Section: Anaesthesia

Original Research Article

A COMPARATIVE STUDY TO EVALUATE THE EFFECT ON RATE PRESSURE PRODUCT INDEX WITH TABLET NIFEDIPINE AND AMLODIPINE IN DE NOVO HYPERTENSIVE PATIENTS PREOPERATIVELY IN A TERTIARY CARE CENTRE

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Abstract

Background: To study the effect of T.Nifedipine 20mg and T. Amlodipine 5mg on Rate Pressure Product index preoperatively and intraoperatively in Denovo hypertensive patients. **Materials and Methods:** Randomised control study done to evaluate the effects of Tab. Amlodipine 5 mg (GROUP A) and Tab. Nifedipine 20 mg (GROUP B) as a easy measure of perfusion to myocardial oxygen demand in controlling Rate Pressure Product Index in denovo hypertensive patients in 18-35 years of age .The patients were randomly allocated for Rx and whose RPI controlled were scheduled for elective surgery and irrespective of the anaesthesia performed patients were monitored for perioperative adverse coronary events. **Result:** Both the groups were comparable in regard to sex, age, BMI. Most commonly patients underwent open surgery and more surgeries under Spinal anaesthesia. HR, SBP and RPI was reduced with both Tab. Amlodipine 5mg and Tab. Nifedipine 20mg but it was significantly reduced to low levels with Tab. Amlodipine. Also we found that no significant perioperative coronary events in low RPI patients (Group A> Group B) and Group B patients required escalation of dose in the post operative period than Group A. **Conclusion:** Tablet amlodipine 5mg significantly decreases the Rate Pressure Product index as easy measure of perfusion of myocardial oxygen demand in De novo Hypertensive patients and reduces the perioperative coronary events on par with Tablet Nifedipine 20mg.

INTRODUCTION

"Health is a state of complete physical, mental, social wellbeing and not merely the absence of disease or infirmity". In a pursuit of living a socially, economically productive life, many attempts have been made since time immemorial to reduce the deleterious effects of comorbidities in a person undergoing surgeries to improve the quality-of-life index.

"Higher the blood pressure; Higher the risk". According to "European Society of Cardiologists and European Society Of Hypertension" guidelines (2021) defines than systolic blood pressure >140 mmHg and diastolic blood pressure > 90 mmHg in adults 16 years or older measured in three office reading with 30 minutes apart is diagnosed as hypertension and to be treated with anti-hypertensive drugs.

The society grades hypertension as follows to outweigh the risks for developing major cardiac events and for treatment optimisation and outcomes. Hypertension being the major risk factor for increased morbidity and mortality leading to stroke, coronary events, heart failure, aortic dissection, chronic kidney disease peripheral venous disease, blindness. Hypertension in the perioperative period is a major risk factor for cardiovascular, cerebrovascular events, bleeding and mortality, thence such patients to be pre optimised for major and minor cardiac or non- cardiac surgeries. Anticipated perioperative outcomes include Acute coronary syndromes, Heart failure, Arrhythmias, LVH, Acute kidney injury with raising serum creatinine levels, and last but not the least affecting the brain leading to acute cerebrovascular accidents.[1]

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Hypertension in the perioperative and postoperative period increases cardiovascular events, cerebrovascular events, bleeding, and mortality and should be controlled prior to major elective noncardiac surgery and cardiac surgery.[2,3] The higher the blood pressure, the greater the risk. A systematic review and meta-analysis of 30 observational studies found that hypertension increased perioperative cardiovascular complications by 35%.[4] As much as 25% of patients having major non-cardiac surgery have perioperative hypertension.[5] As much as 80% of patients having cardiac surgery have perioperative hypertension.[6] Hypertensive comorbidities associated with adverse perioperative outcomes include occult coronary artery disease (Q waves on the electrocardiogram), heart failure, left ventricular hypertrophy, serum creatinine higher than 2.0 mg/dL, and cerebrovascular disease.[7]

Hypertension is the commonest avoidable medical reason for postponing surgery. However, there are no universally accepted guidelines stating the level of blood pressure at which elective surgery should be cancelled. Increased complications including myocardial infarction, myocardial ischemia, dysrhythmias, cerebrovascular events, and renal failure have been reported if the preoperative diastolic blood pressure is 110 mmHg or higher.[8] It has been recommended to cancel elective surgery if the systolic blood pressure is 180 mmHg or higher or if the diastolic blood pressure is 110 mmHg or higher.[9,10]

These perioperative events can be prevented if the Rate- Pressure Product Index in hypertensive patients were optimised prior to surgery. It is also called as double product index, or cardiovascular product index or Robinson index and it is a very reliable index of myocardial oxygen demand. It is measured by SBP X HR /100 and expressed in mmHg. It is clinically used in anaesthesiology and rehabilitation and it is a easy measure of response of perfusion with myocardial oxygen demand. The purpose of this study is to reduce the intraoperative ischemic events in de novo hypertensive patients by optimising the rate pressure product index preoperatively who were identified in the pre anaesthetic clinic. There is difference in effect of nifedipine and amlodipine in optimisation of rate pressure product index in denovo hypertensives preoperatively.

MATERIALS AND METHODS

Randomised control study done by computer generated random numbers using opaque sealed envelope method, envelope selected by the patients included in the study. Sub-population in Osmania General Hospital and all Elite hospitals under Department of Anaesthesiology, Osmania Medical College, Hyderabad done for a period of 18 months.

Number of groups studied:[2]

Group A - Tablet Amlodipine 5mg (70 Patients)

Group B - Tablet Nifedipine 20 mg (70 patients)

Inclusion Criteria:18-35 years of age, identified denovo hypertensive in PAC, Males and Females. Average mean of two standardised measurement of SBP - 140-179 mmHg & DBP 90-110 mmHg.

Exclusion Criteria: Known hypertensive patients who discontinued treatment, Known secondary causes of hypertension, Comorbid Cardiovascular conditions. (Previous stroke, CAD, arrhythmia, heart failure)

Methodology

The patients attending pre anaesthetic clinic for surgery are evaluated according to ASA designed PAC forms and those diagnosed with denovo hypertension after average mean of two standard BP measurements (SBP - 140-179mm Hg / DBP 90-110 mmHg) are selected for the study by double blinded computer generated numbered by opaque sealed envelopes selected by the patient. Group 1 patients are prescribed with Tablet Nifedipine 20 mg monotherapy and 24-hour BP monitoring done for 3 days and patients are asked to continue on the day of surgery. Group 2 patients are prescribed with Tablet Amlodipine 5mg OD monotherapy and 24-hour BP monitoring done for 3 days and patients are asked to continue on day of surgery. Patients who are requiring escalation of doses or poly therapy for control of hypertension are excluded from the study. The product of Heart Rate and SBP is calculated prior to start of treatment and after therapy intraoperative hemodynamics is monitored every 15 mins till the end of the surgery irrespective of type of anaesthesia provided for the patient. Intraoperative complications were noted. Patients who are not willing for anaesthesia are excluded. The ethical considerations are strictly followed and the data obtained from study will be kept confidential and will be disclosed only for scientific purpose(s).

The collected data were analysed with IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY: IBM Corp). To describe the data descriptive statistics frequency analysis and percentage analysis were used for continuous variables. To find the significant difference between independent variable Student unpaired t test was used.

For All the below statistical tools probability value 0.05 is considered as significant level.

Values are expressed in percentage, Mean ± SD, S – significant, NS - non significant.

RESULTS

Demographic details are insignificant on comparision in both groups. [Table 1]

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Table 1: Demographic profile in present study

Sex	Group A	Group B	T score	P value
Males	64%	70%	0.00	0.5 NS
Females	36%	30%	0.00	0.5 NS
Age in years				
Males	32.02 ±3.3	28.9 ± 4.91	0.00	0.5 NS
Females	30.9 ± 3.4	29.35 ± 4.57	0.00	0.5 NS
BMI				
Males	26.62 ± 2.49	25.96±1.59	1.5	0.06 NS
Females	26.12 ± 2.35	25.05± 1.50	1.72	0.058 NS

Table 2: Mean Preop and Post treatment Heart Rate

PREOP Mean HR	Group A	Group B
Males	98.6 ± 9.89	94.12 ± 6.23
Females	93.84 ± 7.28	93.15 ± 6.99
Mean HR	96.9 ± 9.3	93.8 ± 6.42
T Score	2.09	0.56
P Value	0.07 NS	0.57 NS
Mean Post treatment HR		
Males	76.65 ± 6.46	78.74 ± 5.2
Females	74.30 ± 5.42	78.5 ± 5.88
Mean Post treatment HR	75.8 ± 6.21	78.6 ± 5.40
T Score	1.5	0.1
P Value	0.4 NS	0.8 NS

Group A- The difference between two observed means in two independent samples with 95% confidence interval, t statistic = -15.78 with p value<0.0001 which is statistically significant.
Group B - The difference between two observed means in two independent samples with 95 % confidence interval, t statistic = -15.08 with p value < 0.01 which is statistically significant.
Group A & B drugs were able to reduce rate whereas GROUP A drug reduced heart rate better from baseline than GROUP B drug.

Table 3: Mean preop and Post treatment systolic blood pressure

PREOP SBP	Group A	Group B
Males	155.35 ± 7.4	151.22 ± 7.44
Females	154 ± 6.15	152 ± 7.04
Mean preop SBP	154.9 ± 7.01	151.44 ± 7.49
T Score	0.7	0.40
P Value	0.4 NS	0.69 NS
Mean Post treatment SBP		
Males	119.66 ± 6.31	128.24 ± 9.44
Females	120.30 ± 8.71	123.7 ± 6.06
Mean Post treatment SBP	119.7 ± 7.2	126.94 ± 8.81
T Score	0.5	1.9
P Value	0.06 NS	0.051 NS

GROUP - A - The difference between two observed means in two independent samples with 95% confidence interval, t statistic = -29.30 with DF - 138; P value < 0.0001 which is statistically highly significant.
Group B - The difference between two observed means in two independent samples with 95% confidence interval, t statistic = -21.276; DF = 138; P value ,0.001 which is statistically significant.
Group A & B drugs were efficacious in reducing SBP whereas GROUP A drug reduced SBP effectively from baseline than GROUP B drug.

Table 4: Mean preop and Post treatment diastolic blood pressure

PREOP DBP	Group A	Group B
Males	95.53 ± 4.59	93.86 ± 5.43
Females	94.96 ± 4.95	94.25 ± 4.17
Mean preop DBP	95.32 ± 4.73	93.97 ± 5.08
T Score	0.5	0.2
P Value	0.6 NS	0.7 NS
Mean Post treatment DBP		
Males	73.63 ± 6.39	79.14 ± 7.46
Females	73.92 ± 7.45	76.9 ± 8.09
Mean Post treatment DBP	73.74 ± 6.81	78.5 ± 7.65
T Score	0.1	1.1
P Value	0.8 NS	0.2 NS

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Group A-The difference between two observed means in two independent samples with 95% confidence interval, t statistic = -21.775; DF 138; P value < 0.0001 which statistically highly significant.
Group B - The difference between two observed means in two independent Samples with 95% confidence interval, t statistic = -14.09; DF 138; P value < 0.01 which is statistically significant.
Group A & B drugs were efficacious in reducing DBP whereas GROUP A drug reduced DBP effectively from baseline than GROUP B drug.

Table 5: Preop and Post treatment Rate Pressure Product Index

PREOP RPI	Group A	Group B
Males	14874 ± 1269	14243 ± 1269
Females	14552 ± 1316	14168 ± 1330
T SCORE	0.9	0.2
P VALUE	0.3 NS	0.8 NS
Post treatment RPI		
Males	8827 ± 1106	10188 ± 1398
Females	8974 ± 1433	9732 ± 1093
T SCORE	0.4	1.3
P VALUE	0.63 NS	0.2 NS

GROUP A- The difference between two observed means in two independent samples with 95% confidence interval, t statistic = 2.4; RPI was found to reduce from 14759 ± 1295 to 8756 ± 1616 in Group A which is statistically hight significant. (P < 0.0001)
GROUP B- The difference between two observed means in two independent samples with 95% confidence interval, t statistic = 2.4.

Table 6: Mean preop RPI and post treatment RPI

MEAN	Group A	Group B	T Score	P Value
PRE-TREATMENT	14759 ± 1295	14221 ± 1277	2.4	0.01 S
POST TREATMENT	8756 ± 1616	10058 ± 1327	-5.1	0.00001 HS

RPI was found to reduce from 14221 ± 1277 to 10058 ± 1327 in group B which is statistically significant (P < 0.001). It is found that both drugs reduced RPI whereas GROUP A drug has reduced RPI significantly than GROUP B drug.

Table 7: Anaesthesia Technique

	Group A	Group B	P VALUE
SAB	57%	55%	>0.05 NS
GA	36%	38%	>0.05 NS
MAC	7%	7%	>0.05 NS

In this study, selected patients were performed with SAB, GA, MAC depending on the requirement for surgery. The difference in comparison between two groups showed no

Table 8: Mode and Duration of Surgery

	Group A	Group B	P VALUE
SAB	1h38m ± 36m	1h45m ± 35m	> 0.05 NS
GA	2h27m ± 1h7m	2h47m ± 56m	> 0.05 NS
MAC	47m ± 36m	45m ± 14m	> 0.05 NS
OPEN	94%	90%	>0.05 NS
SCOPIES	6%	10%	>0.05 NS

The difference between the mean duration of study by Pearson Chi square test were $\mathcal{X}2 = 0.111$, P = 0.739 > 0.05 which shows no statistical association between mean duration of study and mode of anaesthesia.
In this study 94 % and 90% of patients in GROUP A & B underwent open surgery and only 6% and 10% from group A & B underwent scopic surgeries (laparoscopy, endoscopy, uretroscopy) and the difference between the mean percentage showed no significant association (P > 0.05).

Table 9: Perioperative complications

	Group A	Group B
Cerebrovascular accident	Nil	Nil
Ischemic heart disease	Nil	Nil
Sudden death	Nil	Nil
Heart failure	Nil	Nil
Peripheral artery disease	Nil	Nil

Since both drugs were able to reduce RPP index effectively, none of the patients included in the study had any of such anticipated complications.

DISCUSSION

Hypertension is the leading risk factor for morbidity and mortality accounting for 7% of disability

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adjusted life years.The clinical consequence of high blood pressure underscore a high age- related association with Ischemic heart disease, stroke, renal failure, retinopathy, peripheral vascular disease and overall perioperative morbidity & mortality when untreated. Given the physiologic importance and complexity of blood pressure regulation of hypertension can result from a wide range of primary and secondary process that increase cardiac output, peripheral vascular resistance or both. 5% of the patients having secondary hypertension results from potential demonstrable cause that may be physiologic or pharmacologic. In middle aged adults 10% of hypertension deemed secondary as a consequence of hyperaldosteronism, thyroid dysfunction, renal disorders, obstructive sleep apnea, obesity, sedentary lifestyle or phaechromocytoma. Identifying at an early dynamic spectrum prevents progression of remodelling of small and large arteries, endothelial dysfunction and potential irreversible target end-organ damage. The degree to which some abnormalities are reversible is controversial, but early and effective intervention is essential.

The general therapeutic goal for hypertension treatment is a BP < 140/90 mmHg. However substantial number of people with diagnosed HTN are not attaining this goal due to minimal or adverse response to medications, misdiagnosis or non-compliance with prescribed treatment. There is strong evidence to support hypertensive patients younger than 35 years with a control of BP < 140/90 mmHg with first line of antihypertensive therapy, which includes Diuretics, Calcium channel blockers, ACE inhibitors and ARB's. Although, all the available first line drugs reduce blood pressure, their disparate pharmacology is evident in the reported risk reduction of hypertension related events.[9]

In general elevated blood pressure per se is not a direct prompt to delay surgery for cardiac evaluation in asymptomatic patients without other risk factors. Though guidelines do not support delaying surgery for poorly controlled blood pressure, perioperative hypertension increases blood loss, MI, CVA, volume depletion, loss of vascular elasticity, baroreceptor desensitisation and are more prone to intraoperative hemodynamic volatility. As with any procedure, a management plan for hemodynamic monitoring and a vasoactive drug therapy for hypertensive patients should consider age, functional reserve, preoperative pharmacotherapy and the planned operation.

Accordingly, addition of sympathomodulators (esmolol, metoprolol, labetolol) or titrated calcium channel blocker therapy can facilitate the transition from the operative room to post anaesthesia care unit (PACU) or intensive care unit .We studied the patients attending pre anaesthetic clinic for surgery are evaluated according to ASA designed PAC forms and those diagnosed with denovo hypertension after average mean of two standard BP measurements (SBP - 140-179mm Hg / DBP 90-110 mmHg) are selected for the study by double blinded computer generated numbered by opaque sealed envelopes selected by the patient. Group 1 patients are prescribed with Tablet Nifedipine 20 mg monotherapy and 24 hour BP monitoring done for 3 days and patients are asked to continue on the day of surgery. Group 2 patients are prescribed with Tablet Amlodipine 5mg OD monotherapy and 24 hour BP monitoring done for 3 days and patients are asked to continue on day of surgery. Patients who are requiring escalation of doses or poly therapy for control of hypertension are excluded from the study. The product of Heart Rate and SBP is calculated prior to start of treatment and after therapy intraoperative hemodynamics is monitored every 15 mins till the end of the surgery irrespective of type of anaesthesia provided for the patient. Intraoperative complications were noted.

In the Junichi Minami et al study,[10] autonomic nervous function was evaluated using a power spectral analysis of heart rate variability. Power spectral analyses of heart rate variability have been widely accepted as a non-invasive method of assessing the autonomic nervous function of patients with various cardiovascular disorders. It has been shown that the estimation of heart rate variability by ambulatory monitoring offers prognostic information beyond that provided by the evaluation of traditional cardiovascular risk factors. For example, Tsuji et al,[11] found that reductions in measures of heart rate variability including the LF and HF components were significantly associated with the onset of a cardiac event in subjects who participated in the Framingham Heart Study. In the Junichi Minami et al study nifedipine retard significantly decreased the 24-h and daytime average values of the LF and HF components, while nifedipine CR affected the night time LF component alone and did not change the HF component throughout a 24-h period. These results suggest that nifedipine CR has less influence on the autonomic nervous system than nifedipine retard.

In the Junichi Minami et al study, nifedipine retard significantly decreased the 24-h and daytime average values of the HF component, which represents parasympathetic nerve activity, while nifedipine CR did not change the HF component throughout a 24-h period. These findings are consistent with previous observations, they examined the autonomic effects of nifedipine retard on hypertensive patients in a 4-week comparative study with amlodipine.[12] A significant ($P < 0.01$) decrease in the HF component was observed with nifedipine retard. Although the mechanism of the decrease in parasympathetic nerve activity caused by nifedipine retard was not clarified by the present study, it is suggested that nifedipine affects parasympathetic nervous activity directly.

This study demonstrated that Rate pressure product response to two long acting calcium channel blockers is same at rest. During surgical stress the

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response were markedly different. The product of mean systolic blood pressure and HR difference in group 1 & group 2 respectively was 6003 ± 321 and 4163 ±50 p < 0.001 CI 95% which is highly significant which corresponds to Johan D. Lefrandt, JoÈrg Heitmann, et al,[13] comparison of amlodipine with verapamil where it is concluded that amlodipine controls rate pressure product index well with verapamil. Also found that both the groups were comparable in regard to sex, age, BMI. Most commonly patients underwent open surgery and more surgeries under Spinal anaesthesia. Hence we conclude that HR, SBP and RPI was reduced with both Tab. Amlodipine 5mg and Tab. Nifedipine 20mg but it was significantly reduced to low levels with Tab. Amlodipine 5mg there were no significant perioperative coronary events in low RPI patients (Group A> Group B) and Group B patients required escalation of dose in the post operative period than Group A which needs to be studied further.

Limitations of the study

No confirmative tests done to elicit the stress response. Long term follow up and compliance to medications or escalation of dose is not known. Regional and general anaesthesia had different response to intraoperative reduction of stress response. Inter-observer variations in assesing blood pressure and eliciting PAC.

CONCLUSION

On the basis of present clinical comparative study, we conclude that Tablet amlodipine 5mg significantly decreases the Rate Pressure Product index as a easy measure of perfusion of myocardial oxygen demand in De novo Hypertensive patients and reduces the perioperative coronary events on par with Tablet Nifedipine 20mg.

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