ORIGINAL ARTICLE

Comparison of Efficacy of Clonidine Vs Dexmedetomidine on Hemodynamic Changes in Laproscopic Cholecystectomy

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Abstract

The present study was undertaken to study the attenuation of hemodynamic responses to induction, intubation, creation of pneumoperitoneum, surgical stimulation and extubation under G.A. in patients undergoing laparoscopic cholecystectomy. Ninety patients of either sex, ranging in age from 18 to 60 years, belonging to ASA grade I and II, scheduled for elective laparoscopic cholecystectomy under general anesthesia with endotracheal intubation were taken for the study at GMC Jammu. Patients were randomly allocated to one of the three study groups as under: Group-1: Dexmedetomidine (D) group received dexmedetomidine 1microg/kg. Group-2: Clonidine (C) group received clonidine 1microg/kg. Group-3: Control (R) group received 0.9% normal saline as premedication. Patients received the study drug made in 15ml of Normal saline which was given over a period of 10 mts, 5 mts before induction. Haemodynamic parameters were noted in the three groups and results showed that Dexmeditomidine and clonidine in a dose of 1?g / kg intravenously cause significant attenuation of pressor response and provide significant postoperative sedation and analgesia than control. However, dexmeditomidine causes better attenuation of pressor response and provides better analgesia and sedation than clonidine.

Key Words

Dexmedetomidine, Clonidine, Laparoscopic Cholecystectomy

Introduction

Laparoscopy induces significant hemodynamic changes even in healthy patients and causes increase of systemic vascular resistance, increased pulmonary vascular resistance, an increase of mean arterial pressure and a reduction of cardiac output.(1,2,3). Humorally, mediators like catecholamines, prostaglandins, the enzymes of reninangiotensin system and vasopressin (4) cause an increase in systemic vascular resistance. Whereas these cardiovascular changes should not be hazardous in healthy patients, special care and monitoring are mandatory for patients with impaired cardiac function. In these patients postoperative benefits of laparoscopy should be balanced against intra-operative risks. Various measures have been used to attenuate these hemodynamic responses, both during premedication and induction (5.6), like: deepening level of anesthesia with higher concentration of inhalational and intravenous anesthetics agents,high dose of opioids, antihypertensives like beta-adrenergic blockers (7), Sodium nitroprusside, regional or local neural blockade with local anesthetics (8).In the present study, we have used clonidine and dexmeditomidine which are alpha-2 agonist drugs. These drugs are found to inhibit the release of catecholamines and vasopressin and thus modulate the hemodynamic changes induced by pneumoperitoneum in laparoscopic surgeries. These drugs are simple and easy to use and neither any expertise nor any patient preparation is needed. Moreover, their easy availability and cost-effectiveness have made these drugs one of the most commonly used for premedication in laparoscopic surgeries.(9, 10, 11) Thus, the current study was done to evaluate and compare the efficacy of clonidine and dexmedetomidine premedication in attenuating the hemodynamic changes associated with laparoscopic cholecystectomy.

Material and Methods

After obtaining approval from the hospital ethical committee, a blind prospective study was undertaken for a period of one year. Ninety patients of either sex, ranging in age from 18 to 60 years, belonging to ASA grade I and II, scheduled for elective laparoscopic cholecystectomy under general anesthesia with endotracheal intubation were taken for the study Patients with anticipated difficult intubation, ASA grade III or greater, uncontrolled hypertension, morbid obesity, history of alcohol / drug abuse, severe renal, hepatic, endocrine and cardiac

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dysfunction and pregnancy were excluded from the study: Each patient had detailed preanaesthetic checkup one day prior to surgery. Detailed history, thorough clinical investigation was done. All routine investigations were carried out and any specific investigation as deemed necessary, were also done. VAS analog scale was explained to the patients.

Patients received the study drug made in 15ml of Normal Saline which was given over a period of 10 mts, 5 mts before induction. Patients were randomly allocated to one of the three study groups as under:

*Group-1:*Dexmedetomidine (D) group received dexmedetomidine 1microg/kg.

*Group-2:*Clonidine (C) group received clonidine 1microg/kg.

*Group-3:*Control (R) group received 0.9% normal saline

Anesthetic Technique: All patients were prepared by overnight fasting. Patients received tablet alprazolam 0.25 mg orally at bed time Intravenous line with 20 gauge peripheral cannula was established in anaesthesia ante room. After receiving the patient in operation theatre, routine monitors like electrocardiograph (ECG), pulse oximetry (SPO2) and non-invasive blood pressure (NIBP) were attached and baseline vital parameters like heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and arterial oxygen saturation were recorded. Patients received injection ondansteron 4 mg and injection tramadol 1 mg/kg. After pre-oxygenation with 100 per cent oxygen for 3 minutes, patients were induced with injection propofol 2 mg/kg intravenously and endotracheal intubation was done after giving injection succinylcholine 1.5 mg/kg intravenously. Patients were then connected to the anaesthesia machine. Carbon dioxide was insufflated into the peritoneal cavity @ 2 liter/minute to create pneumoperitoneum. Intra-abdominal pressure was maintained at 12 mmHg throughout the laparoscopic procedure. Anesthesia was maintained with oxygen and nitrous oxide in ratio of 33:66% and halothane 0.5%. Muscle relaxation was achieved with a bolus dose

Table 1. Heart Rate (In Beats Per Minute)

	Group	Heart Rate	Standard Deviation	P Value
Before giving study drug	1	96.17	13.919	0.645
	2	94.03	13.571	
	3	92.70	15.696	
After giving study drug	1	67.53	9.391	≤ 0.0001
	2	75.83	13.298	
	3	88.67	9.785	
Before induction	1	71.37	7.757	≤ 0.0001
	2	83.73	15.835	
	3	86.77	11.473	
After intubation	1	86.87	10.467	≤ 0.0001
	2	100.93	17.485	
	3	106.50	13.159	
Before pneumoperitonium	1	76.70	11.689	≤ 0.0001
	2	95.40	17.348	
	3	96.07	10.339	
Immediately after pneumoperitonium	1	80.40	9.522	≤ 0.0001
	2	103.93	14.737	
	3	111.53	11.470	
5 minutes	1	77.80	6.014	≤ 0.0001
	2	88.70	11.332	
	3	91.10	9.166	
10 minutes	1	79.40	7.582	0.011
	2	82.37	10.896	
	3	87.53	12.085	
15 minutes	1	79.57	8.982	≤ 0.0001
	2	88.97	9.817	
	3	91.63	8.075	
30 minutes	1	84.41	10.074	≤ 0.0001
	2	87.86	6.878	
	3	96.50	8.513	
45 minutes	1	82.856410	13.2450047	0.001
	2	91.111111	6.5877684	
	3	99.000000	5.2644359	
60 minutes	1	77.00	10.924	0.038
	2	93.33	4.726	
	3	95.00	5.292	
At extubation	1	99.40	7.093	≤ 0.0001
	2	93.33	4.726	
	3	118.93	12.089	

Table 2. Systolic Blood Pressure (mm Hg)

	Group	SBP	Standard Deviation	P Value
Before giving study drug	1	130.00	19.387	0.924
	2	131.23	15.885	
	3	129.67	12.299	
After giving study drug	1	117.23	15.000	0.020
	2	116.17	18.086	
	3	126.23	10.881	
Before induction	1	124.13	17.236	0.203
	2	122.80	13.392	
	3	129.90	17.688	
After intubation	1	138.10	17.476	0.041
	2	140.13	17.386	
	3	146.83	12.512	
Before pneumoperitonium	1	122.33	15.323	≤ 0.0001
	2	122.63	13.182	
	3	135.97	15.014	
Immediately after pneumoperitonium	1	133.93	16.347	≤ 0.0001
	2	136.27	14.844	
	3	153.90	23.475	
5 minutes	1	133.30	15.004	≤ 0.0001
	2	127.47	15.133	
	3	148.87	25.797	
10 minutes	1	128.90	15.287	≤ 0.0001
	2	132.80	16.516	
	3	148.53	16.165	
15 minutes	1	126.40	17.164	0.001
	2	130.33	14.990	
	3	141.20	13.366	
30 minutes	1	126.15	18.841	0.002
	2	134.07	18.344	
	3	141.73	8.905	
45 minutes	1	128.64	22.030	0.241
	2	130.17	23.498	
	3	143.50	5.425	
60 minutes	1	122.25	19.259	0.037
	2	132.00	15.100	
	3	144.00	9.899	
At extubation	1	132.13	12.045	≤ 0.0001
	2	138.80	17.484	
	3	154.40	12.952	

of injection atracurium 0.5 mg/kg intravenously and muscle relaxation was maintained with intermittent top-up doses of injection atracurium 0.1 mg/kg intravenously. Intra-operative hypertension if any was managed by infusion of nitroglycerine 0.5 to 1microg/kg/minute. Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and SPO2 was measured before giving study drug (baseline); after giving study drug; before induction; after intubation; before pneumoperitoneum (P0); immediately after pneumoperitoneum; and thereafter at 5, 10, 15, 30 and 45 minutes and then after every 15 minutes till the end of the surgery and after extubation. At the end of operation, residual neuromuscular block was reversed by giving neostigmine (0.05 mg/kg) and glycopyrollate (0.01 mg/kg) and tracheal extubation was performed. Postoperative pain was evaluated using a Visual Analogue Scale (VAS) 0 to 10 cm 0 - no pain at all; 4 - moderate pain and 10 - worst pain imaginable. This was noted at emergence from anaesthesia and at 30 minutes, 1, 1.5, 2, 4, 6, 12 and 24 hours after surgery. VAS score of >3 was considered as inadequate analgesia and rescue analgesia was deemed necessary. Pain relief in the postoperative period was provided by injection tramadol in a dose of 1 mg/kg intravenously followed by doses of 0.5 mg/kg intravenously as and when needed to a maximum dose of 3 mg/kg in all the three groups of patients. Time to first dose of rescue analgesia and total tramadol required during first 24 hours postoperatively was recorded. Any adverse effect like sedation, hypotension, bradycardia, nausea, vomiting and dryness of mouth, if observed, were recorded. All the observations were recorded in the attached proforma for subsequent statistical analysis.

Results

Data was presented as *tables (1-4)*. Variables were reported as mean and standard deviation. Statistical significance of qualitative variables was assessed with the use of chi-square test. Intergroup comparisons were made post-hoc by Bonferroni's t-test. All analysis was done in accordance to intention to treatment principal. A

Table 3: Diastolic Blood Pressure (in mm Hg)

	Group	DBP	Standard deviation	P Value
Before giving study drug	1	76.37	9.845	
	2	76.33	8.483	0.230
	3	80.00	9.910	
After giving study drug	1	72.73	7.144	
	2	70.30	11.201	0.001
	3	79.03	6.820	
Before induction	1	71.23	9.619	
	2	72.07	9.187	0.001
	3	81.73	14.446	
After intubation	1	82.13	13.831	
	2	89.73	15.088	0.001
	3	95.23	11.596	
Before pneumoperitonium	1	73.77	9.298	
	2	79.33	12.877	0.0001
	3	86.33	11.171	
Immediately after pneumoperitonium	1	84.03	10.374	
	2	86.97	11.702	0.001
	3	95.03	11.260	
5 minutes	1	82.93	7.847	
	2	80.93	7.216	0.001
	3	89.17	10.626	
10 minutes	1	76.63	8.904	
	2	82.07	7.524	0.0001
	3	89.50	5.507	
15 minutes	1	76.20	8.782	
	2	81.83	4.942	0.0001
	3	87.83	5.100	
30 minutes	1	73.11	9.419	
	2	82.96	6.203	0.0001
	3	85.70	3.344	
45 minutes	1	77.07	13.992	
	2	79.67	9.929	0.055
	3	88.88	4.086	
60 minutes	1	73.75	9.674	
	2	79.00	4.000	0.246
	3	87.50	10.607	
At extubation	1	80.60	6.463	
	2	84.67	6.048	0.0001
	3	96.13	9.261	

p-value <0.05 was considered as statistically significant. VAS score and rescue analgesia was analyzed between 3 groups by statistical tests like chi square, ANOVA and p-value. The demographic parameters like age, sex, weight and height of all the three groups were statistically comparable (p-value >0.05). Mean number of Doses of Rescue Analgesia in Study Group 1, 2 and 3 are 1.33, 1.43 and 2.06 respectively in 24 hours.

Discussion

The demographic parameters & Duration of surgery was comparable. There was no statistically significant difference in heart rate (p value 0.6450), systolic blood pressure (p-value 0.924), diastolic blood (p-value 0.230) and mean arterial pressure (p-value 0.901) amongst the groups before the administration of study drug. On the intergroup comparison there was statistically significant difference in mean heart rate in between group 1, group 2 and group 3 after giving study drug (*Table 1*). After giving study drug the fall in heart rate was more in group 1 (from 97.17 ± 13.919 to 67.53 , p-valve ?0,05) as compared to group 2 (from 94. 03 ± 13.571 to 75.83 ±13.298) and there was mild fall in heart rate in group 3 (94.30 ± 14.334 to 88.67 ±9.785) as compared to group 1 and 2 which was statistically insignificant. The fall in heart rate after giving intravenously dexmedetomidine and clonidine in our study is supported by Bloor *et al*, (12), Petrozet *et al*, (13), Yuen *et al*, (14), Nayek *et al*, (15), Kumar S *et al*, (11). Similarly, on the intergroup comparison there was statistically significant difference in the fall in blood pressure in between group 1, group 2 and group 3 after giving study drug. In Group I, mean SBP was 130±19 which drop to 117±15 after giving study drug. In Group II, the mean SBP was 131.23±15 which drop to 116±18 and in Group III, SBP was 129±12 drop to 126±0.08. Intra operatively the SBP remained stable in Group I and II, whereas in Group III there was greater fluctuation in SBP at the time of intubation 129.9±17.688 to 146±12.512 and at time of pneumoperitonium it rose

Table 4: Mean Arterial Pressure (in mm Hg)

	Group	MAP	Standard Deviation	P Value
Before giving study drug	1	98.63	10.591	0.901
	2	97.47	10.194	
	3	98.20	9.133	
After giving study drug	1	88.43	13.011	0.034
	2	87.57	14.088	
	3	95.00	7.348	
Before induction	1	93.10	10.924	0.067
	2	90.93	11.070	
	3	98.33	14.979	
After intubation	1	103.57	10.679	0.119
	2	108.90	15.626	
	3	110.17	12.186	
Before pneumoperitonium	1	87.07	22.950	0.001
	2	96.67	12.030	
	3	103.23	11.458	
Immediately after pneumoperitonium	1	99.77	20.041	0.001
	2	103.67	12.277	
	3	115.73	15.452	
5 minutes	1	102.10	8.248	0.004
	2	99.80	10.274	
	3	110.03	16.068	
10 minutes	1	96.43	9.085	0.021
	2	100.47	10.969	
	3	105.60	16.298	
15 minutes	1	95.87	9.992	0.002
	2	99.73	6.797	
	3	104.43	9.891	
30 minutes	1	92.00	10.206	0.0001
	2	101.07	9.502	
	3	106.27	4.941	
45 minutes	1	96.93	16.537	0.261
	2	98.06	12.651	
	3	106.71	3.039	
60 minutes	1	89.75	12.685	0.269
	2	97.33	7.095	
	3	106.50	10.607	
At extubation	1	98.90	6.920	0.0001
	2	104.30	9.237	
	3	115.37	9.974	

from 135.9±15.01 to 153±23.47. Again at the time of extubation mean SBP in Group III rose to 154.40±12. The The fluctuation in SBP was found to be lower with Group I and II, as compared to Group III peri-operatively. Our study is supported by Yazbek (16) who concluded that dexmedetomidine has many desirable clinical benefits that encourage its use perioperatively Kumar S *et al*, (11) also stated that fluctuation in SBP are attenuated in both clonidine and dexmedetomidine group during different phases of anaesthesia and laproscopy. Similarly, in diastolic blood pressure (SBP), the fluctuation was found to be statistically less in Group I and Group II, as compared to Group III (*Table 3*). Our results are supported by Malek *et al*, (17) who used clonidine and study drug and found a significant drop in incidence of hypertension for systolic and diastolic blood pressure intraoperatively. Gupta K *et al*, (10) also came to the same conclusion in his study. Mean arterial pressure also showed the same results (*Table 4*) with Group I and Group II where using the study drug as premedication significantly stabilized the mean blood pressure perioperatively. It is supported by Carabine (9) who

showed that clonidine remarkably decreased mean arterial pressure and gave better quality of haemodynamic stability. Our results are also supported by Dorsayetal, (18), Joris *et al*, (19), Nayek *et al*, (15), Das *et al*, (20), Sreeraghu GM *et al*, (21)

The reflex pressor response to intubation, pneumoperitonium and extubation was severe in group 3 compared to group 1 and 2. Comparing the heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure at time of extubation with base line shows statistically significant difference between group 1 and 3, between group 2 and 3 and between group 1and 2. The heart rate control was better in group 1 as compared to group 2. The mean VAS score of group 1 was 1.030± 0.368390, group 2 was 1.181a ± 0.228798 and group 3 was 1.394 ±0.324739. The difference was statistically significant between group 1 and group 3; and between group 2 and group 3 (p-value <0.0001). Although mean VAS score was lower in group 1 than group 2 but the results were not statistically significant (p-value <0.05).Kumar S *et al*, (11), Tripathi *et al*, (22) patients were more sedated in dexmedetomidine as compared to clonidine group. The mean number of intramuscular tramadol injections received during first 24 hours of post-operative period in group 1 was 1.33, in group 2 were 1.43 and in group 3 were 1.06.Our results are supported by Yu *et al*,(23), Sreeraghu GM *et al*, (21).The patients in clonidine group were less sedated, required less postoperative monitoring and were more cooperative. This reflects the more sedative property of dexmedetomidine than clonidine and it also shows that the sedative property of the alpha 2 agonists is proportional to their analgesic action as we can see here that dexmedetomidine is better analgesic but with more sedation. But none of the patient in our study had sedation score > 4, so none of the patient required any type of airway or ventilator support. We found a statistically significant decrease in the incidence of postoperative nausea and vomiting compared to the control group in our study. There was no complication noted in the study except bradycardia in 3 patients in clonidine which was not statistically significant and did not require any intervention. Thus, both the drugs were found to be safe.

Conclusion

Dexmeditomidine and clonidine in a dose of 1microg /kg intravenously, cause significant attenuation of presser response and provide significant postoperative sedation and analgesia than control. However, dexmedetomidine causes better attenuation of presser response and provides better analgesia and sedation than clonidine.

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