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Efficacy of Intravenous Clonidine as Compared to Oral Clonidine on Hemodynamic Changes during Laparoscopic Cholecystectomy - A Randomized Controlled Trial

Authors
Anuraj V T[1], Sethunadh R[2*]
[1]Assistant Professor, Department of Anaesthesia, Government Medical College, Kottayam, Kerala
[2]Assistant Professor, Department of Anaesthesia, Government Medical College, Kottayam, Kerala
*Corresponding Author
Sethunadh R
Assistant Professor, Department of Anaesthesia, Government Medical College, Kottayam, Kerala

Abstract
Background: *Laparoscopic technique has almost replaced the open method of cholecystectomy. The anesthesia for laparoscopic cholecystectomy is very challenging because of the effects of pneumoperitoneum on various organ systems mainly the cardiovascular system. In this study we have compared the efficacy of intravenous clonidine as compared to oral clonidine in reducing the hemodynamic effects of pneumoperitoneum.*
Materials and Methods: *This prospective randomized controlled study was performed in 70 patients posted for elective laparoscopic cholecystectomy in a tertiary care centre. Patients were randomized into two groups, Group 1 patients receiving 3 µg/kg of oral clonidine and Group 2 patients receiving 3 µg/kg of intravenous clonidine. Blood pressure, Heart rate were monitored at appropriate intervals*
Results: *Patients in both groups had reduced hemodynamic responses to pneumoperitoneum. The incidence of hypotension and bradycardia were more common in the in the iv Clonidine group.*
Conclusion: *Premedication with oral clonidine is equally efficacious as intravenous clonidine in reducing the hemodynamic stress response to pneumoperitoneum.*
Keywords: *Laparoscopic cholecystectomy, pneumoperitoneum, clonidine.*

Introduction

Laparoscopy is a minimally invasive procedure, which involves the insufflations of the abdomen by a gas so the endoscope can visualize the intra - abdominal contents without being in direct contact with the viscera or tissues. It is a relatively safer procedure but anesthesia during the procedure is challenging because of the pneumoperitoneum created during laparoscopy as well the positioning needed during the procedure.[1]

The physiologic effects of prolonged carbon dioxide insufflations into an endocavity combined with variations in positioning has a major impact on cardiopulmonary function particularly in American society for Anaesthesiologists (ASA) grade III and IV patients[2] Various recent studies have shown that intra operative cardiovascular stress not only affects the immediate perioperative outcome but may enhance the mortality and incidences of cardiovascular complications for as

long as two years after surgery. Different methods including volatile agents, propofol infusion, beta blockers have been tried to attenuate the hemodynamic changes observed during laparoscopic surgeries. Even though Clonidine, an alpha-2 adrenergic agonist has been extensively studied and is often used to treat hypertension, only few attempts have been made to evaluate its efficacy, especially the intravenous preparation in laparoscopic surgeries[3.]

Aim

1. The study was aimed to evaluate and compare the clinical effects of intravenous and oral clonidine premedication in attenuating the hemodynamic changes during the period of pneumoperitoneum in patients undergoing laparoscopic cholecystectomy.
2. An attempt was made to find the degree of hemodynamic changes that usually occur in such patients during the period of insufflations
3. The efficacy in preventing the hemodynamic response during intubation was compared.
4. The major side effect profile was also observed.

Materials and Methods

This prospective, randomized study was conducted, after obtaining appropriate ethics committee approval, on seventy consecutive ASA I and II patients posted for elective laparoscopic cholecystectomy.

Preoperative Evaluation

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

Inclusion Criteria

1) ASA 1 and 2
2) Age group 20 —60
3) Patients undergoing laparoscopic cholecystectomy

Exclusion Criteria

1) ASA 3 and 4
2) Patients with history of hypertension, ischemic heart disease, aortic stenosis, left ventricular failure and AV conduction block
3) Patients concomitantly taking clonidine, methyl dopa, beta blocking drugs, Benzodiazepines and MAO inhibitors.
4) Patients with documented allergy to clonidine

Those patients in whom the procedure was converted to an open surgery, in whom there was difficulty in intubation and those in whom the end tidal carbon dioxide was not kept between 35 to 40 mm of Hg during the period of pneumoperitoneum were also to be excluded from the surgery.

Methods

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

Group I (oral clonidine group) receiving 3µg/kg [rounded off to the nearest figure of 25] of oral clonidine

Group II [intravenous clonidine group] receiving 3µg/kg of inj.Clonidine.

The clonidine preparation used contained clonidine 100µg tablets and the injectable preparation of clonidine, containing 150µg of clonidine per ml. The drug produced by the same pharmaceutical company was used for all patients.

Patients age, weight, sex noted after a thorough pre anaesthetic examination.

Premedication

All patients in both groups were given 10mg Diazepam on the previous night. Oral Ranitidine 150mg and oral metoclopramide 10mg night before surgery and early morning on the day of surgery was also prescribed. At 6:30 am on the morning of surgery the patients were given the selected oral drugs with sips of water. All cases posted as the first case of the day.

All emergency medication to treat hypotension, hypertension and bradycardia are kept ready,

anaesthesia machine and equipments are kept ready prior to starting the procedure.

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 anaesthesia, in the contra lateral arm to which blood pressure cuff was applied, and normal saline infusion was started based on the Holliday-Segar formula. Intravenous Granisetron 1mg, Glycopyrrolate 0.2mg were given to all patients in both groups. Premedication with intravenous Fentanyl Iμg/kg, Midazolam 0.02mg/kg were given. Following 3 min of preoxygenation with face mask, general anaesthesia was induced with Thiopentone sodium 5mg/kg. Endotracheal intubation is facilitated by Lignocaine 1.5mg/kg and Succinyl choline 1.5mg/kg of body weight. Any hypotension (MAP <60mm of Hg) were to be treated with intravenous fluids. Any bradycardia (heart rate <50/min or <20% of baseline associated with hypotension, whichever is lower) were to be treated with intravenous atropine. Orotracheal intubation was done by an experienced anaesthesiologist. End tidal CO_2 monitor was attached. Anaesthesia was maintained with 50% nitrous oxide in oxygen and isoflurane using the Bains circuit. Isoflurane concentration were adjusted to maintain hemodynamic stability by an experienced anaesthesiologist: mean arterial pressure was not allowed to increase more than 20% above pre induction value. Relaxation was maintained with Vecuronium.

During surgery, minute ventilation was controlled and adjusted to keep the end tidal CO_2 between 35 to 45 mm of Hg. Immediately after intubation nasogastric tube was introduced with the help of laryngoscope and Magill's forceps in all patients in both groups. Urinary bladder was also catheterized using appropriately sized Foley's catheter in all patients in both groups. At this time all patients in both groups were given intramuscular Diclofenac Sodium 75mg for post op analgesia.

The insufflation flow rates for achieving pneumoperitoneum were kept initially at 1-1.5 L/min. Once adequate pneumoperitoneum has been achieved the flow rate was increased to 3 - 4 L/min. Gas flow was set to stop automatically once the preset pressure set on the insufflators is reached so that intra-abdominal pressure was automatically maintained at 12 mm of Hg during laparoscopy. After creating pneumoperitoneum, necessary adjustments in ventilator settings will be made to maintain normocapnia. Throughout the procedure, any rise in mean arterial pressure more than 20% from the baseline was treated with nitroglycerine drip.

At the end of surgery, once the patient shows signs of recovery, all patients in both groups were reversed with intravenous neostigmine 5μg/kg and glycopyrrolate 10μg/kg and extubated and patients transferred to recovery room. In the post anaesthesia care unit, they are monitored for any evidence of complications or adverse events

Monitoring

The blood pressure was recorded every 2minutes for the first 30 min of pneumoperitoneum and there after every 5min for the rest of the operation. Heart rate was monitored continuously. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were taken in the following intervals for analysis.

Baseline (at the time of connecting to the monitors)	T1
Prior to induction (after all premedications are given)	T2
Three minutes after endotracheal intubation	T3
Before pneumoperitoneum	T4
Fifteen minutes after pneumoperitoneum	T5
Thirty minutes after pneumoperitoneum	T6
Ten minutes after the release of carbon dioxide	T7
Ten minutes after extubation	T8

In addition, Oxygen saturation and End tidal carbon dioxide tension were monitored and ST variations in ECG were also looked for.

Patients were shifted to PACU and later to post-operative ward and were monitored for 24 hours. In the PACU vitals were monitored half hourly for

four hours. The patients were monitored every fourth hourly in the ward post operatively. The vitals were taken and checked whether any of the patients had bradycardia/hypotension or not. Bradycardia was taken as heart rate of less than 60/min, hypotension as calculated as systolic BP of less than 80mm of Hg or a fall of more than 20% in the baseline MAP. The incidence of major side effects namely shivering, nausea and vomiting and sedation were also enquired about.

Analysis and Results

Statistical Analysis

Data were analysed using the 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 test was used as nonparametric test. Student's t test was used to compare two groups. Duncan's multiple range tests were also employed as post hoc analysis to elucidate the difference between two groups. For all statistical evaluations, a two tailed probability value <0.05 was considered significant. Results are reported as mean±standard deviation.

Observation and Results

The patients were randomized into Oral and Intravenous (IV) clonidine group. The two groups were comparable in respect to age, sex, height, weight and ASA physical status as shown in the following tables

Tables and figures showing comparison of the demographic background

Table 1: percentage distribution of the sample based on age

Age	Oral		IV		χ^2	p
	Count	Percent	Count	Percent		
20-39	14	43.8	18	58.1	1.29	0.256
40-59	18	56.3	13	41.5		
Average	40.5±7.3		38±9.8			

Table 2: Percentage distribution of the sample based on weight

Weight (Kg)	Oral		IV		χ^2	p
	Count	Percent	Count	Percent		
50-59	8	25.0	10	32.3	0.45	0.799
60-69	20	62.5	17	54.8		
70+	4	12.5	4	12.9		
Average	63.5±5.2		61.0±5.7			

Table 3: Distribution of sample based on ASA status

ASA	Oral		IV		χ^2	p
	Count	Percent	Count	Percent		
I	27	84.4	26	83.9	0.003	0.956
II	5	15.6	5	16.1		
I:II	27:5		26:5			

Tables showing comparison of intraoperative monitoring variables

Table 4: Comparison of pulse rate at various time intervals in both groups

Stage	Oral		IV		t	p	Sig
	Mean	SD	Mean	SD			
Before premedication	75.1	8.4	74.8	7.8	0.13	0.901	NS
Before Induction	73.5	10.4	67.7	11.4	2.11	0.039	S
After Intubation	76.4	9.2	69.9	12.6	2.36	0.022	S
Before pneumoperitoneum	73.9	8.7	69.3	11.7	1.78	0.080	NS
After pneumoperitoneum (15min)	75.3	8.0	73.1	10.9	0.94	0.353	NS
After pneumoperitoneum (30min)	77.4	8.4	74.8	12.3	0.98	0.329	NS
After release of CO2	76.6	9.9	70.2	9.4	2.66	0.010	S
After extubation	78.2	10.0	71.6	10.4	2.54	0.013	S

Table 5: Comparison of Systolic BP at various time intervals in both groups

Stage	Oral		IV		t	p	Sig
	Mean	SD	Mean	SD			
Before premedication	127.8	9.3	124.1	10.2	1.53	0.132	NS
Before Induction	110.0	17.7	99.8	13.1	2.61	0.011	S
After Intubation	117.2	18.9	102.5	15.1	3.41	0.001	HS
Before pneumoperitoneum	108.2	15.4	101.6	14.0	1.77	0.082	NS
After pneumoperitoneum (15min)	109.0	13.7	104.0	14.8	1.4	0.167	NS
After pneumoperitoneum (30min)	112.0	12.8	107.0	15.0	1.44	0.154	NS
After release of CO2	107.6	12.6	102.3	13.6	1.62	0.111	NS
After extubation	118.1	15.4	104.9	12.7	3.69	0.000	HS

Table 6: Comparison of Diastolic BP at various time intervals in both groups

Stage	Oral		IV		t	p	Sig
	Mean	SD	Mean	SD			
Before premedication	76.6	7.5	75.1	6.7	0.83	0.408	NS
Before Induction	70.3	10.2	65.2	7.7	2.22	0.030	S
After Intubation	72.7	9.1	66.3	6.7	3.18	0.002	HS
Before pneumoperitoneum	67.3	8.5	64.5	7.0	1.41	0.164	NS
After pneumoperitoneum (15min)	70.0	7.4	66.6	6.2	1.94	0.057	NS
After pneumoperitoneum (30min)	70.9	7.9	67.8	5.1	1.83	0.072	NS
After release of CO2	69.5	7.4	66.2	6.2	1.88	0.064	NS
After extubation	75.7	8.5	67.9	6.8	4.02	0.000	HS

Table 7: Comparison of Mean BP at various time intervals in both groups

Stage	Oral		IV		t	p	Sig
	Mean	SD	Mean	SD			
Before premedication	93.7	6.4	91.5	6.3	1.4	0.167	NS
Before Induction	83.5	11.0	76.8	8.9	2.68	0.009	HS
After Intubation	87.5	10.7	78.3	8.7	3.73	0.000	HS
Before pneumoperitoneum	80.9	9.5	76.9	8.5	1.77	0.081	NS
After pneumoperitoneum (15min)	83.0	8.2	79.1	8.1	1.91	0.061	NS
After pneumoperitoneum (30min)	84.6	8.4	80.9	7.8	1.83	0.073	NS
After release of CO2	82.2	7.2	78.2	8.1	2.04	0.045	S
After extubation	89.8	8.7	80.2	8.0	4.56	0.000	HS

Table showing comparison of postoperative complications

		Oral		IV		p
		Count	Percent	Count	Percent	
Sedation	1	4	12.5	2	6.5	0.71
	2	15	46.9	16	51.6	
	3	13	40.6	13	41.9	
	4	0	0	0	0	
Nausea & Vomiting	Absent	30	93.8	30	96.8	0.512
	Present	2	6.3	1	3.2	
Shivering	Absent	29	90.6	28	90.3	0.649
	Present	3	9.4	3	9.7	
Bradycardia	Absent	29	90.6	24	77.4	0.138
	Present	3	9.4	7	22.6	
Hypotension	Absent	27	84.4	24	77.4	0.352
	Present	5	15.6	7	22.6	

Discussion

Several studies showed the hemodynamic changes associated with the creation of pneumoperitoneum during laparoscopic surgeries like an immediate decrease in cardiac index and an increase in mean arterial blood pressure and systemic vascular resistance[4,5]. The study was conducted to evaluate the effects of intravenous clonidine as compared to oral clonidine in attenuating the hemodynamic changes during pneumoperitoneum in patients undergoing laparoscopic cholecystectomy, is discussed below. 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 clonidine premedication. Seventy ASA I and Il patients posted for elective laparoscopic cholecystectomy were studied. They were randomized into two equal groups.

Group A (Oral clonidine group) receiving 3µg/kg of tablet clonidine orally, Group B (iv clonidine group) receiving clonidine 3µg/kg iv.

As evidenced by statistical analysis both groups were similar in distribution in age, gender, and weight. ASA grading and duration of surgery were also similar in both groups. Seven patients were withdrawn from the study because the proposed laparoscopic cholecystectomy surgery was converted to open cholecystectomy. Apart from these seven patients, 63 patients completed the analysis.

Heart rate in both oral and iv groups were comparable (p = 0.901). After giving clonidine as premedication in both groups, there was a significant fall in heart rate, which was more pronounced in the iv group (p=0.039). In fact, bradycardia was seen in 3 patients of the oral group (9.4%) and 7 patients in the clonidine group (22.6%).

Following intubation, the heart rate increased from, 73.5±10.4 to76.4±9.2 in the oral group and 67.7±11.4 to 69.9±12.6 in the iv group. The rise in pulse rate, which showed the stress response to intubation was more in the oral group when compared with that of the iv group, the rise was statistically very highly significant (p=0.001). In a study done by Kulka et alit was shown that clonidine premedication can provide excellent hemodynamic stability to intraoperative stressful events [6].

With the institution of pneumoperitoneum, the pulse rate increased in both groups and it shows a rising trend over time (15min and 30 min after creating pneumoperitoneum). However, over the entire period of pneumoperitoneum, pulse rate in the iv group was lower when compared to the oral group. In both groups the increase in pulse rate was less than 20% from the baseline.After the release of CO_2 pulse rate came down to baseline values, and there was a significant difference between oral and iv group (p=0.010).

Analysis of the MAP shows(Table 7), with the administration of clonidine in both groups, the MAP experience a significant fall, 93.7±6.4 to 83.5±11.0 in the oral group and 91.5±6.3 to 76.8±8.9 in the iv group and the difference is statistically highly significant (p=0.009). This may be due to the sympatholytic effects of clonidine, combined with the hypotensive effects of other premedication drugs. The period of intubation is stressful with tachycardia and hypertension, but with the addition of clonidine there is only an increase of 4 mm of Hg in the oral group and 1.5 mm of Hg in the iv group. Here the iv group exhibits a superiority over the oral group in reducing the stress response to intubation.

Laryngoscopy and tracheal intubation after induction of anaesthesia are frequently associated with transient hypertension, tachycardia and arrhythmias. This stress response produced is probably of no consequence in healthy individuals, but it is potentially hazardous in those with hypertension, coronary artery disease or cerebrovascular disease. From clinical observations in hypertensive patients, Dingle[7] (1966) has found a rise in systolic pressure of more than 100 mm of Hg following tracheal intubation. A rise in pressure of this order is potentially dangerous and maylead to left ventricular failure and cerebral haemorrhage. Shribman and colleagues[8](1987) have shown that laryngoscopy alone generates the same pressor response and sympathoadrenal response in terms of circulating catecholamine concentration. Several studies have been done in this field, comparing the efficacy of various drugs like verapamil, diltiazem, nifedipine, fentanyl, nitroglycerine, labetalol etc to prevent the stress response to laryngoscopy and intubation. The present study clearly shows that iv clonidine is a very good drug for preventing the hemodynamic response during laryngoscopy and intubation.

Creation of the pneumoperitoneum causes the MAP to rise, both in the oral group and the iv

group from the previous values (i.e. before pneumoperitoneum), but the rise is only 3.7 mm of Hg in the oral group and3.9 in the iv group and the difference is statistically not significant. It is to be noted that the MAP never crossed the baseline also.

The overall changes correlate with results obtained by various studies reported by Joris et al and Sung CS et al. By 10 min after exsufflation, the MAP appears to return to the baseline values.

Analysis of the MAP variations in the iv groups shows that it is an excellent route of administration of clonidine for reducing the stress response to intubation (p=0.000).

Analysis of the systolic and diastolic blood pressure (Table 5 and 6) also on the whole shows a similar result. Evaluating the systolic blood pressure, one can observe, that even with the administration of clonidine, a potent stress attenuator, the systolic blood pressure increases after intubation, but to a smaller extent. This is obviously due to the stress produced by laryngoscopy and intubation. With the institution of pneumoperitoneum, the systolic BP still rises, from 108.2±15.4 to 112±12.8 in the oral group and from 101.6±14 to 107±15.0 in the iv group, but here also, the values have not crossed the baseline levels, suggesting suppression of the stress response to pneumoperitoneum.

The incidence of postoperative complications was also compared. Sedation levels were monitored using a four-point sedation scale at each the patient was assessed postoperatively. At the end of 24 hours, the maximal sedation score noted for a patient at any time till then was given for that patient. Data shows that patients in both groups had significant sedation (13 patients in the oral group with score 3 and 13 patients in the iv group with score 3). Here the difference between the two groups was not statistically significant.

Shivering was present in 3 patients in the iv group (9.67%) and 3 patients in the oral group (9.375%). This finding was in contrary with the finding of Nicolaou et al[9], where they concluded that clonidine inhibits cold thermoregulatory response due to an effect on central integration control and output from the thermoregulatory centres.

Nausea and vomiting were present only in one patient (3.22%) in the iv group and 2 patients (6.25%) from the oral group.

Bradycardia as defined by a pulse rate of <60 or <20% from the baseline was seen in 7 patients (22 5%) of the iv group and 3 patients (9.37%) in the oral group and the difference is statistically significant also. Hypotension as defined by a systolic BP of <80mm of Hg was seen in 5 patients (15.62%) in the oral group and 7 patients in the iv group (22.58%), and the difference was statistically significant. Adequate preloading with iv fluids before administering clonidine as a premedicant needs to be considered.

Summary

This study was conducted to find out the efficacy of intravenous clonidine as compared to oral clonidine in reducing the hemodynamic responses to pneumoperitoneum. Various studies have proven the efficacy of oral clonidine in reducing the hemodynamic stress response to pneumoperitoneum during laparoscopy. But there is a paucity of studies using intravenous clonidine for preventing the hemodynamic stress response in the literature. This prospective randomized study was conducted on 70 patients posted for elective laparoscopic cholecystectomy. Except for the different routes of administration of clonidine, all other steps in providing anaesthesia to the two groups were kept identical.

Analysis of the monitored data shows that, the patients in both groups had a reduced stress response to the pneumoperitoneum, when compared with the results from various studies. On intubation, changes are observed to occur in both groups, with minimal changes in the iv group. But the incidence of bradycardia and hypotension is also more in the iv group.

Analysis of the various postop complications yield important information about the pharmacodynamics of clonidine. Sedation was the most common side effect, present in both groups

with equal frequency. Incidences of postoperative nausea and vomiting and shivering, are very low when compared with the results from various studies as controls and is also comparable in both groups. Postoperatively also, hypotension and bradycardia are more common in the iv group.

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 must be carefully tided over, especially in the high-risk patients. However, the stress response appears to be effectively controlled by clonidine whether given orally or intravenously, with no statistically significant difference in the values.

Conclusion

- Premedication with oral clonidine is equally efficacious as intravenous clonidine in reducing the hemodynamic stress response to pneumoperitoneum.
- Hypotension and bradycardia are seen as main side effects with clonidine premedication, with more frequency in the intravenous group.
- Intubation stress response is best prevented with intravenous clonidine.
- Premedication with oral clonidine can be considered as a useful and inexpensive method to ensure hemodynamic stability during pneumoperitoneum in patients undergoing laparoscopic cholecystectomy.

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