral Labetalol with oral Nifedipine in mild preeclampsia.

Materials and Methods: This study was conducted on a total of 100 antenatal mild full term pre-eclamptic women at Ain-Shams University Maternity Hospital ICU and obstetric theater. They were divided into two groups; first group (group A): oral Labetalol was started with a dose of 200 mg and second group (group B): oral Nifedipine was started at dose of 20 mg.

Results: Group B had significantly higher number of side effects when compared to group A. None of the patients developed grave complications such as HELLP syndrome, pulmonary edema, coagulopathy, postpartum collapse, the maternal mortality was nil. Thus when patients with preeclampsia are identified and treated at an earlier stage the morbidity and mortality associated with preeclampsia can be significantly reduced.

Conclusion:Both oral labetalol and oral Nifedipine are equally efficacious in the control of hypertension in mild preeclampsia. Regarding the drug side effects and tolerability, labetalol was significantly better than Nifedipine. There was no significant difference in the neonatal outcome between the two groups. Thus, labetalol is a better alternative to Nifedipine,as it had lesser side effect profile. However, in a limited resource setting, Nifedipine is an equally effective, cheap and easily available drug for mild preeclampsia.

Key Words: Blood pressure, cesarean section, labetalol, Nifedipine, pre-eclampsia

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INTRODUCTION

Complications of pre-eclampsia are serious and may affect both the mother and the fetus; acutely pre-eclampsia can be complicated by several types of strokes either ischemic or hemorrhagic which may lead to intracerebral hemorrhage. Other serious complication is HELLP syndrome.

Recently, this syndrome undergoes new classification made by University of Mississippi, which classified the disease into 3 classes according to degree of thrombocytopenia, evidence of suggestive hemolysis and evidence of Hepatic dysfunction, another classification made by University of Tennessee, which has the same criteria[1].

The usage of anti-hypertensive drugs in mild pregnancy-induced hypertension or pre-eclampsia is not strongly recommended, only when blood pressure is greater than 150/100-millimeter mercury (mmHg), Labetalol or Nifedipine are advised as drug of choice.

Despite that the conventional treatment of pregnancy-induced hypertension is methyldopa (Aldomit), recent studies revealed that beta-blockers and calcium-channel blockers seems to be more effective than methyldopa as they reduce overall risk of developing proteinuria/pre-eclampsia when either are compared with methyldopa[2].

Labetalol is a nonselective, competitive beta-adrenergic and a selective, competitive alpha1-adrenergic blocking agent. The mechanism of action is exerted by reduction of peripheral vascular resistance without compromising blood flow to the brain and peripheral, coronary, or renal systems[3].

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Potential benefits include quick onset of action and less risk for reflex tachycardia. Labetalol, however, should be avoided in patients with moderate-to-severe asthma, bradycardia (heart rate <60 beats per minute), or congestive heart failure[3].

Nifedipine is an oral, type 2 calcium channel blocker that inhibits the inward flow of calcium across slow channels of cellular membranes. It reduces BP without compromise to placental blood flow. Nifedipine should only be given as an oral short-acting preparation in an initial dose of 10 to 20 milli-gram(mg) orally every 30 minutes for a maximum dosage of 50 mg. Common side effects include tachycardia, headaches, and palpitations[4].

AIM OF THE WORK

To compare the anti-hypertensive efficacy of oral Labetalol with oral Nifedipine in mild preeclampsia and to study the maternal and perinatal outcome in mild preeclampsia following treatment with oral Labetalol or oral Nifedipine.

PATIENTS AND METHODS

This double blinded randomized controlled trial was conducted on 100 pregnant term women with mild pre-eclampsia undergoing elective cesarean section; a superiority with allocation ratio 1:1 at Ain-Shams University Maternity Hospital ICU and obstetric theater during a period of 6 months.

The study included pregnant full-term women with mild pre-eclampsia undergoing elective cesearian section. While patients on any antihypertensive treatment in the preceding 72 hours. Patients with chronic hypertension, gestational hypertension, severe preeclampsia or eclampsia, patients with history of heart rhythm abnormality and heart failure, patients with asthma, Patients with allergy to either Nifedipine or labetalol, patient with kidney, liver, central nervous system disease, patients with coagulopathies and blood diseases and patients with abnormal CTG, Patients whom arranged for vaginal delivery were excluded from the study.

Informed written consents were taken from all patients before being enrolled in the study. All Patients were assigned randomly by computer to two equal groups (50 patients per group): First group (group A) received oral Labetalol was started with a dose of 200 mg and Second group (group B) received oral Nifedipine was started at dose of 20 mg.

All of our patients were submitted to the following; history and clinical examination were done. Once the diagnosis of mild preeclampsia was made, all patients were admitted. The baseline arterial blood pressure was measured and Mean Arterial pressure (MAP) was calculated according to formula:

$$MAP \simeq DP + \frac{1}{3}PP$$

where PP is the pulse pressure $SP - DP$

Investigations such as complete blood count, blood sugar, liver function test, renal function test, prothrombin time, clotting time, bleeding time, ultrasound abdomen were done.

Patients with blood pressure 150/100 mm of Hg and above were started on antihypertensive drug (NICE Guidelines 2011). The 100 patients were distributed in two groups randomly; group A received labetalol 200 mg. and group B received Nifedipine 20 mg as starting dose

The follow-up setting: Blood pressure of the patients was monitored as follows; every 30 minutes in first hour after giving medication, then every hour till arranged time of elective CS which is 6 hours from the start of treatment. The initial dosage of antihypertensive drug of both groups was observed and titrated according to the blood pressure and the side effects associated with the drug taken were documented. If the mean arterial blood pressure > 110 mmHg after the 1st hour an additional dose of 100 mg labetalol for group A and 10 mg Nifedipine for group B is taken. If the mean arterial blood pressure > 100 mmHg after the 2nd hour or at any hour before surgery additional dose of 100 mg labetalol for group A and 10 mg Nifedipine for group B is taken. If the Mean arterial blood pressure > 100 mmHg after the 3rd hour the subject considered out of trial and shifted to Hydralazine to control the blood pressure. Magnesium sulphate was added to patients who developed severe pre-eclampsia and eclampsia. Antihypertensive efficacy, disease progression, drug side effects and neonatal complications were documented.

Post-operative settings: the blood pressure was measured every 2 hours for 24 hours. The antihypertensive was continued if BP ≥ 150100/ mm Hg. Patients who were on antihypertensive during the postnatal period were advised to continue the drug till 12 weeks postpartum and then tapered according to their blood pressure.

STATISTICAL ANALYSIS:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were

expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. The following tests were done: independent-samples t-test of significance was used when comparing between two means, Mann Whitney Z test for two-group comparisons in non-parametric data, Chi-square (x2) test of significance was used in order to compare proportions between two qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following *p-value <0.05* was considered significant.

RESULTS

Mean blood pressure of both study group at different periods of follow up with *p- value >0.05* which is statistically insignificant. Majority of the patients required dose between 200 and 400 mg. Majority of the patients required dose between 20 and 30 mg.

Control of blood pressure: In group A all 50 patients had adequate control of blood pressure; while in group B all 50 patients had adequate control of blood pressure.

Among the patients in group A taking oral Labetalol 14% progressed to severe preeclampsia. Among the patients in group B taking oral Nifedipine 20% progressed to severe preeclampsia. The difference was not statistically significant. Onset of eclampsia in group A and group B 2% of the patients had eclampsia.

Drug side effects: In group A none of the patients developed drug side effects and in group B 12% of the patients had side effects. Out of which 6% had headache, 4% had palpitation and 2% had giddiness.

There was statistically significant difference between the two groups; group B had significantly higher side effects than group A.

Neonatal admission: In group A 4 (8%) babies born had neonatal admission and in group B 5 (10%) babies born had neonatal admission. There was no statistical difference between the two groups. The most common reasons being respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN). As regards postpartum follow up, in group A 48 patients (96%) did not require anti-hypertensive in their post-partum period and the remaining 2 patients (4%) required treatment.

However, in group B 46 patients (92%) did not require anti-hypertensive in their post-partum period and the remaining 4 patients (8%) required treatment.

Table 1: Mean blood pressure follow up

Time	Group A		Group B		Total		
	Mean	SD	Mean	SD	t	df	*p-value*
Baseline	113.90	5.72	112.61	5.67	1.061	86	0.291
30min	96.52	8.04	94.32	8.85	1.219	86	0.226
1st hr	91.21	7.16	90.15	7.67	0.670	86	0.504
2nd hr	91.47	5.83	89.81	8.92	1.031	74.286	0.306
3rd hr	87.59	5.61	87.57	7.02	0.014	69	0.989
4th hr	87.84	4.24	84.38	5.54	2.027	31	0.051
5th hr	86.33	4.29	85.33	4.47	0.420	13	0.681
termination	87.88	6.55	85.61	7.25	1.542	86	0.127

N: number. χ2:statistic. Df: degree of freedom; t: statistics

Table 2: Required dose of the drug-group A, oral Labetalol

Dose (mg)	Group A (n=50)	(100%)
200	17	34.0%
300	13	26.0%
400	11	22.0%
500	7	14.0%
600	2	4.0%

Table 3: Required dose of the drug-group B, oral Nifedipine

Dose (mg)	Group B (n=50)	(100%)
20	14	28.0%
30	24	48.0%
40	12	24.0%

Table 4: Control of blood pressure

Control BP	Group A		Group B		Total		Statistical inference
	(n=50)	(100%)	(n=50)	(100%)	(n=100)	(n=100)	
Control	50	100.0%	50	100.0%	100	100	Nil

Table 5: Progression to severe pre-eclampsia

	Group A No=50	%	Group B No=50	%	Total	%	Statistical inference
Progression to severe preeclampsia	7	14	10	20	17	17	X2=0.870 Df=2 0.602>0.05 Not significant

Table 6: Onset of Eclampsia

Eclampsia	Group A		Group B		Total		Statistical inference
	(n=50)	(%)	(n=50)	(%)	(n=100)	(%)	
1	1	2.0%	1	2.0%	2	2.0%	X2=.000 Df=1 1.000>0.05 Not Significant

Table 7: Drug side effects

Drug side effects	Group A		Group B		Total		Statistical inference
	(n=50)	(%)	(n=50)	(%)	(n=100)	(%)	
Giddiness	0	0%	1	2.0%	1	1.0%	
palpitation	0	0%	2	4.0%	2	2.0%	X2=11.383 Df=3 .049<0.05 Significant
Headache	0	0%	3	6.0%	3	3.0%	

Table 8: Neonatal admission and postpartum need of antihypertensive drugs

	Group A		Group B		Total		Statistical inference
	(n=50)	(100%)	(n=50)	(100%)	(n=100)	(100%)	
Neonatal admission	4	8.0%	5	10.0%	9	9.0%	X2=1.111 Df=2.132>0.05 Not Significant
Postpartum need of antihypertensive drugs	2	4.0%	4	8.0%	6	6.0%	X2=.709 Df=1.400>0.05 Not Significant

DISCUSSION

Pre-eclampsia hypertension is one of the major causes of maternal and fetal mortality and morbidity and as long as its exact cause is unknown, its prophylaxis is uncertain [6].

In both the groups, adequate control of blood pressure was achieved. Although both oral Labetalol and oral Nifedipine are equally efficacious the mean arterial pressure was indifferent between both study groups over a period of follow up and was insignificant as *p-value >0.05*. As the mean arterial pressure in patients treated with labetalol group on admission was 113.90 mmHg while after 6 hours it was reduced to 91.21mmHg. With Nifedipine group, the mean arterial pressure on admission was 112.61mmHg which reduced to 90.15mmHg after 6 hours. The *P value was >0.05* which is statistically insignificant and there was no statistical difference between both groups regarding control of BP.

This result is consistent with a meta-analysis by Peter *et al.*(2007). Here the efficacy of oral labetalol and Nifedipine were analyzed in mild preeclampsia. They have proved that both the drugs are effective, safe and rapid in their onset of action.

This is also consistent with the study by Bharathi *et al.*[7]. Here anti-hypertensive efficacy in mild preeclampsia was studied and it was proved that both oral Labetalol and oral Nifedipine are equally effective.

In contrary to this study, Patel *et al.*[8] have proved that oral Labetalol has better efficacy than oral Nifedipine in mild preeclampsia.

Even though adequate control of blood pressure was achieved in both the groups the basic pathology behind the disease could not be altered. This is evident because in both the groups few patients progressed to severe preeclampsia with adequate blood pressure control.

In group A, patients 14% progressed to severe preeclampsia. Among them 2% developed eclampsia.

In group B, patients 20% progressed to severe preeclampsia. Among them remaining 2% of them developed eclampsia. Thus even though the rate of disease progression to severe preeclampsia was higher in group B, it was not statistically significant.

Regarding the drug side effects, in group A patients who took Labetalol none of them developed any side effects. In group B patients who took Nifedipine 12% of them developed side effects. This difference was statistically significant. The most common side effect being headache (6%) followed by palpitation (4%) and

giddiness (2%). Thus proving that Labetalol was well tolerated and without any side effect.

In the same study by Bharathi *et al.*[7] both drugs had side effects but the side effects were higher in Nifedipine group. Similar to our study the most common side effect with Nifedipine was headache. But in contrary to this study, where there were no side effects with Labetalol, in the study by Bharathi *et al.*[7] the most common side effect with Labetalol was headache.

Regarding the neonatal outcome, in group A 8% of the babies were admitted in NICU ward and in group B 10% of the babies were admitted in NICU ward. The most common reason being respiratory distress of new born.Thus in both the groups there is no significant difference in the neonatal outcome.

This is consistent with the results of study by Waterman *et al.*[9], which showed that there are no differential effects on utero placental or fetal hemodynamics with the use of Labetalol and Nifedipine in hypertension in pregnancy. The same study proved no differential effects on neonatal outcome including birth weight.

In contrary to this, the study by Patel *et al.*[8] the neonatal outcome was better with Labetalol as there was lower incidence of respiratory distress of new born. This is because Labetalol maintains adequate placental perfusion and there by tissue oxygenation.

Post-partum follow of the patients in both the groups, 4% patients in group A Labetalol and 6% patients in group B Nifedipine required continuation of antihypertensive in the post-partum period.

In this study, none of the patients developed life threatening complication of preeclampsia such as coagulopathy, pulmonary edema, HELLP syndrome and postpartum colapse. There was no maternal or fetal mortality in this study.

However, given the potential for bias, data on outcomes should be interpreted with caution. The results of our study concluded that both labetalol and Nifidepine are effective in controlling blood pressure in patients with mild pre-eclampsia, but labetalol is safer than Nifedipine due to less maternal and fetal side effects.

CONCLUSION

From this study it is prudent that both oral labetalol and oral Nifedipine are equally efficacious in the control of hypertension in mild preeclampsia. In both the groups, there was progression to severe preeclampsia in an average of 16% of the patients even though their blood pressure was under control. There by showing that the pathology of disease was not altered significantly in both the groups. Regarding the drug side effects and tolerability, labetalol was significantly better than Nifedipine. There was no significant difference in the neonatal outcome between the two groups. Thus labetalol is a better alternative to Nifedipine, as it had lesser side effect profile. But in a limited resource setting, Nifedipine is an equally effective, cheap and easily available drug for mild preeclampsia.

CONFLICT OF INTEREST

There are no conflicts of interests.

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