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Efficacy of Oral Atenolol and Oral Vitamin C Premedication on Hemodynamic Response in Patients Undergoing Elective Laparoscopic Cholecystectomy

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ABSTRACT

Back Ground & Objectives: *Physiologic effects of prolonged carbon dioxide insufflation have a major impact on cardiopulmonary function. Atenolol, has been extensively studied but only few attempts have been made to evaluate it in laparoscopic surgeries. Study was aimed to evaluate the clinical effects of oral Atenolol premedication in attenuating the hemodynamic changes during the period of pneumoperitoneum in patients undergoing laparoscopic cholecystectomy.*

Methods: *Prospective, randomized, double blinded study was conducted, on fifty ASA I & II patients, 30 to 60 years, for elective laparoscopic cholecystectomy. Group I (Atenolol): Atenolol tablet. Group II (Placebo): Vitamin C tablet. Premedication, preoxygenation, induction intubation and maintenance was standardised for both groups. Monitoring data was recorded every 2 minutes for the first 30 minutes of pneumoperitoneum and thereafter every 5 minutes for the rest of the operation.*

Results: *Comparisons of values bring out the difference in the hemodynamics between the two groups, with a statically significant lower level in Atenolol group.*

Conclusions: *Atenolol 50mg premedication elective laparoscopic cholecystectomy can bring in a stable hemodynamics compared to placebo.*

Keywords: *Atenolol, Cholecystectomy, Hemodynamics, Laparoscopy, Premedication.*

Introduction

Laparoscopy (Greek: lapara = flank or laparos = soft; skolphin = to look) is a relatively modern procedure; it involves the insufflation of the abdomen by a gas, so the endoscope can visualise the intra-abdominal contents without being in direct contact with the viscera or tissues[1]. The physiologic effects of prolonged carbon dioxide insufflation into an endocavity combined with variations in positioning has a major impact on cardiopulmonary function. [2],[3] ,[7].

Various recent studies have shown that intra operative cardiovascular stress not only affects the immediate perioperative outcome, but may enhance the mortality and incidence of cardiovascular complications for as long as two years after surgery[2]. Different methods including volatile agents, propofol infusion, beta blockers has been tried to attenuate the hemodynamic changes observed during laparoscopic surgeries[3]. Even though Atenolol, a beta blocker, has been extensively studied and is often used to prevent the stress response associated with intubation and

perioperative myocardial infarction, only very few attempts have been made to evaluate its efficacy in laparoscopic surgeries.

Objectives

The study was aimed to evaluate the clinical effects of oral Atenolol premedication in attenuating the hemodynamic changes during the period of pneumoperitoneum in patients undergoing laparoscopic cholecystectomy.

An attempt was made to find the degree of hemodynamic changes that usually occur in such patients during the period of insufflation and the extent to which this is attenuated with Atenolol premedication.

The effect in preventing the hemodynamic response during intubation was also compared.

Methodology

This prospective, randomized, double blinded study was conducted, after obtaining appropriate ethics committee approval, on fifty consecutive ASA I & II patients posted for elective laparoscopic cholecystectomy in Medical College, Thiruvanant-hapuram, Kerala.

Inclusion Criteria

- ASA I & II patients
- Age between 30 and 60 years
- Patients undergoing elective laparoscopic cholecystectomy
- Body weight no more than 20% above ideal body weight.

All patients were examined clinically and base line investigation results reviewed preoperatively, by the same anaesthetist (primary investigator) and informed consent was obtained.

Exclusion Criteria

- ASA III & IV patients
- Presence of acute cholecystitis
- Coexisting cardio respiratory disease
- History of drug intake
- History of drug allergy
- Anticipated difficult airway

Those patients in whom there was difficulty in intubation and those in whom the end tidal carbon dioxide was not kept between 34-40 mm Hg during the period of pneumoperitoneum were also to be excluded from the study.

Methods

Patients were randomized into two groups by drawing of lots by a person not involved in the study.

Group I (Atenolol group) receiving 2 mg/kg [rounded off to the nearest figure of 25] of oral atenolol hydrochloride.

Group II (Placebo group) receiving a similar size & shaped vitamin C tablet.

The patients and investigator were blinded to the randomized groups. The atenolol preparation used contained atenolol hydrochloride 25/50 mg/tablet. The drug produced by the same pharmaceutical company was used for all patients

Premedication

All patients in both groups were given 10 mg Diazepam on the previous night and were advised nil per oral from 10.00 pm on the previous night. Oral Ranitidine 150 mg and oral Metocloperamide l0 mg night before surgery and early morning on day of surgery was also prescribed. At 6.30 am on the morning of surgery the patients were given the selected oral drug with sips of water. All cases were posted as the first case of the day.

Monitors

After shifting the patient to the theatre, monitors including non-invasive blood pressure monitor, electrocardiogram (lead II) and pulse oximeter were attached and the base line reading was noted.

Technique

Intravenous access was secured under local anesthesia, in the contra lateral arm to which blood pressure cuff was applied, and normal saline infusion was started based on Holliday-Segar formula. Intravenous Granisetron1mg, glycopyr-rolate 0.2mg, were given to all patients in both groups. Premedication with intravenous Pethidine 0.5mg/kg, promethazine 0.25mglkg, midazolam 0.02mg/kg were given. Following three minutes of preoxygenation with 6 litres of oxygen using simple face mask, general anaesthesia was induced with

Thiopentone sodium 5mg/kg, lignocaine 1.5mg/kg, succinyl choline 1.5mg/kg. Any hypotension (MAP <60mmHg) were to be treated with intravenous fluids. Any bradycardia (heart rate <50/minute or <20% baseline whichever is lower) were to be treated with intravenous atropine. Orotracheal intubation was done by an experienced anaesthesiologist. End tidal C02 monitor was attached. Anaesthesia was maintained with 50% air in oxygen and isoflurane using Bains circuit. Isoflurane concentrations were adapted to maintain hemodynamic stability by an experienced anaesthesiologist: mean arterial pressure (MAP) was not allowed to increase more than 20% above preinduction value. Relaxation was maintained with vecuronium. During surgery minute ventilation was controlled and adjusted to keep the end tidal C02 between 34-40 mmHg.

Immediately after intubation Ryles tube was introduced with the help of laryngoscope and Magills forecps in all patients in both groups. Urinary bladder was also catheterized using appropriate sized Foley's catheter in all patients in both groups. At this time all patients in both groups were given intra muscular Diclofenac sodium 75 mg for post op analgesia.

The insufflation flow rates for achieving pneumoperitoneum were kept initially at 1-1.5 L/minute. Once adequate pneumoperitoneum has been achieved (1-2.5 L) the flow rate was increased to 3-4 L/ minute. Gas flow was set to stop automatically once the preset pressure set on the insufflator is reached so that the intra abdominal pressure was automatically maintained at 12 mmHg during laparoscopy.

At the end of surgery, once patient showed signs of recovery, all patients in both groups were reversed with intravenous neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg and extubated.

The blood pressure was recorded as follows for analysis:

Baseline (on connecting monitors)	T1
Preintubation (1 minute after induction)	T2
Post intubation (immediately after)	T3
Five minutes after insufflation	T4
Ten minutes after insufflation	T5
Fifteen minutes after insufflation	T6
Twenty minutes after insufflations	T7
Thirty minutes after insufflation	T8
Forty minutes after insufflation	T9
Ten minutes after exsufflation	T10

Head up position to 30o (reverse trendelenburg) was done ten minutes after insufflation. (corresponding to T5) in all cases after discussing with the surgeon.

Analysis and Results

Data were analyzed using computer software, Statistical Package for Social Sciences (SPSS) version 10. Data are expressed in its frequency and percentage as well as mean and standard deviation. To elucidate the associations and comparisons between different parameters, Chi square ($\chi 2$) test was used as nonparametric test. Student's t test was used to compare two groups. Analysis of variance (One Way ANOVA) was performed as parametric test to compare between time intervals. Duncan's multiple range tests were also employed as post hoc analysis to elucidate difference between groups. For all statistical evaluations, a two-tailed probability of value, < 0.05 was considered significant. Results are reported as mean ± standard deviation.

Results

The patients were randomised into Placebo group and Atenolol group. The two groups were comparable in respect of age, height, weight and ASA physical status as shown in Table 1.

Table 1 Patient Parameters in Placebo and Atenolol Groups

Parameter	Placebo group		Atenolol group		t value	p value
	Mean	± SD	Mean	± SD		
Age (yrs)	45.44	3.10	43.79	5.04	1.232	> 0.05
Height (cm)	156.65	4.00	155.20	5.20	0.987	> 0.05
Weight (kg)	54.15	3.08	55.30	3.90	1.045	> 0.05
Duration of surgery (min)	133.75	24.0	126.00	14.00	1.684	> 0.05
Sex (male: female)	4:16		8:12		2.451	> 0.05
ASA Grade (I:II)	17:3		18:2		2.014	> 0.05

The changes monitored in the mean arterial pressures (MAP) in the placebo group and atenolol group at various time intervals are compared with the base line value. They clearly show that in the placebo group the stress persisted for a longer duration than the atenolol group. To know the extent of benefit obtained by the addition of atenolol, the MAP of these two groups at the corresponding time intervals are contrasted in Table 2. This comparison clearly brings out the difference in the hemodynamics between the two groups, with a statically significant lower level in patients belonging to atenolol group.

The changes in the systolic blood pressures (SBP) in the placebo group and atenolol group at various time intervals are compared with the base line value and is shown in table 3. In the placebo group the stress persisted for up to 20 minutes after the onset of pneumoperitoneum, while in the atenolol group stable hemodymanics is rapidly attained. Comparison of the systolic blood pressures of the two groups shows that the subjects in the atenolol group have experienced a hemodynamically stable period of pneumoperitoneum.

Table 2 Mean Arterial Pressure: Placebo Group and Atenolol Group

Time intervals compared	MAP in placebo group (range)		MAP in Atenolol group (range)		p value
	Mean	± SD	Mean	± SD	
T1	103.23	10.94	95.73	16.60	> 0.05
T2	92.83	12.14	88.13	10.30	> 0.05
T3	119.95	17.20	111.22	13.10	> 0.05
T4	117.58	12.80	103.48	10.00	< .001
T5	115.92	13.40	103.70	7.60	< 0.01
T6	117.72	11.40	103.42	6.80	< 0.001
T7	115.83	10.40	104.23	7.20	< 0.001
T8	114.42	9.00	101.85	7.90	< 0.001
T9	114.25	9.30	101.10	7.40	< 0.001
T10	105.83	10.80	96.18	5.00	< 0.01

Table 4 portray the alterations in the diastolic blood pressures (DBP) in the placebo group and atenolol group. The values at various time intervals monitored are compared with the base line value of the corresponding group. While the entire period of pneumoperitoneum was stressful for the subjects in the placebo group, the DBP returns to non significant levels by twenty minutes. Even though the initial period shows a significant change in the atenolol group, the increase is significantly lesser when compared with change in the placebo group.

Table 5 illustrate how much the heart rate is increased from base line in the placebo group and atenolol group. In spite of the fact that there is a statistically significant lower heart rate at the beginning (Table 5) in the atenolol group, there is increase from the base line throughout the duration of surgery in both groups. On the whole atenolol appears to provide a more stable heart rate during the period of pneumoperitoneum.

Table 3 Systolic Blood Pressure: Placebo Group and Atenolol Group

Time intervals compared	SBP in placebo group (range)		SBP in Atenolol group (range)		p value
	Mean	± SD	Mean	± SD	
T1	127.40	16.80	114.80	26.56	> 0.05
T2	110.80	12.90	105.95	12.20	> 0.05
T3	142.65	18.10	132.80	15.00	> 0.05
T4	140.10	15.30	123.85	11.90	< 0.01
T5	140.55	15.80	123.20	8.80	< 0.001
T6	140.10	14.70	124.00	7.90	< 0.001
T7	136.95	12.10	125.40	9.20	< 0.01
T8	135.70	12.00	122.70	10.00	< 0.01
T9	135.40	11.60	121.05	8.10	< 0.001
T10	126.75	12.30	116.30	5.30	< 0.01

Table 4 Diastolic Blood Pressure: Placebo Group and Atenolol Group

Time intervals compared	DBP in placebo group (range)		DBP in Atenolol group (range)		p value
	Mean	± SD	Mean	± SD	
T1	79.05	10.10	76.65	9.00	> 0.05
T2	74.85	12.49	70.30	9.50	> 0.05
T3	97.25	17.00	89.65	12.70	> 0.05
T4	95.05	11.40	83.10	9.40	< 0.01
T5	91.30	21.40	84.20	7.50	> 0.05
T6	95.35	9.50	82.85	7.10	< 0.001
T7	94.70	9.70	83.05	6.70	< 0.001
T8	93.15	8.00	81.00	6.90	< 0.001
T9	93.10	9.00	81.15	8.10	< 0.001
T10	84.90	11.10	76.05	6.80	< 0.01

Table 5 Heart rate: Placebo Group and Atenolol Group

Time intervals compared	HR per minute in placebo group (range)		HR per minute in Atenolol group (range)		p value
	Mean	± SD	Mean	± SD	
T1	74.00	7.49	68.65	5.59	< 0.05
T2	82.80	15.90	79.05	11.42	> 0.05
T3	96.60	16.40	85.05	10.86	< 0.05
T4	86.00	8.00	78.65	12.60	< 0.05
T5	86.40	7.70	79.60	10.30	< 0.05
T6	86.75	8.90	78.35	10.10	< 0.01
T7	84.95	8.80	75.45	11.50	< 0.01
T8	83.00	8.90	75.70	9.70	< 0.05
T9	81.90	9.60	73.90	8.40	< 0.01
T10	75.05	9.20	68.15	6.20	< 0.01

Discussion

An attempt was made to find the degree of hemodynamic changes that usually occur in such patients during the period of insufflation and extent to which this is attenuated with atenolol premedication. Fifty ASA I and II patients posted for elective laparoscopic cholecystectomy were studied.

As evidenced by statistical analysis (Table-1) both groups were similar in distribution in age, gender, height and weight. ASA grading and duration of surgery was also similar in both groups.

In the placebo group, with the induction of anaesthesia, the mean arterial pressure MAP shows a significant fall in the range of 10 mmHg (Figure 1) , followed by a rise of 27 mmHg (from baseline T1 value). These changes are as expected of the cardiovascular depressant effect of the inducing agents (T2) followed by stress associated with laryngoscopy and intubation (T3).

With the institution of pneumoperitoneum the MAP shows a statistically significant rise (10-12 mmHg from baseline) throughout the entire period of pneumoperitoneum till exsufflation. In addition to the initial dip seen in the MAP at T5 10 minutes after insufflation), the overall trend of MAP is one of gradual decline The initial dip at T5 may be related to the head up tilt instituted around that time.

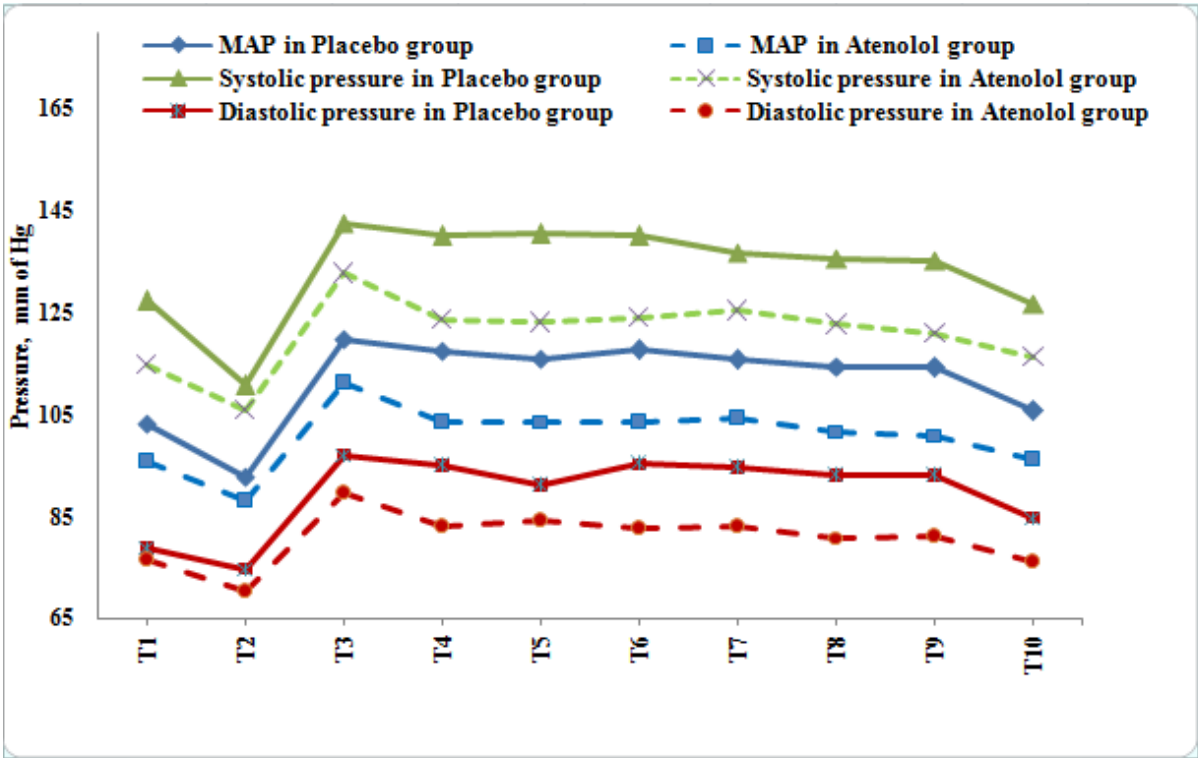

Fig 1. Variations of Study Parameters in Placebo and Atenolol Group

The overall changes correlate with results obtained by various studies reported by [4], [5], and [6]. The studies by [4] reported a rise of 28±10 mmHg, while [5] reported a change of around 10-12 mmHg during pneumoperitoneum. By 10 minutes after exsufflation the MAP was seen to return back to almost the base line values.

Analysis of the Atenolol group (Fig 1) shows a similar general trend, with an initial fall of 6 mmHg on induction (T2), pursued by a hike of 16 mmHg following intubation (T3). The increase in MAP during intubation is contrary to the protection offered by beta blockers. This is because the attenuation of stress response to intubation is usually abolished by intravenous administration of a more potent short acting beta blocker like esmolol.

The MAP at T3 (5 minutes after intubation) shows a significant decrease in the Atenolol group. Additive action of atenolol with lignocaine given intravenously to both the groups might be responsible for this dip. The effect of atenolol in suppressing stress response is seen throughout the procedure and also to the time of exsufflation (Fig 1). Lignocaine was used in the Atenolol group also because randomization was done pre-operatively and it was considered unethical to deny a proved stress response attenuator to the patients likely to be allotted to the placebo group.

Another point to be considered is whether this hemodynainic stabilizing effect of lignocaine, exert any influence on the hemodynamic profile during pneumoperitoneum, thereby altering the study result obtained. Study by Stanley et al [8] shows that the maximum effect of intravenous lignocaine is at 3 minutes, and by even 5 minutes the hemodynamic effects were almost nil.

The extent of the benefit obtained from oral Atenolol premedication during pneumoperitoneum is revealed best when the MAP's of the two groups are compared with each other (Table 2). Even though the base line values (TI) of the two groups do not differ statistically, the atenolol group show a clinically relevant lower MAP (10-14 mmHg) than the placebo group. This meaningful clinical difference is also observed during induction (T2) and intubation (T3).

In spite of the fact that both groups show significant alteration from their respective baseline values (TI) during the period of pneumoperitoneum, the Atenolol group has a statistically significant difference (10-14 mmHg) from the placebo group throughout the entire period of pneumoperitoneum and after exsufflation (T10).

Analysis of systolic (SBP) and diastolic blood pressure (DBP) also on the whole shows a similar result. Evaluating the systolic blood pressure, one can observe that, patients in placebo group (Fig 1) have experienced statistically significant stress during induction, intubation and early period of pneumoperitoneum. In contrast, the atenolol group (Fig 1) shows hemodynamic stability during pneumoperitoneum, with only very little increase from the baseline values.

The heart rate (HR) when compared between the two groups shows significant decrease in the Atenolol group from the T3 to T10. The heart rate shows statistically significant difference between the two groups (Table-5) at baseline itself (TI). Even though HR showed marked increase with intubation in both groups, the entire period of pneumoperitoneum is characterised by significant disparity between the two groups, with Atenolol group showing a lower HR compared to the placebo group.

Conclusion

Analysis of the monitored data shows that, the patients in the Atenolol group had all their baseline values at a lower level when compared to the placebo group and is significant. Even though the difference in systolic blood pressure was not statistically significant, from a clinical point of view the difference is appreciable.

In agreement with various previous studies, considerable alterations in the hemodynamic variables were noted during the period of pneumoperitoneum, emphasizing the fact that the period is indeed a very stressful time which has to be carefully tided over, especially in high risk

patients. Use of oral Atenolol proved to be very effective in providing a very stable hemodynamic condition during the entire period of insufflation. All parameters observed were on a clinically and statistically significant lower level compared to the placebo group.

Premedication with oral Atenolol can be considered as a useful and inexpensive method to ensure hemodynamic stability during pneumoperitoneum in patients undergoing laparoscopic cholecystectomy.

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