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Original Research Article

Comparison of Efficacy of Labetalol with Nifedipine in Patients of Severe Preeclampsia

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Abstract

Background: In severe pre-eclampsia marked by blood pressure ≥160/110 mmHg, administration of antihypertensive agents become mandatory. The desired antihypertensive should have a quick action and should not have any maternal or perinatal side effect. Nifedipine and Labetalol are two first-line alternatives recommended for management of severe pre-eclampsia. The present prospective comparative study was conducted in Department of Obstetrics and Gynaecology, to compare the efficacy and safety of intravenous labetalol and oral nifedipine in management of severe pre-eclampsia.

Methodology: A total of 50 pregnant women meeting the inclusion criteria were enrolled in the study after taking detailed history, examination and routine investigations. Thereafter these women were randomized into two groups; Groups A in which i.v Labetalol was given & Group B where oral nifedipine was given. Outcome was noted on the basis of time taken to achieve target BP, number of doses and crossover need.

Results: Group A has all the patients who achieved targeted BP without crossover, however in Group B, two patients required cross-over to other group to achieve the targeted BP. Mean time taken to achieve targeted BP was slightly lower in Group A (33.60±14.97 min) as compared to that in Group B (39.57±20.99 min).In Group A, maximum patients achieved targeted BP with one dose only (48%) but in Group B after excluding 2 cases who required cross-over, maximum required two doses (47.9%).However these differences were not significant statistically.

Conclusion: The finding of present study showed both labetalol as well as nifedipine to be equivalent as far as number of doses required and time taken to achieve the targeted BP is concerned however, given the safety profile and increased crossover need, labetalol is found to have better safety profile.

Keyword: Nifedipine, Labetalol and Severe Preeclampsia.

Introduction

Pre-eclampsia is a multi-organ disease process of unknown aetiology[1] characterized by the development of hypertension and proteinuria after 20 weeks of gestation. India has the incidence of pre-eclampsia, as recorded from hospital statistics, varying widely from 2 to 15% [1,2,3,4,5].

The predominant pathology of pre-eclampsia is endothelial dysfunction which sets in early 8–18thweeks of gestation, but the signs and symptoms appear in late mid trimester or in the advanced stage of the disease [1]. Main features in pathogenesis of pre-eclampsia are abnormal trophoblastic invasion of arteries, inappropriate endothelial cell activation and exaggerated inflammatory response^{0}.

Severe pre-eclampsia is defined as systolic blood pressure equal to or more than 160mmHg or diastolic blood pressure equal to or more than 110mmHg on two occasions 6 hours apart with significant proteinuria (at least 1g/L) [2].

In cases with severe pre-eclampsia marked by blood pressure $\geq$160/110 mmHg, administration of antihypertensive agents become mandatory [2]. The desired antihypertensive should have a quick action and should not have any maternal or perinatal side effect. Nifedipine and Labetalol are two first-line alternatives recommended for management of severe pre-eclampsia. Many authorities recommend nifedipine and labetalol as the first-line alternatives for severe hypertension therapy during pregnancy [2,3].

Nifedipine is a calcium channel blocker agent and has been found to be clinically useful for management of severe pre-eclampsia [2]. It does not have any serious side effect affecting the mother or the fetus [27]. Nifedipine has otherwise been used for management of preterm labour too and has not been shown to have any adverse perinatal effect [2]. Its safety has been recognized in all the trimesters of pregnancy and it is one of the most commonly used anti-hypertensives during the third trimester of pregnancy [2]. Nifedipine has the advantage of being cost effective, rapid onset of action, long duration of action and can be administered orally, however it is known to cause sudden maternal hypotension and fetal distress caused by placental hypo perfusion, palpitation and transient neuromuscular weakness when used concomitant with magnesium sulphate [2].

Labetalol, a combined α- and β-blocker, is another antihypertensive drug recommended for treatment of hypertension during pregnancy [2,3]. Its advantages include little placental transfer, less palpitation and less maternal tachycardia, however neonatal hypotension and neonatal bradycardia has been observed in some trials. Despite these stated advantages, Labetalol is often criticized for its high-cost burden.

For a developing economy like ours where cost is a major decisive factor in the selection of a pharmacological modality, the selection of a drug with higher cost can only be done if it has proven higher efficacy as compared to other available alternatives. Hence, the present study was carried out with an aim to compare the efficacy and safety of intravenous labetalol and oral nifedipine in severe pre-eclampsia.

Material and Method

The present prospective comparative study was conducted in Department of Obstetrics

and Gynaecology, Era's Lucknow Medical College &Hospital, Lucknow over a period from January 2017 –June 2018.

The study population include women with viable fetus at 20 weeks of gestation or more with severe pre-eclampsia (≥160/110mm Hg) but exclude women with history of heart rhythm abnormality, heart failure, history of asthma and with non pregnancy related hypertension.

The study was approved from the institutional ethical committee of Era's Lucknow Medical College & Hospital, Lucknow. Informed consent was obtained from all participants. Patients were enrolled in the study after taking detailed history performing complete physical examination and routine investigations such as: Complete blood count, ABO-Rh grouping, coagulation profile, GTT after 2 hrs of 75 gm of glucose, VDRL, HIV, HCV, Hbs Ag, urine (for protein, sugar, pus cell and epithelial cells), LFT, KFT, USG, fundoscopy were carried out. The patients were then allocated into two groups by computer generated randomization as follows:

GROUP A(n=25): These patients were given intravenous labetalol 20mg initially followed by 40mg after 20 minutes then 80 mg every 20 minutes till the target blood pressure (150/100mmHg) is achieved or up to maximum dose of 220 mg.

GROUP B(n=25): These patients were given oral nifedipine 20mg initially and was repeated half hourly till target BP (150/100mmHg) was achieved or up to maximum dose of 80 mg.

In case of non-achievement of targeted BP with maximum dose, crossover of treatment was done. The process was repeated till the targeted BP was not achieved.

Blood pressure measurements were done after every 10 minutes and time taken to achieve the target blood pressure, number of doses used, side effects were noted.

Non stress test was done after achieving target BP and its outcome was noted.

The data was analyzed using Statistical Package for Social Sciences, version 21.0. Data has been shown as number, percentage, mean and standard deviation. Chi-square test and student't'-test were used to analyze the data. The confidence level of the study was kept at 95% and 'p' value less than 0.05 was considered statistically significant.

Results

Table-1 shows sociodemographic status of the patients. Majority of women in both the groups were in the age group of 20-25 years (48% in group A and 32% in group B). Mean age of women was 26.72±4.89 years in Group A and 27.20±3.56 years in Group B. Although women with gravida 4 were also included in the study However, maximum numbers of women in both the groups (44% in Group A and 52% in Group B) were primigravida (Gravida 0). Majority of patients in Group A (76%) and all the patients in Group B presented between 32 to 40 weeks. Statistically, there was no significant difference between two groups with respect to age, gravida status and gestational age.

The clinical data of the women are described in Table-2 which shows Body mass index (BMI), blood pressure and pulse rate of women. Majority of women in both the groups were in normal weight category. It also shows In Group A, mean SBP, DBP and PR values were 180.80±22.72 mmHg, 118.40±12.14 mmHg and 90.88±8.60 bpm respectively whereas in Group B, these values were 177.20±16.21 mmHg, 113.60±4.90 mmHg and 87.88±5.38 bpm respectively. Statistically, there was no significant difference between two groups with respect to any of these parameters. In terms of proteinuria, In Group A, maximum had proteinuria >0.3 g/dl (n=10; 40%) but In Group B, maximum had protein status ++

(n=8; 32%) On comparing the data between two groups, the difference was not found to be significant statistically.

In Table -3, Group A has all the patients who achieved targeted BP without crossover, however in Group B, two patients required cross-over to other group to achieve the targeted BP. Mean time taken to achieve targeted BP was slightly lower in Group A (33.60±14.97 min) as compared to that in Group B (39.57±20.99 min).In Group A, maximum patients achieved targeted BP with one dose only (48%) but in Group B after excluding 2 cases who required cross-over, maximum required two doses (47.9%).However these differences were not significant statistically

In Table-4 Group A patients had side effects which were nausea (36%), vomiting (12%), tremor (4%) and dizziness (8%) whereas in Group B, the noted side effects were nausea (25%), tachycardia (44%) and headache (20%) respectively. Statistically no significant difference was observed between two groups for any of the side effects except for tachycardia ($p<0.001$) and headache($p=0.018$). Tachycardia and headache were seen in 44% and 20% of Group B cases as compared to none of the Group A

Table 1: Sociodemographic Data Of Two Groups

SN	**Characteristic**	**Group A (n=25)**		**Group B (n=25)**		**Significance of difference**	
		No.	**%**	**No.**	**%**	**χ^2**	**'p'**
1.	20-25 Years	12	48	8	32	2.99	0.393
2.	26-30 Years	8	32	13	52		
3.	31-35 Years	4	16	4	16		
4.	>35 Years	1	4	0	0		
	Mean Age±SD (Range) in years	26.72±4.89 (20-38)		27.20±3.56 (21-35)		't'=0.397; p=0.693	
SN	**Gravida**	**Group A (n=25)**		**Group B (n=25)**		**Significance of difference**	
		No.	**%**	**No.**	**%**	**χ^2**	**'p'**
1.	G0 (Primi)	11	44	13	52	1.26	0.869
2.	G1	6	24	5	20		
3.	G2	5	20	5	20		
4.	G3	2	8	2	8		
5.	G4	1	4	0	0		
SN	**Period of gestation**	**Group A (n=25)**		**Group B (n=25)**		**Significance of difference**	
		No.	**%**	**No.**	**%**	**χ^2**	**'p'**
1.	≤32 weeks	2	8	0	0	7.23	0.065
2.	32-36 weeks 6 days	8	32	13	52		
3.	37-40 weeks	11	44	12	48		
4.	>40 weeks	4	16	0	0		

Table 2: Comparison of Clinical Data of two Groups

SN	BMI Status (kg/m^2)	Group A (n=25)		Group B (n=25)		Significance of difference	
		No.	%	No.	%	χ^2	'p'
1.	Normal (18.5-23.9)	24	96	24	96	0	1
2.	Overweight (25.0-29.9)	1	4	1	4		
Mean BMI±SD (Range) in kg/m^2		22.11±1.95 (18.7-25.1)		22.12±1.89 (19.5-26.5)		't'=0.029; p=0.977	
SN	**Parameters**	**Group A (n=25)**		**Group B (n=25)**		**Significance of difference**	
		Mean	**SD**	**Mean**	**SD**	**'t'**	**'p'**
1.	SBP (mmHg)	180.80	22.72	177.20	16.21	0.645	0.522
2.	DBP (mmHg)	118.40	12.14	113.60	4.90	1.834	0.073
3.	PR (bpm)	90.88	8.60	87.88	5.38	1.577	0.121

Table 3: Comparison of Efficacy of Interventions Between two Groups

SN	Variable	Group A (n=25)		Group B (n=25)		Significance of difference	
		No.	%	No.	%	χ^2	'p'
1.	Target achieved without crossover	25	100	23	92.0	2.083	0.149
		n=25		n=23			
2.	Mean time taken to achieve target±SD (min)	33.60±14.97		39.57±20.99		't'=1.141; p=0.260	
3.	No. of dosages 1 2 3 4	 12 (48.0%) 9 (36.0%) 4 (16.0%) 0 (0.0%)		 9 (39.1%) 11 (47.9%) 3 (13%) 0 (0.0%)		χ^2=0.689; p=0.708	

Table 4: Comparison Of Side Effects Of Interventions Between Two Groups

SN	Variable	Group A (n=25)		Group B (n=25)		Significance of difference	
		No.	%	No.	%	χ^2	'p'
1.	Nausea	9	36	6	24	0.857	0.355
2.	Vomiting	3	12	0	0	3.191	0.074
3.	Tremor	1	4	0	0	1.020	0.312
4.	Dizziness	2	8	0	0	2.08	0.149
5.	Tachycardia	0	0	11	44	14.1	<0.001
6.	Headache	0	0	5	20	5.56	0.018

Discussion

Severe preeclampsia has grave consequences for both maternal and neonatal health, associated with 50,000–100,000 annual deaths globally [19], Maternal complications associated with preeclampsia include eclampsia, HELLP syndrome, acute kidney injury, pulmonary oedema and placental abruption. Severe preeclampsia is a significant risk factor for intrauterine fetal demise, with an estimated stillbirth rate of 21/1000 [20]. It is also responsible for preterm delivery which subsequently increases risks of neonatal death and serious morbidity due to prematurity.

Owing to these consequences management of severe preeclampsia is quite essential in order to ensure successful continuation of pregnancy and to reduce maternal, fetal and neonatal morbidity and mortality. Blood pressure control is an essential step for management of severe preeclampsia. It is necessary that the women with severe preeclampsia should be stabilized before delivery. Targeting a systolic blood pressure (SBP) of <140-150 mmHg and diastolic blood pressure (DBP) of 80-90 mmHg minimises the risk of haemorrhagic stroke, as auto regulation is impaired when the mean arterial pressure (MAP) exceeds 145mmHg. Common therapeutic agents being used for management of severe preeclampsia include labetalol, nifedipine, hydralazine and methyldopa. Among various pharmacological modalities used for management of severe preeclampsia, nifedipine and labetalol have been recommended as first-line alternatives for management of severe hypertension during pregnancy [21,22].

Although, Labetalol and Nifedipine have been proposed as alternatives, yet owing to cost considerations, use of Labetalol is often limited in economies like India where consideration cost is a major factor driving healthcare decision making.

In present study, age of women enrolled in the study ranged from 20 to 38 years and majority of women were aged in 20-30 years age group (n=41/50; 82%). Only five women in i.v. labetalol group and four women in oral nifedipine group were aged above 30 years, thus comprising 18% of study population. Similar to findings of present study, Gavit *et al [24]*. had 85% of study population within 30 years of range. On the other hand, Thakur *et al [25]*. had 91% of women within 30 years of age. Singh *et al [27]*. similar to present study reported the mean age of women in i.v. labetalol and oral nifedipine groups as 25.3 and 25.87 years respectively, thus showing that age group >30 years is less common in different studies from India. However, advancing age is an issue in different studies from abroad as shown by Webster *et al [28]*. who reported the mean age of women in two groups of their study as 36 and 35 years respectively. Duro-Gomez *et al [29]*. too in their study from abroad reported the mean age of patients to be 30.6 and 36 years respectively in two groups of their study. These findings thus indicate that with the variable age profile of women in India and abroad and the possible effect of age on drug-interaction needs to be studied in Indian context In present study, maximum numbers of cases in both the groups (44% and 52% respectively) were primigravida. Relationship between preeclampsia and parity is well known. A number of studies have shown that women in their first pregnancy have a higher risk of preeclampsia [30,31]. Dominance of nulliparous women in present study also endorsed this risk. Dhali *et al [32]*. had as many as 81% of primigravida in their study whereas Shekhar *et al [111]*. had 76.7% primigravida in their study. Similarly, Das *et al [33]*. had 54% primigravida in their study.

In present study, a total of 42% patients had gestational age 32-36 completed weeks and 46% patients had gestational age between

37-40 weeks, thus showing that most of the patients presented in late third trimester or at term. Similar to present study, most of the other studies too have also reported gestational age at presentation to be late third trimester or term. Das *et al [33].* n their study had 82% patients in 38-40 weeks of pregnancy and 13% in 36-37 weeks of gestational age. Shi *et al [34].* also reported mean gestational age as 37.6 and 37.1 weeks respectively in two groups of their study and thus implied that most of the patients in their study also presented in late third trimester and at term.

In present study except for one overweight patient in each group, all the other patients had normal BMI. Mean BMI of patients in two groups was 22.11 and 22.12 kg/m^2 respectively. Obesity is a recognized risk factor for hypertension, and western studies report a relatively higher BMI of women (>30 kg/m^2) with hypertensive disorders in pregnancy [35]. However, some other studies from abroad have designed their study in such a way to exclude obese women. The mean BMI of present study was similar to that reported by Giannubilo *et al [36].* who reported mean BMI of patients as 23.9 and 24.2 kg/m^2 for the two groups in their study? Shi *et al [37].* also reported mean BMI of patients as 24.1 and 23.7 kg/m^2 which might have affected the study findings.

In present study, mean systolic blood pressure in two groups was 180.80±22.72 and 177.20±16.21 mmHg respectively while mean diastolic blood pressure in two groups was 118.40±12.14 and 113.60±4.90 mmHg respectively. Statistically, there was no significant difference between two groups for both systolic as well as diastolic blood pressure.

Similar to our study, Kumari *et al [37].* reported the mean systolic blood pressure in two groups was 172.2 and 170.6 mmHg and diastolic blood pressure as 114.8 and 115.2 mmHg respectively. Gavit *et al [38].* on the other hand, reported mean systolic blood pressure in two groups as 176.05±12.87 and 171.75±12.45 mmHg and diastolic blood pressure as 112.35±5.10 and 112.85±5.29 mmHg respectively. All these studies included patients with severe preeclampsia/eclampsia only. Das *et al [33].* reported mean systolic blood pressure as 186.2±12 and 175±12 mmHg respectively in the two groups and mean diastolic pressure as 118.11±8 and 112±8 mmHg respectively which is close to the observation made in present study.

In present study, urinary albumin levels were ++ or +++ on dipstick strips in majority of cases in both the groups (68% and 62% respectively), which is in agreement with the severe preeclampsia profile of the patients as it is marked by presence of significant proteinuria. However, the two groups did not differ significantly with respect to severity of proteinuria.

In present study, all the cases in i.v. Labetalol group achieved the targeted blood pressure reduction without cross-over as compared to 23/25 (92%) of those in oral Nifedipine group, although proportion of patients achieving the same without cross-over was higher in Labetalol group as compared to Nifedipine group, yet this difference was not significant statistically. With respect to mean time taken to achieve this target it was found that duration was shorter in i.v. Labetalol group (33.6±14.97 min) as compared to that in Oral Nifedipine group (39.57±20.99 min). Although proportion of patients requiring more than 1 dose to achieve the targeted blood pressure was also higher in oral Nifedipine group (60%) as compared to i.v. Labetalol group (39.1%) yet this difference was not significant statistically.

As far as cross-over need is concerned, most of the studies similar to present study have shown a non-significant difference between two groups, though with variable proportion of cases requiring cross-over. In present study, none of the patients in i.v.

Labetalol and 8% cases in oral Nifedipine group required crossover, whereas Kumari *et al [37]*. in their study reported cross-over need in 14% of cases in both the groups. Padmaja and Sravanthi [38] too in their study reported cross-over need in 12.5% of Labetalol and 17.5% of oral Nifedipine group patients but did not find a significant difference between two groups. Shi *et al [34]*. on the other hand, did not report crossover need in either of two groups of their study. Thus, these findings suggest that although there is variability in proportion of cases requiring crossover in different studies yet the differences between two groups were not significant statistically in any of these studies as also observed in present study. In present study, we followed a protocol in which patients were managed using intravenous labetalol 20mg initially followed by 40mg after 20 minutes then 80 mg every 20 minutes till the target blood pressure (150/100mm Hg) was achieved or up to maximum dose of 220mgor were alternatively, managed using oral nifedipine 20mg initially and was repeated half hourly till target BP(150/100mmHg) was achieved or up to maximum dose of 80 mg. Compared to present study, Shi *et al [34]*.used oral nifedipine (10 mg tablet, up to five dosages) or intravenous labetalol (in a dose regimen of 20, 40 and 80 mg) every 15 min until achieved the effective blood pressure control (≤150/100 mmHg). Similarly, Padmaja and Sravanthi [38] used Nifedipine 10 mg orally 20 mins interval up to a maximum of 5 doses i.e. 50 mg and Labetalol 20mg intravenous injection which was repeated at 20 mins interval in an escalating dose regimen of 40, 80, 80 and 80 mg up to maximum of 300 mg to achieve the target blood pressure. Thus, variability in dose as well as maximum ceiling for crossover could be responsible for difference in rate of crossover in different studies. Moreover, influence of individual patient characteristics could also not be ruled out.

With respect to time taken to achieve the targeted blood pressure, compared to present study where i.v. labetalol was shown to consume lesser time to achieve target blood pressure as compared to oral nifedipine, most of the other studies have shown mean time taken to achieve target blood pressure to be shorter in oral nifedipine group as compared to intravenous labetalol group.

Similar to findings of present study, a number of studies did not find a significant difference between two groups with respect to time taken to achieve target blood pressure [9,33,34,37,38,39]. However, few studies have shown significantly lower time in oral nifedipine group as compared to i.v. Labetalol group [27,29,32,40]. Although despite showing a non-significant difference between two groups, most of the previous studies have shown relatively shorter time in oral nifedipine group as compared to i.v. Labetalol group which is slightly contradictory to the findings of present study. The reason for this could be cited as difference in protocol of oral Nifedipine administration. In present study, we administered oral Nifedipine at half hourly interval as compared to most of the previous studies that have administered Nifedipine at 20 min interval [27,32], owing to this protocol, the pharmacokinetics of the Nifedipine must have been affected slightly.

With respect to side effects, there were no serious side effects in either of two groups, however, proportion of those showing headache and tachycardia was significantly higher in oral Nifedipine as compared to i.v. Labetalol group. Similar observations have been stated by the previously mentioned studies too.

The findings of present study showed Labetalol as well as Nifedipine to be equivalent as far as time taken to achieve target BP and number of doses required to achieve the targeted blood pressure, however, given the safety profile and

increased crossover need, Labetalol could be said to have a better safety and efficacy. In general, the findings of present study are in agreement with the previous studies, however, in view of slightly changed protocol for the interval of administration for the repeat dose in nifedipine group, it is difficult to state that the better outcome for Labetalol was attributable was because of this change, hence further studies keeping a standardized dose-schedule protocol are recommended

Conclusion

The findings of present study, shows that in comparison with oral nifedipine group, i.v. labetalol group is equally effective in management of severe preeclampsia. Intravenous labetalol group was 100% successful without crossover and caused fewer side effects as compared to oral nifedipine. Despite a small sample size, the study was able to provide meaningful results for clinical decision-making, however, further studies to corroborate the findings of present study and to accumulate more evidence in favour of i.v. labetalol are recommended.

Ethics approval and informed consent: Ethical clearance was obtained from the institutional Ethical Committee for human research of Era Lucknow Medical College & Hospital Lucknow India. Written informed consent was obtained from all women participating in the study.

Conflict of interest:

The authors declare that they have no conflict of interest.

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Reference

1. Salvig JD, Olsen SF, Secher NJ. Effects of fish oil supplementation in late pregnancy on blood pressure: a randomised controlled trial. Br J Obstet Gynaecol. 1996;103(6):529–533
2. Chappell LC, Enye S, Seed P, Briley AL, Poston L, Shennan AH. Adverse Perinatal Outcomes and Risk Factors for Preeclampsia in Women with Chronic Hypertension A Prospective Study. Hypertension. 2008; 51:1002-1009.
3. Dutta DC. Hypertensive disorders in pregnancy. In: Textbook of obstetrics including perinatology and contraception. 6th ed. Calcutta: New Central Book Agency; 2004. p. 221-42.
4. 4.Prakash J, Pandey LK, Singh AK, Kar B. Hypertension in pregnancy: hospital-based study. J Assoc Physicians India. 2006 Apr; 54:273-8.
5. Anand S, Kirshnanand. Perinatal Outcome in Growth Retarted Babies Born to Normotensive and Hypertensive Mothers: A Prospective Study. People's Journal of Scientific Research 2012; 5(1): 24-28.
6. Sajith M, Nimbargi V, Modi A, Sumariya R, Pawar A. Incidence of pregnancy induced hypertension and prescription pattern of antihypertensive drugs in pregnancy. International Journal of Pharma Sciences and Research 2014; 5(4): 163-170.
7. Dhall K. Epidemiology of Preeclampsia and Eclampsia. Asia-Oceania Journal of Obstetrics and Gynecology 2014; 10(1): 89-93.
8. Arias F. Practical Guide to High Risk Pregnancy and Delivery, 4th Edition. p. 201.
9. Raheem IA, Saaid R, Oral Nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy, International Journal of Obstetrics and Gynecology 2012;119:78-85.
10. Belfort MA, Anthony J, Buccimazza A, Davey DA. Hemodynamic changes associated with intravenous infusion of the calcium antagonist verapamil in the treatment of severe gestational proteinuric hypertension. Obstet Gynecol, 1990; 75:970–974.

11. Xia Y Went H, Bobs S, Day MC, Killers RE. Maternal auto antibodies from preeclamptic patients activate angiotensin receptors on human trophoblast cells. J Soc Gynecol Invest 2003; 10: 82–93.
12. Dragun D, Muller DN, Brasen JH, Fritsche L, NieminenKelha M, Dechend R, Kintscher U, Rudolph B, Hoebeke J, Eckert D, Mazak I, Plehm R, Schonemann C, Unger T, Budde K, Neumayer HH, Luft FC, Wallukat G. Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection. N Engl J Med 2005; 352: 558 –569.
13. De Alvarez RR. Renal glomerular tubular mechanisms during normal pregnancy. I. Glomerular filtration rate, Renal plasma flow and creatinine clearance. Am J Obstet Gynecol 1958; 75: 931–944.
14. Lafayette RA, Druzin M, Sibley R, Derby G, Malik T, Huie P, Polhemus C, Deen WM, Myers BD. Nature of glomerular dysfunction in pre-eclampsia. Kidney Int 1998; 54: 1240 – 1249.
15. Quaas L, Wilhelm C, Klosa W, Hillemanns HG, Thaiss F. Urinary protein patterns and EPH-gestosis. Clin Nephrol 1987; 27: 107–110.
16. Winkler U, Lison AE, Seitzer B, Niedner W. Urinary protein patterns for early detection of preeclampsia. Contrib. Nephrol 1988; 68: 227–229.
17. MacLean PR, Paterson WG, Smart GE, Petrie JJ, Robson JS, Thomson D. Proteinuria in toxaemia and abruptio placentae. J Obstet Gynaecol Br Common 1972; 79: 321-326.
18. Roberts JM. Endothelial dysfunction in preeclampsia. Semen Reprod Endocrinol 1998;16: 5–15.
19. 19.Oyston CJ, Stanley JL, Baker PN. Potential targets for the treatment of preeclampsia. Expert Opin Ther Targets. 2015;19(11):1517–1530.
20. Lewis G. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers Lives: reviewing maternal deaths to make motherhood safer – 2003-2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. London: CEMACH; 2007.
21. Xia Y, Wen H, Bobst S, Day MC, Kellems RE. Maternal auto antibodies from preeclamptic patients activate angiotensin receptors on human trophoblast cells. J Soc Gynecol Invest 2003; 10: 82–93.
22. Dragun D, Muller DN, Brasen JH, Fritsche L, NieminenKelha M, Dechend R, Kintscher U, Rudolph B, Hoebeke J, Eckert D, Mazak I, Plehm R, Schonemann C, Unger T, Budde K, Neumayer HH, Luft FC, Wallukat G. Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection. N Engl J Med 2005; 352: 558 –569.
23. Stang A. Randomized Controlled Trials—an Indispensible Part of Clinical Research. Deutsches Ärzteblatt International. 2011; 108(39): 661-662.
24. Gavit Y, Sharma D, Dixit PV. A comparative study of oral nifedipine and intravenous labetalol in control of acute hypertension in severe pre-eclampsia and eclampsia. Int J Reprod Contracept Obstet Gynecol. 2018 Feb;7(2):719-724.
25. Thakur V, Thakur A, Saroshe S. Comparison of effect of nifedipine, labetalol and methyldopa in treatment of hypertension in pregnancy in a tertiary care government hospital. Int J Reprod Contracept Obstet Gynecol. 2016 Jan;5(1):17-22.
26. Chawla D, Khatri R, Minal, Nayyer PS. A comparative study of intravenous labetalol versus oral nifedipine in severe hypertension in pregnancy in a tertiary hospital, New Delhi. IOSR

Journal of Dental and Medical Sciences (IOSR-JDMS) 2018; 17(3) Ver. 6: 56-59.
27. Singh D, Singh S, Singh S, Rani R, Verma U, Nigam AK, Yadav N. Comparative Evaluation of Efficacy & Safety of Intravenous Labetalol and Oral Nifedipine in Severe Hypertension of Pregnancy. J. Med. Sc. & Clin. Res. 2017; 5(3): 18941-18947.
28. Webster LM, Myers JE, Nelson-Piercy C, Harding K, Cruickshank JK, Watt-Coote I, *et al.* Labetalol Versus Nifedipine as Antihypertensive Treatment for Chronic Hypertension in Pregnancy: A randomized controlled trial. Hypertension. 2017 Nov;70(5):915-922.
29. Duro-Gomez J, Rodriguez-Marin AB, de Azcarete MG, Duro-Gomez L. A trial of oral nifedipine and oral labetalol in preeclampsia hypertensive emergency treatment. J Obs Gyn. 2017; 37: 864-866.
30. Long PA, Abell DA, Beischer NA. Parity and pre-eclampsia. Aust N Z J Obstet Gynaecol. 1979 Nov;19(4):203-6.
31. Hernández-Díaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. BMJ 2009;338:b2255.
32. Dhali B, Bhattacharya S, Ganguly RP, Bandopadhyay S, Mondal M, Dutta M. A randomized trial of intravenous labetalol & oral nifedipine in severe pregnancy induced hypertension. . Int J Reprod Contracept Obstet Gynecol. 2012 Dec;1(1):42-46.
33. Das S, Biswas S, Das P, Mahapatra B. Comparative Study of Intravenous Labetalol and Oral Nifedipine for Control of Blood Pressure in Severe Preeclampsia. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 2015; 14(10): 22-27.
34. 34.Shi DD, Yang FZ, Zhou L, Wang N. Oral nifedipine vs. intravenous labetalol for treatment of pregnancy-induced severe pre-eclampsia. J Clin Pharm Ther. 2016 Dec; 41(6):657-661.
35. Webster LM, Myers JE, Nelson-Piercy C, Harding K, Cruickshank JK, Watt-Coote I, *et al.* Labetalol Versus Nifedipine as Antihypertensive Treatment for Chronic Hypertension in Pregnancy: A randomized controlled trial. Hypertension. 2017 Nov; 70(5):915-922.
36. Giannubilo SR, Bezzeccheri V, Cecchi S, Landi B, Battistoni GI, Vitali P, Cecchi L, Tranquilli AL. Nifedipine versus labetalol in the treatment of hypertensive disorders of pregnancy. Arch. Gynecol. Obstet. 2012; 286(3):637-42.
37. Kumari VR, Saraswathi K, Srilaxmi A. Oral nifedipine versus intravenous labetalol for control of blood pressure in severe preeclampsia. J. Evolution Med. Dent. Sci. 2016; 5(20): 994-997.
38. Padmaja A, Lakshmi Sravanthi V. A study of oral Nifedipine and intravenous Labetalol in severe hypertension in pregnancy at teaching hospital. IAIM, 2017; 4(8): 12-19.
39. Sivaranjani BSV, Aruna V. Comparison of Efficacy of Intravenous Labetalol versus Oral Nifedipinein Control of Acute Hypertension in Severe Pre-Eclampsia/ Eclampsia. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 2016; 15(12) Ver. X: 71-74.
40. Shekhar S, Sharma C, Thakur S, Verma S. Oral nifedipine or intravenous labetalol for hypertensive emergency in pregnancy: a randomized controlled trial. Obstet Gynecol. 2013 Nov; 122(5):1057-63.