

## ASSESSMENT OF PERIOPERATIVE HAEMODYNAMICS AFTER PRETREATMENT WITH TWO DOSES OF $\beta$ BLOCKER IN NEWLY DIAGNOSED STAGE 1 AND STAGE 2 HYPERTENSIVE PATIENT

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### ABSTRACT

In an attempt to observe the haemodynamic parameters in the perioperative period by treating newly detected patients of hypertension (Grade 1 and Grade 2, JNC VII) with two doses of oral atenolol, this study has been taken up in Assam Medical College and Hospital, Dibrugarh, in an endeavour to determine and compare the efficacy of such pre-treatment against placebo and also to determine the adverse effects encountered.

### METHODS & MATERIALS

This randomised placebo controlled study was conducted in Assam Medical College & Hospital, Dibrugarh from July 2005 to June 2006, under the Department of Anaesthesiology and Critical Care, with prior permission from the hospital authorities after fulfilling all the norms and after taking informed consent from all patients included in this study.

### RESULTS

The results of the present study reconfirm the fact that altered haemodynamics in the perioperative period; particularly the heart rate can be effectively kept within the normal range with the use of oral beta blocking drugs like atenolol.

### CONCLUSION

Considering the above facts, it can be concluded that long-acting beta blockers like atenolol can be used effectively to prevent tachycardia and its deleterious effects like myocardial ischaemia and various forms of arrhythmias in the perioperative period can be reduced effectively. In presence of intensive monitoring facilities, unnecessary cancellation of cases can be avoided and hence reduction in hospital stay and cost of treatment can be achieved safely.

### KEYWORDS

Perioperative, Pretreatment,  $\beta$  Blocker, Hypertensive Patient, Haemodynamic, atenolol.

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**INTRODUCTION:** The key factor in the development of modern anaesthesia and surgery is the safe outcome. In the past few decades, there has been a tremendous achievement in reducing morbidity and mortality in surgical patients. This has been possible due to better understanding of the effects of surgery and anaesthesia leading to morbidity and mortality, development of measures to revert or control such deleterious effects and to availability of better monitoring facilities. A more refined knowledge and a better understanding of various physiologic and pharmacologic bases have led to a safer practice of anaesthesia. One of the most important among these effects is understanding the series of stress response or sympathoadrenal response and related pathophysiologic effects (Arthur C. Gyton and Hall 1988).<sup>1</sup> The net effect of this stress response is seen on various systems, but chiefly the cardiovascular system and the heart in particular. Although tolerated well by normal subject in patients with other comorbid conditions like hypertension, these effects are much more pronounced and might be life threatening.

By application of modulatory therapeutic measures at optimum time, surgical procedures can be carried out safely in patients with such comorbidities like hypertension (Edward Lin et al., Singh, Manorama 2003).<sup>2</sup> This in turn would reduce the number of cases that would otherwise be postponed in fear of adverse effects encountered in the perioperative period due to presence of comorbid conditions. It would hence, also avoid the prolongation of morbidity due to the surgical condition per se.

It has been established that pre-treatment with beta adrenergic blocking drugs reduces both, perioperative as well as longterm cardiac morbidity and mortality (Stone G et al 1988, Auerbach A. D, Goldman L 2002, Edward J. Norris, Ronald D. Miller 2005).<sup>3</sup>

This is said to happen in terms of preventing the various pathophysiologic changes in the cardiovascular system due to the neuro-hormonal or stress response. These pathophysiologic changes can alter the myocardial oxygen demand and supply balance and this in turn can either lead to myocardial ischaemia or predispose the heart to and of make it more susceptible to ischaemia.

Hence improved haemodynamic stability, particularly in terms of controlled heart rate (M. Zaugg et al 2002)<sup>4</sup> in the perioperative period underlies the cardio-protective effects of beta blockers.

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**MATERIALS & METHODS:** This randomised placebo controlled study was conducted in Assam Medical College & Hospital, Dibrugarh from July 2005 to June 2006. Under the Department of Anaesthesiology and Critical Care, with prior permission from the hospital authorities after fulfilling all the norms and after taking informed consent from all patients included in this study. One hundred patients aged between 40-65 years of both sexes awaiting any abdominal surgery under general anaesthesia with endotracheal intubation, except caesarean section were included in the study based on their following criteria.

**Inclusion Criteria:** Inpatients only, physical status ASA II, Elective case only, Systolic blood pressure >140 mmHg and/or Diastolic blood pressure >90 mmHg.

**Exclusion Criteria:**

- Physical status more than ASA II.
- Patients with target organ involvement, determined by the following.
  1. Fundoscopic examination of the retina showing features of 'Hypertensive Retinopathy', namely-narrowing of blood vessels and obliteration of distal flow, focal spasms, haemorrhage, exudates and papilledema.
  2. Serum creatinine more than 1.2 mg/dL, suggesting presence of renal pathology.
  3. 12-lead resting ECG, showing any form of coronary artery disease, old or recent or any degree or type of heart block or gross hypertensive heart diseases.
- Systolic BP >180 mmHg and /or Diastolic BP >110 mmHg.
- Pulse rate ≤60 or >120 beats/min.
- Patients with known contraindication to beta blockers.
- Age below 40 and above 65 years.
- Emergency or Outpatient operation.
- Suffering or suffered from any other systemic disease or infection within the past 1 month.
- Current use of anticonvulsants, any psychoactive drugs or any adrenergic augmenting or depleting drugs.

The patients were grouped randomly into two groups of 50 cases each, irrespective of age and sex.

**Group A (Control):** These patients received pretreatment with a placebo and Tab alprazolam 0.5 mg at bed time on the evening prior to surgery.

**Group B (Case):** These patients received pretreatment with Tab atenolol 50 mg, 1<sup>st</sup> dose in the evening prior to surgery with Tab alprazolam 0.5 mg at bed time and 2<sup>nd</sup> dose of Tab atenolol 50 mg in the morning of surgery at 6 AM.

**RESULTS & OBSERVATIONS:**

Age Group (Yrs.)	Group A		Group B	
	No.	Percentage	No.	Percentage
40-45	12	24%	10	20%
46-50	15	30%	14	28%
51-55	8	16%	9	18%
56-60	6	12%	7	14%
61-65	9	18%	10	20%
Minimum age	40		40	
Maximum age	63		65	
Mean	51.28		52.26	

*Table 1: Age Distribution of Patients under Study*

From Table 1, it can be seen that, the mean age group in Group A is 51.28 years. The youngest patient in Group A aged 40 and the oldest one was 63 while in Group B the youngest was 40 and the oldest was 65. The mean age Group B was calculated to be 52.26. Hence the age distribution of patients in the two groups was comparable.

Operative Procedures	Group A		Group B	
	No.	Percentage	No.	Percentage
Appendectomy	5	10%	6	12%
Cholecystectomy	22	44%	26	52%
Hernioplasty/rrophy	14	28%	11	22%
Nephrolithotomy	2	4%	3	6%
Hysterectomy	7	14%	4	8%
<b>TOTAL</b>	<b>50</b>	<b>100%</b>	<b>50</b>	<b>100%</b>

*Table 2: Surgical Procedures*

From Table 2, it can be seen that highest number of patients in both the groups were operated for Cholecystectomy. The type and extent of abdominal surgeries selected in the two groups were comparable. The haemodynamic variables observed in the study were Heart rate, Systolic Blood Pressure, Diastolic Blood Pressure, Mean arterial Pressure and Rate Pressure Product. The averages of the variables at specified time intervals were calculated and compared between the two groups. Intra and inter group percentage changes (Increase or Decrease) from baseline were also calculated.

Statistical significance of changes observed was determined by student's t-test'. Intra group comparisons were done using paired t – test while, inter group comparisons were calculated by independent sample t–test. Continuous lead II ECG with ST segment monitoring and analysis was done to detect any alteration in the ST segment and/ or cardiac rhythm.

'P' value determined gave the following inferences:

- 'P' value >0.05: Not significant
- <0.05: Just significant
- >0.01: Definitely significant
- <0.001: Highly significant

Time Interval	Group A		Group B		'P' Value
	% Age Change Compared to Baseline	'P' Value	% Age Change Compared to Baseline	'P' Value	
Pre-op (Baseline)					<0.001
Before intubation	0.78%	>0.05	-2.24%	<0.001	<0.001
During intubation	5.38%	<0.001	1.09%	>0.05	<0.001
Just after intubation	10.43%	<0.001	4.22%	<0.001	<0.001
1 min. after intubation	22.82%	<0.001	8.55%	<0.001	<0.001
3 min. after intubation	33.20%	<0.001	15.82%	<0.001	<0.001
5 min. after intubation	34.74%	<0.001	2.52%	>0.05	<0.001

**Table 3: Percent Change in Heart Rate during Induction (Comparison to Baseline Values & between Group A & B)**

From Table 3, it can be seen that the mean pre-operative (Baseline) heart rates in Group A and Group B differed significantly ( $0 < 0.001$ ). The change in heart rate observed at various intervals during induction and tracheal intubation showed an overall rising trend but the degree of heart rate fluctuations from the baseline was much more in Group A.

The peak mean heart rate in Group A was 116.20 beats/min., 5 min. after tracheal intubation and that of Group B was 80.66 beats/min. observed at 3 min. after intubation. The differences in heart rate observed between the two groups, recorded at various time intervals at the time of induction of anaesthesia were all found to be highly statistically significant ( $p < 0.001$ ).

Time Interval	Group A		Group B		'P' Value
	% Age Change Compared to Baseline	'P' Value	% Age Change Compared to Baseline	'P' Value	
Pre-op (Baseline)					<0.001
30 Min.	25.64%	>0.001	-7.63%	<0.001	<0.001
1 hour	27.49%	>0.001	-10.89%	>0.001	<0.001
1 hr. 30 min.	28.97%	>0.001	-9.85%	<0.05	<0.001

**Table 4: Percent Change in Heart Rate during Maintenance (Comparison to Baseline Values & between Group A & B)**

Table 4 shows that a very highly significant ( $p < 0.001$ ) difference of heart rate was observed between Group A and Group B throughout the period of maintenance of anaesthesia. From Table 6.1, the overall mean heart rate during the period of maintenance of anaesthesia in Group A was 109.84 beats/min. and that of group B was 63.05 beats/min. Also from Figure 6, it can be seen that as compared to the baseline heart rate (Pre-operative), the average heart rate was much higher in Group A while there

was a fall in heart rate from the pre-operative (Baseline) level in the patients in Group B. Again Table 6.2 shows that the rise in heart rate from baseline values observed in Group A was highly statistically significant ( $p < 0.001$ ). Additionally, from Table 4 when comparing the values of standard deviation observed in the two groups. It can be seen that there were much wider fluctuations of heart rate in Group A.

Time Interval	Group A		Group B		'P' Value
	% Age Change Compared to Baseline	'P' Value	% Age Change Compared to Baseline	'P' Value	
Pre-op (Baseline)					<0.001
Before extubation	19.01%	<0.001	17.11%	<0.001	<0.001
During extubation	25.27%	<0.001	21.76%	<0.001	<0.001
Just after extubation	32.79%	<0.001	24.12%	<0.001	<0.001
1 min. after extubation	34.36%	<0.001	6.66%	<0.001	<0.001
3 min. after extubation	33.34%	<0.001	-1.37%	<0.001	<0.001
5 min. after extubation	30.98%	<0.001	-1.81%	<0.001	<0.001

**Table 5: Percent Change in Heart Rate during Extubation (Comparison to Baseline Values & Between Group A & B)**

From Table 5, it can be said that at the end of surgery and just before extubation, the mean heart rate in Group A was 102.64 beats/min. while that in Group B was 81.56 beats/min., the difference being very highly statistically significant ( $p < 0.001$ ). The pattern of heart rate changes also differed significantly between the two groups. The maximum mean heart rate in Group A was found to be 115.88 beats/min. seen 1 min. after tracheal extubation while that in Group B was 86.44 beats/min., observed just after tracheal extubation.

It can be concluded that while heart rate in Group A remained significantly higher ( $p < 0.001$ ) than baseline till 5 minutes after tracheal extubation, heart rate touched baseline at 3 minutes after extubation and was lower than pre-operative level by 5 minutes after extubation in Group B. The fluctuations in heart rate were observed to be less in Group B than in Group A. Also, the difference of heart rate compared between the two groups at specified time intervals were all found to be very highly significant ( $p < 0.001$ ).

Time Interval	Group A		Group B		'P' Value
	% Age Change Compared to Baseline	'P' Value	% Age Change Compared to Baseline	'P' Value	
Pre-op (Baseline)					<0.001
12 hrs.	14.33%	<0.001	-8.04%	<0.001	<0.001
24 hrs.	17.25%	<0.001	-5.39%	<0.001	<0.001
36 hrs.	16.60%	<0.001	-5.97%	<0.001	<0.001
48 hrs.	12.70%	<0.001	-7.35%	<0.001	<0.001
60 hrs.	9.50%	<0.001	-7.81%	<0.001	<0.001
72 hrs.	7.74%	<0.001	-7.81%	<0.001	<0.001

**Table 6: Percent Change in Heart Rate in the Post-Operative Period (Comparison to Baseline Values & Between Group A & B)**

From Table 6, it can be seen that the mean heart rate up to 72 hours in the post-operative period averaged 97.47 beats/min. in Group A and 64.72 in Group B. It can be seen that heart rate in Group A remained persistently elevated up to 72 hours in the post-operative period. When compared to baseline values and the difference noted was observed to be highly significant statistically ( $p < 0.001$ ). On the other hand, in Group B, the heart rate was never above the baseline (Pre-operative) up to the recorded 72 hours of post-operative period. Also the decreased heart rate observed in Group B patients in the post-operative period showed a significant statistical difference ( $p < 0.001$ ) when compared to the baseline. Again, when heart rate was compared between the two groups, the difference was highly significant ( $p < 0.001$ ) all throughout the post-operative period.

**DISCUSSION:** The results of the present study reconfirm the fact that altered haemodynamics in the perioperative period; particularly the heart rate can be effectively kept within the normal range with the use of oral beta blocking drugs like atenolol. Various authors in the past have studied the beneficial effects of longer acting  $\beta$ -blocking drugs in non-cardiac surgeries. Stone and colleagues (1988)<sup>5</sup> had used a single, oral perioperative dose of three different  $\beta$  blockers, while Denis T. Mango and colleagues (1997) as well as Wallace and colleagues (1998)<sup>6</sup> administered intravenous atenolol pre-operatively. In the present study we have used two doses, 50 mg each of oral atenolol as a premedicant drug. The dose was selected as the minimum antihypertensive dose of atenolol to start with.

In our study, we tried to observe the beneficial effects of pretreatment with oral atenolol in mild to moderate, previously untreated, hypertensive patients.

The beneficial effects were expressed in terms of more controlled haemodynamic variables in the perioperative period. As depicted in the results, the demographic variables of the two groups matched in terms of age, sex, and male: female ratio, body weight and type of surgical procedure to be undertaken. Hence demographic confounding factors influencing the perioperative haemodynamics were minimised.

In the present study, premedication, anaesthetic technique and drugs used were also kept constant to exclude any variations of haemodynamic variables due to drugs or techniques. Intra and postoperative hypoxia and hypercarbia were avoided. Intra-operative ETCO<sub>2</sub> was maintained between 30-40 mmHg and SpO<sub>2</sub> was maintained above 97% in every case. Continuous Lead II ECG with ST segment monitoring and analysis was done. Pre-induction values were taken as baseline and on time specified manner, both intra-group and inter-group comparisons were made.

**Heart Rate:** Study of the heart rate in Placebo group at various stages throughout the perioperative period revealed that there was significant rise in heart rate as compared to baseline. From the baseline heart rate of 86.24±8.18 beats/min., the rise in heart rate appeared first with direct laryngoscopy and tracheal intubation, during which it was 5.38% above the baseline. Heart rate was further observed to rise steadily till 5 minutes after intubation and was recorded as 34.74% higher than baseline.

Subsequently, during maintenance of anaesthesia, the increased heart rate persisted and remained at a mean of

27.36% above the baseline. Increase in heart rate was again observed during emergence and tracheal extubation and was seen to be highest at 1 minute after extubation.

Heart rate gradually declined in the postoperative period, but it never touched baseline up to 72 hours in the postoperative period. It can be observed that the increase in heart rate from the baseline observed all throughout the perioperative period in Placebo group was very highly statistically significant ( $p < 0.001$ ). Apart from the persistence of increased heart rate all throughout the perioperative period, it was observed that, in most occasions in the intra-operative period and fewer ones in the post-operative period, the heart rate exceeded the critical value of 110 beats/min.

Considering atenolol treated group, the mean pre-induction (Baseline) heart rate in this group was  $69.64 \pm 8.17$  beats/min. Unlike Placebo group, in this group, the rise in heart rate above the baseline values were seen only during the time of induction and tracheal intubation as well during emergence and extubation. Heart rate remained below the baseline values during maintenance of anaesthesia and the postoperative period. This lowered heart rate was found to be highly significant ( $p < 0.001$ ).

At each specified time interval throughout the perioperative period, the difference of heart rate between the two groups was found to be highly significant ( $p < 0.001$ ) and at no occasion, in any patient, the heart rate crossed the critical value of 110 beats/min. Many authors have established the increased occurrence of tachycardia in the perioperative period in patients with pre-existing hypertension, particularly those who are untreated (Prys Roberts C 1979, Foster ED 1986).<sup>7</sup>

When comparing the heart rate patterns between the two groups of patients, the results clearly indicate that the appearance of tachycardia was effectively and almost completely abolished in patients receiving atenolol pre-treatment. In the present study, the efficacy of atenolol in preventing tachycardia in hypertensive patients during the perioperative period was found to be highly significant ( $p < 0.001$ ).

Zaugg Michael et al (1999)<sup>8</sup> found similar results. Using the Bonferroni-Dunn post hoc test ( $p < 0.017$  is significant), they found highly significant difference of heart rate between the atenolol and placebo group, all through the perioperative period and the heart rate in atenolol treated patients remained significantly lower than baseline values during maintenance as well as the post-operative period. They concluded that atenolol significantly reduced the incidence of tachycardia and high rate pressure product, particularly during emergence and extubation and in the post-operative period, times which have been associated with increased haemodynamic instability and myocardial ischemia. The haemodynamic effects of atenolol persisted up to 72 hrs. post-operatively. These findings are similar to our study.

Additionally, in the study made by Sear. J. W and Colleagues in 1990,<sup>9</sup> baseline heart rate in mild untreated hypertensive patients was found to be  $86 \pm 15$  beats/min.,

while it was  $66 \pm 10$  beats/min. in patients who received beta blockers. These findings are also similar to the present study.

Similar to the present study, when comparison was made, the intra and inter group changes in heart rate was found to be statistically significant in terms of increases and decreases in placebo and study groups respectively.

**Blood Pressure:** The mean pre-operative (Baseline) systolic blood pressure in placebo group was  $156.22 \pm 9.84$  mmHg and that in atenolol treated group was found to be  $149.04 \pm 7.57$  mmHg. Systolic blood pressure increased in both the groups during tracheal intubation and extubation. During intubation, though there was significant increase in systolic blood pressure from baseline in both the groups, it remained lower in atenolol treated group as compared to placebo group and when compared at specified time intervals, this difference was found to be statistically significant in most occasions. While, at the time of extubation, the difference in systolic pressure between the two groups was found to be significant after 1 minute had passed after extubation, before which the difference was not significant.

On the other hand, during maintenance of anaesthesia, in placebo group, mean systolic blood pressure remained higher than baseline by 10.37% and in atenolol treated group it was lower than baseline 5.28%. In the postoperative period, at different specified time intervals up to 72 hours, it was observed that in placebo group, the mean systolic blood pressure remained close to baseline values while in atenolol treated group it was found to fall progressively below the baseline. The lowest systolic blood pressure in the postoperative period was noted to be 7.19% below the baseline 72 hours after surgery.

The results of the present study show a slightly different trend when we consider the diastolic blood pressure. The pre-operative (Baseline) diastolic blood pressure in placebo group was  $96.88 \pm 5.08$  mmHg while that in atenolol treated group was  $89.96 \pm 6.5$  mmHg. This difference was found to be statistically significant. With tracheal intubation, this statistical difference was no longer found to be significant. During maintenance of anaesthesia, the diastolic blood pressure is found to be at an average of 5.3% lower than baseline values in atenolol related group. Diastolic blood pressure was found to be around baseline values in Placebo group during the maintenance period. The difference of diastolic blood pressure throughout the maintenance period was found to be significant.

Subsequently, during emergence from anaesthesia, the difference of diastolic blood pressure between the two groups was no longer found to be significant. Significant difference was observed only 1 minute after tracheal intubation and the significance persisted throughout the postoperative period. In the post-operative period, there was progressive lowering of diastolic blood pressure in both the groups. In atenolol treated group, this lowering was found to be significant when compared to the baseline, whereas it was not in placebo group. By 72 hrs. after

surgery, the diastolic blood pressure in atenolol treated group was 6.44% lower than baseline values.

The results and observations made on the fourth haemodynamic variable, that is Mean Arterial Pressure were found to be very similar to the findings of diastolic blood pressure in terms of increase or decrease from the baseline in both the groups. The findings differed from those of diastolic blood pressure in terms of lesser degree as well as duration of statistical significance while comparing the mean arterial pressures of the two groups during the period of maintenance of anaesthesia. Zaugg Michael et al (1999)<sup>8</sup> found similar results.

**CONCLUSION:** In conclusion, it can be stated that the use of oral atenolol as a premedicant drug effectively prevents occurrence of tachycardia in the perioperative period. Also, it can be said that though atenolol premedication did not prevent significant fluctuation in blood pressure responses during tracheal intubation, emergence and extubation, but during maintenance of anaesthesia and in the postoperative period there was significant lowering of blood pressure from baseline on most occasions. Moreover, ECG monitoring of patients under study revealed decreased incidence of ST segment alterations and a lesser propensity of developing arrhythmias in atenolol treated patients.

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