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"A Comparative Study between Oral Labetalol and Nifedipine in Hypertensive Diseases of Pregnancy"

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Abstract:
BACKGROUND
Hypertensive disorders of pregnancy represent the most common medical complication of pregnancy. It affects between 7%-15% of all gestations and is attributable for approximately one-fourth of all antenatal admissions. Both Nifedipine and Labetalol are effective antihypertensive agents belonging to different pharmacological classes and with different mechanisms of action. This study compares both the drugs.
MATERIALS AND METHODS
A hospital based prospective randomized case control study was conducted with 150 antenatal patients belonging to age group of 20-30yrs to compare the effect oral nifedipine and labetolol on pregnancy induced hypertension.
RESULT
In our study we found that oral therapy with antihypertensives is safe and effective. Both oral labetalol and nifedipine is effective and does not affect the perinatal outcome nor is detrimental to wellbeing of the baby, labetalol being comparatively faster acting and more efficacious than nifedipine in controlling hypertension.
CONCLUSION:
Hypertensive disorders in pregnancy continue to be a significant risk factor for maternal mortality and morbidity even in the modern era. Proper tools for early diagnosis and timely intervention can prevent much of the associated complications and ensure a smooth and healthy journey on the road to childbirth.

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I. Introduction

Hypertensive disorders of pregnancy represent the most common medical complication of pregnancy (Ventura and colleagues, 2000) that affects between 7%-15% of all pregnancies [1]. Preeclampsia is characterized by newly diagnosed hypertension and proteinuria or hypertension and evidence end-organ damage with or without proteinuria at and beyond 20 weeks of gestation.It is strongly associated with fetal and maternal morbidity and mortality [5]. It is generally indicated that severe hypertension requires antihypertensive therapy. But in mild and moderate hypertension the need for antihypertensive therapy is to prevent progression to severe hypertension. The commonly used antihypertensive drugs in pregnancy are Nifedipine and Labetalol. Both the drugs are effective antihypertensive agents belonging to different pharmacological classes and with different mechanisms of action. This study compares both the drugs.

II. Material And Methods

This was a randomized controlled trial on booked ANC cases from OPD and in-patients admitted through labour room at obstetrics and gynecology department with gestational hypertension and preeclampsia
Place of study- Kalinga Institute of Medical Sciences and PBMH, Patia, Bhubaneswar
Duration of Study- From October 2018 to September 2020.
Study population- booked ANC cases from OPD and in-patients admitted through labour room at obstetrics and gynecology department with gestational hypertension and preeclampsia**.**

Sample size-150

Inclusion criteria-

1. All patients with gestational age from 20 weeks up to 38 weeks who were previously normotensive with current blood pressure recordings of systolic BP >/=150 and or diastolic BP >/= 90 mm Hg more than 4 hours apart will be included in the trial.

2. Patients who are sure of their LMP with regular cycles or those with first trimester ultrasound will be taken in the study

Exclusion criteria-

1. Patients who do not consent for participation in the study
2. Patients with chronic hypertension i.e. known cases of hypertension or hypertension diagnosed first time in pregnancy but before 20 weeks of gestational age.
3. Patients diagnosed with severe preeclampsia and eclampsia (Blood pressure >160 /110 mm Hg), and proteinuria of more than 2+ will be excluded from the study.
4. Women with a history of heart rhythm abnormality, heart failure, asthma, allergy to either of the drugs, non-pregnancy related hypertension are to be excluded from the study.
5. Patients receiving any other antihypertensive drug preceding 72 hours of admission will also be excluded from study.

Procedure methodology

It is a prospective randomized case study. Sample size was calculated using proper statistical tools. They have been randomly categorized into two groups: Group A- Nifedipine and Group B- Labetalol. A computer generated simple randomization technique has been adopted to randomly allocate the patients into two groups.

Labetalol was started with an initial dose of 100 mg BD and the dose was increased as required. The maximum dose of 100 mg TDS was given. Nifedipine was started with an initial dose of 10 mg BD and the dose was increased up to 20 mg TDS. Proper counselling regarding the study was done. Consent was taken for the patients prior to enrolment of the cases with full disclosure regarding handling and usage of the data.

Enrolled patients were required to visit the OPD daily for the first 3 days. BP was measured as per guidelines once on the day of diagnosis followed by every 24 hours for the next 2 days to assess the speed of recovery of the same. The treatment in any of the drugs was not prolonged beyond 38 weeks. The patients were followed up till delivery and the outcome of the same along with details of the baby were also noted.

Statistical analysis

Data was analyzed using SPSS version 20. Graphical representation was done in MS-Excel 2010.Quantitative data was presented with the help of Mean and Standard deviation. Qualitative data was presented with the help of frequency and percentage table. Association among the study groups is assessed with the help of Fisher's test, Student 't' test and Chi square test.The 'p' value less than 0.05 was taken significant.The Chi square statistic was used for testing relationships on categorical variables. Student t-test was used to compare the means of a normally distributed interval dependent variable for two independent groups. The Fisher's exact test was used when we wanted to conduct a Chi-square test, but one or more of cells had an expected frequency of five or less.

III. Result

In Group 1(Labetalol group) the mean SBP was 169.25 ± 5.89 mm Hg and for Group 2 (Nifedipine group) was 167.97 ± 6.60 mm Hg but this could not be proved statistically significant (P value >0.05).
The mean difference of SBP Labetalol to Nifedipine was 1.28 mm Hg

In Group 1 the mean DBP was 112.72 ± 4.15 mm Hg and Group 2 was 113.55 ± 4.61 mm Hg but this was statistically insignificant (P value >0.05) .The mean difference of DBP was -0.827.

After 24 hours,
In Group 1 mean SBP and DBP were 145.25 ± 11.79 and 91.60 ± 5.23 mm Hg. Mean fall in SBP and DBP was approximately 24 and 21.1 mm Hg.
In Group 2, mean SBP and DBP were 155.12 ± 8.70 and 97.65 ± 6.11 mm Hg and mean fall in SBP and DBP were approximately 12.8 and 15.9 mm Hg.
This was proved statistically significant (P value <0.05). The mean difference of SBP Labetalol to Nifedipine was -9.87 mm Hg (SBP) and -6.053 (DBP).

At 48 hours of therapy,
In Group 1 mean SBP was 133.73 ± 12.43 and DBP was 85.9 ± 9.93. Mean fall in SBP and DBP was approximately 11.5 and 5.7 mm Hg.
In Group 2, mean SBP and DBP were 135.07 ± 13.20 and 83.25 ± 10.9 mm Hg and mean fall in SBP and DBP were approximately 20.05 and 14.3. But this was statistically insignificant (P value >0.05). Mean difference was -1.33 and -1.70 mm Hg.

At 72 hours of therapy,
In Group 1 mean SBP was 126.24 ± 10.30 mm Hg and DBP was 79.60 mm Hg. Mean fall in SBP and DBP was approximately 7.49 and 6.3.
In Group 2, mean SBP and DBP were 124.83 ± 10.92 and 76.59 ± 7.28 mm Hg and mean fall in SBP and DBP were approximately 10.24 and 6.66.This was proved statistically significant (P value <0.05).

Trend and analysis of fall in SBP and DBP both groups during treatment:

SBP	Group	Mean	Std. Deviation	p-value	Mean Difference (L-N)	Std. Error Difference	95% Confidence Interval of the Difference	
							Lower	Upper
SBP on diagnosis	Labetalol Group (1)	169.25	5.89	.212	1.28	1.02	-.74	3.30
	Nifedipine Group (2)	167.97	6.60					
SBP after 24 hours of therapy	Labetalol Group (1)	145.25	11.79	.000	-9.87	1.69	-13.21	-6.52
	Nifedipine Group (2)	155.12	8.70					
SBP after 48 hours of therapy	Labetalol Group (1)	133.73	12.43	.525	-1.33	2.09	-5.47	2.80
	Nifedipine Group (2)	135.07	13.20					
SBP IN 72HRS	Labetalol Group (1)	126.24	10.30	.416	1.41	1.73	-2.01	4.84
	Nifedipine Group (2)	124.83	10.92					

Table 1: Analysis of response to antihypertensive therapy of both groups (systolic BP)

DBP	Group	Mean	Std. Deviation	p-value	Mean Difference * (L-N)	Std. Error Difference	95% Confidence Interval of the Difference	
							Lower	Upper
DBP on Diagnosis	Labetalol Group (1)	112.72	4.15	.251	-.827	.717	-2.24	0.59
	Nifedipine Group (2)	113.55	4.61					
DBP after 24 hours of therapy	Labetalol Group (1)	91.60	5.23	.000	-6.053	.929	-7.89	-4.22
	Nifedipine Group (2)	97.65	6.11					
DBP after 48 hours of therapy	Labetalol Group (1)	85.92	9.93	.119	2.667	1.703	-0.70	6.03
	Nifedipine Group (2)	83.25	10.90					
DBP IN 72 HRS	Labetalol Group (1)	79.60	6.87	.010	3.013	1.155	0.73	5.30
	Nifedipine Group (2)	76.59	7.28					

TABLE 2: Analysis of response to antihypertensive therapy of both groups (diastolic BP)

After 72 hours of therapy,
In Group 1, 9 patients showed poor response (12%) and required added drugs
In Group 2, 12 patients showed similar response (16 %.)
Thus success rate of labetalol was calculated as 88% and nifedipine as 84%.

Table 3. Failure to respond after 72 hours of therapy

S.no.	Groups	Frequency (n)	Percent (%)
1.	Group1 (Labetalol)	9	12
2.	Group 2 (Nifedipine)	12	16

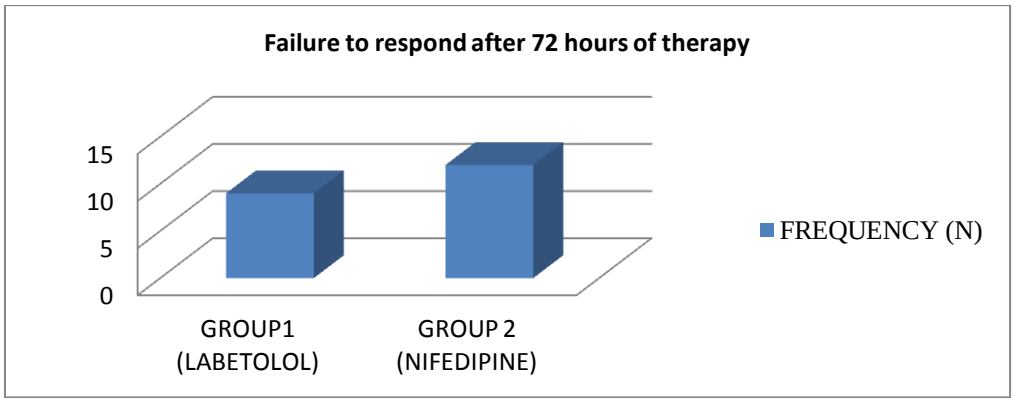

Figure 1: distribution of patients with failure of respond to therapy

IV. Discussion

Hypertensive disorders of pregnancy have been known to pose serious risks for both mother and fetus. Pharmacological therapy with antihypertensive agents is indicated in severe PIH in order to improve feto-maternal outcome.

This current study includes 150 patients with hypertensive disorders of pregnancy. All patients were treated in Kalinga Institute of Medical Sciences, Patia (Bhubaneswar) from 5th October 2018 to 5th September 2020 (18 months). This study was aimed to study the efficacy and time required by both drugs to control hypertension.

From table 1 we find that for the labetalol group (group 1), majority (93.33 %) of patients had systolic blood pressure readings ranging from 160-179 mm Hg and 4% having recordings between 140-159 mm Hg and 2.6 % having readings between 180-199 mm Hg. Whereas, the diastolic blood pressure recordings showed that 78.66% patients were in the range of 110-119 mm Hg followed by 16% lying between 100-109 mm Hg and 5.33% ranged between 120-130 mm Hg. A similar interventional study done by **Thomas Easterling et al [3]** also had maximum cases (65%) in Labetalol group with pre-interventional SBP 160-179 mm Hg and 63% of cases with pre-interventional DBP between 110-119 mm Hg.

As per table 1, After 24 hours of initiating tab Labetalol therapy maximum patients (45%) had their blood pressure recordings lowered to a range of 140-159 mm Hg followed by 37% of the patients having recordings between 120-139 mm Hg and 17.33% of patients had recordings lying within the range of 160-180 mm Hg. Whereas, the diastolic blood pressure recordings showed that 65.33% patients were in the range of 84-93 mm Hg followed by 29.33% lying between 94-110 mm Hg and 5.33% between 70-83 mm Hg. This **shows a significant fall in BP within the first 24 hours. This was statistically significant (P value 0.000). Labetalol was more efficacious in the initial 24 hours of therapy.** This corroborates with a study **by Dr. K Vijya Lakshmi et al in 2016 [4] they concluded that the mean time taken to achieve target BP were 2.95 ± 1.52 days in Labetalol group. However, effective BP control was considered when the target BP recording was below 140/90 mm Hg which was achieved by most patients by 48 hours which was evidenced as per Table 1.**

After continuing 48 hours of Tab Labetalol, maximum patients (48%) had their blood pressure recordings lowered to a range of 110-129 mm Hg followed by 36% of the patients having recordings between 130-149 mm Hg and 16% of patients had recordings lying within the range of 150-170 mm Hg. Whereas, the diastolic blood pressure recordings showed that 66.66% patients were in the range of 70-79 mm Hg followed by 29.33% lying between 90-109 mm Hg and 4% between 110-129 mm Hg. **Target BP was achieved by most patients at around 48 hours in our study as the mean BP was 133.73 ± 12.43 by 85.9 ± 9.93 mm Hg** as evident from table 1.

After continuing 72 hours of Tab Labetalol, maximum patients (72%) had their blood pressure recordings lowered to a range of 120-139 mm Hg followed by 14.6% of the patients having recordings between 140-159 mm Hg and 12% of patients had recordings lying within the range of 100-119 mm Hg. 1.3% of patients had a recording of 160-189 mm Hg range. Whereas, the diastolic blood pressure recordings showed that 86.66% patients were in the range of 70-89 mm Hg followed by 13.33% lying between 90-109 mm Hg. Thus**, labetalol is an effective antihypertensive agent for hypertensive disorders in pregnancy.**

For the nifedipine group (group 2), maximum (89.33 %) number of patients had systolic blood pressure readings ranging from 160-179 mm Hg followed by 5.33% having recordings between 140-159 mm Hg and 5.33 % having readings between 180-199 mm Hg. Whereas, the diastolic blood pressure recordings showed that 74.66% patients were in the range of 110-119 mm Hg followed by 18.66% lying between 100-109 mm Hg and 6.66% between 120-130 mm Hg. The study **by Thomas Easterling et al [3]** also had maximum cases (64%) in

Nifedipine group with pre-interventional SBP 160-179 mm Hg and 68% of cases with pre-interventional DBP between 110-119 mm Hg.

After 24 hours of initiating Tab Nifedipine therapy maximum patients (61.33%) had their blood pressure recordings lowered to a range of 140-159 mm Hg followed by 32% of the patients having recordings between 160-180 mm Hg and 6.66% of patients had recordings lying within the range of 120-139 mm Hg. Whereas, the diastolic blood pressure recordings showed that 56% patients were in the range of 100-110 mm Hg followed by 38.33% lying between 90-99 mm Hg and 5.33% between 80-89 mm Hg. According to the study **by Dr. K Vijya Lakshmi et al [4]**, the mean time taken to achieve target BP were 4.45 ± 0.99 days in nifedipine group which is similar **to the present study as fall in BP in first 24 hours is less than that of group 1 but most achieved target BP by 48-72 hours as evidenced by table 1.**

After 48 hours of initiating Tab Nifedipine therapy maximum patients (80%) had their blood pressure recordings lowered to a range of 120-139 mm Hg followed by 10.66% of the patients having recordings between 140-159 mm Hg and 9.33% of patients had recordings lying within the range of 160-180 mm Hg.

Whereas, the diastolic blood pressure recordings showed that 54.66% patients were in the range of 80-89% followed by 29.33% lying between 70-79 mm Hg and 16% between 100-110 mm Hg.

After 72 hours of initiating Tab Nifedipine therapy majority of patients (69.33%) had their blood pressure recordings lowered to a range of 120-139 mm Hg followed by 17.33% of the patients having recordings between 100-119 mm Hg and 13.33% of patients had recordings lying within the range of 140-159 mm Hg. Whereas, the diastolic blood pressure recordings showed that 84% patients were in the range of 70-89 mm Hg followed by 12% lying between 90-109 mm Hg and 4% had a recording of <70 mm Hg.

At diagnosis the mean SBP in Labetalol group (group 1) was 169.25 ± 5.89 mm Hg and that of the Nifedipine group (Group 2) was 167.97 ± 6.60 mm Hg (P value >0.05). The mean difference of SBP Labetalol to Nifedipine was 1.28 mm Hg. The DBP at diagnosis for group 1 was 112.72 ± 4.15 mm Hg and group 2 was 113.55 ± 4.61 mm Hg **(P value >0.05) and mean difference was -0.827.**

After 24 hours, it was observed that in group 1 mean SBP for group 1 was 145.25 ± 11.79 and DBP was 91.60 ± 5.23 mm Hg. Mean fall in SBP and DBP was approximately 24 and 21.1 mm Hg. In group 2, mean SBP and DBP were 155.12 ± 8.70 and 97.65 ± 6.11 mm Hg and mean fall in SBP and DBP were approximately 12.8 and 15.9 mm Hg. **P value <0.05, which is statistically significant. The mean difference of SBP Labetalol to Nifedipine was -9.87 mm Hg (SBP) and -6.053 (DBP). Thus, in our study labetalol was faster to act in the first 24 hours.**

At 48 hours of therapy, it was evident that in group 1 mean SBP for group 1 was 133.73 ± 12.43 and DBP was 85.9 ± 9.93. Mean fall in SBP and DBP was approximately 11.5 and 5.7 mm Hg. In group 2, mean SBP and DBP were 135.07 ± 13.20 and 83.25 ± 10.9 mm Hg and mean fall in SBP and DBP were approximately 20.05 and 14.3. **P value >0.05. Mean difference was -1.33 and -1.70 mm Hg.**

At 72 hours of therapy, it was seen that in group 1 mean SBP was 126.24 ± 10.30 mm Hg and DBP was 79.60 mm Hg. Mean fall in SBP and DBP was approximately 7.49 and 6.3. In group 2, mean SBP and DBP were 124.83 ± 10.92 and 76.59 ± 7.28 mm Hg and mean fall in SBP and DBP were approximately 10.24 and 6.66. **P value <0.05. This was statistically significant**.

Overall**, both the drugs achieved actual target BP approximately at the same time that is between 24 to 48 hours, the fall was faster initially in the labetalol group.** This is similar to a study **by Kathrin J Sharma et al** in 2016 [5] stating that the time to achieve BP control in their study was similar between labetalol and nifedipine groups (37.6 hours versus 38.2 hours, p = 0.51). **Rose DT, 2019** [6] also concluded that both labetalol and nifedipine were equally efficacious in controlling the BP in their study.

As per table 3, after 72 hours of therapy, in the Labetalol group, 9 patients (12%) showed poor response i.e., even after 72 hours of optimal therapy patient was still hypertensive with BP >150/90 mm Hg and required added drugs. In Nifedipine group 12 patients showed similar response (16%). They will be considered as failure of treatment. Thus **success rate of labetalol was calculated as 88% and nifedipine as 84%. Thomas Easterling [3]** in their 2019 study also found that 84% of patients in Nifedipine group and 77% of patients in Labetalol group showed response to treatment.

V. Conclusion

In our study we found that oral therapy with antihypertensives is safe and effective. Both oral labetalol and nifedipine are effective, labetalol being comparatively faster acting and more efficacious than nifedipine in controlling hypertension.

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