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Comparison of Clonidine and Dexmedetomidine for Attenuation of Hemodynamic Responses of Intubation and Pneumoperitoneum During Laparoscopic Cholecystectomy: A Randomized Double Blind Placebo Controlled Trial

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Abstract: Hemodynamic derangements, associated with intubation and pneumoperitoneum during laparoscopic surgery can be attenuated by use of α2 agonist drugs like clonidine and dexmedetomidine. To compare the attenuating effects of clonidine and dexemedetomidine on hemodynamic responses during intubation and pneumoperitoneum. It was a placebo control double blind randomized trial, conducted in Department of Anesthesia of a teaching hospital. Seventy five patients who were scheduled for laparoscopic cholecystectomy were equally divided in to three groups; placebo group (group P) received intravenous normal saline; Clonidine group (group C) received injection clonidine 2µg/kg bolus; and dexmedetomidine group (group D) received injection dexmedetomidine 1µg/kg bolus followed by continuous infusion @ 0.5µg/kg/ hour). Changes in mean blood pressure and heart rate were primarily compared. To compare quantitative variables between these groups, ANOVA test was employed, followed by Tukey's HSD. Qualitative parameters were analyzed by chi square test. Mean arterial pressure during intubation, creation of pneumoperitoneum, desufflation and extubation was lower in group D in comparison to group C. Similarly heart rate was also lower in group D in comparison to group C during these events except during pneumoperitoneum at 45 minutes and desufflation when it was comparable in both the groups. Incidence of bradycardia and hypotension was also comparable in both the groups. Dexmedetomidine is more effective than clonidine in attenuating hemodynamic responses of intubation and pneumoperitoneum, without increasing the side effects.
Keywords: α2 agonists, tachycardia, hypertension, intraoperative period.

INTRODUCTION

Introduction of laparoscopy has revolutionized the abdominal surgeries. In comparison to conventional surgery, laparoscopic procedures offer many benefits like early ambulation, small scar, short hospital stay and less postoperative respiratory and gastrointestinal disturbances [1]. But CO_2 insufflation for creation of pneumoperitoneum affects the hemodynamic stability in these patients. Pneumoperitoneum promotes release of catecholamine and vasopressin, and activates rennin angiotensin system leading to increase in heart rate and blood pressure [2]. The same changes are observed during anesthetic maneuvers like laryngoscopy, intubation and extubation also. Reverse trendelenburg position required for cholecystectomy further exacerbates these parameters by decreasing the venous return [3]. All these effects ultimately decrease the cardiac output, and increase the risk of cerebrovascular stroke and cardiac ischemia particularly in elderly and haemodynamically unstable patients [4].

Various pharmacological agents like nitroglycerine, beta- blockers and opioids have been used to attenuate the hemodynamic disturbances, but these drugs have their own side effects [5]. Now newer agents like α_2 receptor agonists - clonidine and dexmedetomidine are increasingly being (or are preferred) used in clinical practice, as these drugs not only provide hemodynamic stability through their sympatholytic effects but have sedative, analgesic and opioid sparing properties also [6]. Dexmedetomidine may be considered better than clonidine due to its 8 times more specific α_2 agonist property and minimal respiratory depression [7, 8]. Results of previous studies

comparing hemodyanamic effects of clonidine and dexmedetomidine are variable.

The present study was designed to compare the hemodynamic effects of clonidine and dexmetedomidine against each other and against placebo, during premedication, intubation, induction, insufflations, desufflation and extubation in patients undergoing laparoscopic cholecystectomy. Amongst the hemodynamic parameters compared, changes in mean arterial blood pressure and heart rate were between clonidine and dexmedetomidine groups were our primary outcome measures. Secondary outcome measures included effect on recovery time.

MATERIALS AND METHODS

After approval of the institutional ethics committee and written informed consent of patients, present randomized placebo controlled double blind trial was carried out over a period of one year extending from February 2012 to January 2013 to in Department of Anesthesia of a tertiary care teaching hospital of. It included 75 cases of either sex, between 30-60years age group, belonging to ASA physical status I and II who were scheduled for laparoscopic cholecystectomy. Patients with co-morbid conditions such as diabetes mellitus, cardiovascular or respiratory problems, or those receiving drugs like methyldopa, beta-blockers, benzodiazepines, psychotropic agents or MAO inhibiters were excluded from the study. Pregnancy and allergy to study drugs were also the exclusion criteria.

Clinical and demographic details including age, sex, weight, ASA physical status and Mallampati grade of all patients satisfying above criteria were recorded during pre-anesthetic check up. At arrival in operation theatre mulitpara monitor was attached and baseline vital parameters like heart rate and mean arterial blood pressure (MAP) were noted. An IV canula of 20 G was secured with all aseptic precautions and an infusion of ringer lactate was started. All the patients were premedicated with injection glycopyrrolate (0.004mg/kg), injection midazolam (0.01mg/kg) and injection fentanyl (2µg/kg).

Using pre-sealed opaque envelopes, all the patients were randomized in to three groups: placebo group (group P) received intravenous normal saline 10 ml, over 10 minutes followed by infusion of normal saline @ 0.25ml/kg/hour; Clonidine group (group C) received injection clonidine 2µg/kg in 10 ml normal saline over 10 minutes, followed by infusion of normal saline @ 0.25ml/kg/hr; and dexmedetomidine group (group D) received injection dexmedetomidine 1µg/kg in 10 ml normal saline over 10 minutes followed by infusion of dexmedetomidine @ 0.25ml/kg/hour (100µg of dexmedetomidine in 50 ml normal saline) (infusing dexmedetomidine @ 0.5µg/kg/ hour). Drugs were prepared by a separate nursing staff that had opened the envelopes. Both the patients and observers (anesthetists and all those who had recorded the parameters) were blinded to the group assignment. Code was broken during analysis of data only.

During drug infusion patients were pre-oxygenated via ventimask. Anesthesia was induced with 2.5% injection thiopentone sodium (5mg/kg) followed by succinyl choline (2mg/kg) to facilitate tracheal intubation choosing cuffed, disposable endotracheal tube of appropriate size. Anaesthesia was maintained with inhalational isoflurane (0.8-1.2%) in blended oxygen (air oxygen mixture 50:50) and injection atracurium (0.3mg/kg) bolus followed by 0.1 mg/kg intermittently for maintenance of neuromuscular blockade. Pneumoperitonium was created by insufflations of carbon dioxide at the rate of 2 liter per min and operation table was tilted to about 15º reverse Trendelenburg position. Intra abdominal pressure (IAP) was not allowed to exceed 15 mm Hg throughout the surgical procedure. After pneumoperitonium, ventilator settings (tidal volume, respiratory rate) were adjusted to maintain normocarbia. At the end of surgery (surgical closure), the infusion of study drug was stopped, and neuromuscular blockade was reversed with injection neostigmine 50µg/kg plus injection glycopyrrolate 10µg/kg intravenously. Sustained head lift for five seconds was used as extubation criteria. Following extubation patients were transferred to post-anesthesia care unit.

Vital parameters including MAP and heart rate were recorded during drug infusion (at 5 and 10 minutes), induction, intubation, pneumoperitonium (at 5,15, 30 and 45 minutes), desufflation(at 5 min)and at extubation. Episodes of bradycardia (heart rate less than 50 beats per min or a 20% decrease from the baseline) were treated with injection atropine, and tachycardia (heart rate more than110 per minute or a 20% increase from the baseline) were treated with injection esmolol. Episodes of hypotensi (MAP lower than 60 mmHg or 20% less than the baseline) were treated with 200ml fluid challenge (lactated ringer), if not improved then with injection mephentermine. Hypertensive episodes (MAP over 150 mmHg or a 20% increase from the baseline) were treated with injection nitroglycerine drip.

In recovery room, modified Aldrete score was recorded at every one minute till a score of ≥9. At this score, patients were shifted to post operative ward and duration of stay in recovery was noted.

After transferring all the collected data in to microsoft excel sheet, they were analyzed by Graph Pad software. Qualitative data were presented as proportion (or percentage) and were analyzed using Fisher's exact test. Quantitative data were expressed as mean±SD and to find out the significant difference among three groups ANOVA test followed by Tukey HSD (honestly significant difference) was applied. For statistical

purposes both sides p value <0.05 was considered significant.

Sample size –For sample size calculation MAP stability during insufflations was considered as primary outcome. Based on previous study results; MAP at 30 minutes of insufflations in clonidine group 92.10 rounded off to 92 mmHg, in dexmedetomedine group 84.50 rounded off to 84 mmHg and pooled SD 7.07 rounded off to 7, and keeping α error 5% and power 99%, sample size was calculated to be 20 in each group [9].

RESULTS

Total 75 consecutively admitted patients fulfilling our criteria were enrolled in to the study and were randomized in to three groups. Each group P, C and D had equal 25 participants, and received intended treatment. Clinical and demographic characteristics including age, sex, weight, ASA physical status, Mallampatti grading, duration of surgery and laryngoscopy, and baseline haemodynamic parameters (heart rate, and MAP) were comparable in all the three groups (Table-1).

During first 5min of bolus drug infusion MAP was comparable in all the three groups (ANOVA test, p>0.171). But at 10min of drug infusion, induction, intubation, pneumoperitoneum (5, 15, 30, 45min), desufflation (5min) and at extubation MAP was lower in both the group D and C in comparison to group P (Tukey's HSD, p<0.01 for both) and it was lower in group D in comparison to group C (Tukey's HSD, p<0.05) (Table-2).

During bolus infusion of drugs (at 5 min and 10min) heart rate was more stable in group C and D in comparison to group P (Tukey's HSD, p<0.05), with no difference in mean heart rate between group C and D (Tukey's HSD, p>0.05). At induction, intubation, pneumoperitonium (at 5, 15, and 30minutes), and at extubation heart rate was more stable in group D in comparison both group P and C (Tukey's HSD, p<0.01 for both) except at pneumoperitonium (at 45min)and at desufflation(at 5min) where group C and D were comparable(Tukey's HSD, p>0.05) (Table-3).

In group P 17/25 (68%) patients had tachycardia in comparison to none in both group C and D. Incidence of bradycardia was comparable in both group D 7/25(28%) and group C 3/25(12%) (Fisher's exact test, p-0.289). Similarly incidence of hypotension in both group C (1/25, 4%) and D (2/25, 8%) was again comparable (Fisher's exact test, p-1). No patient in group P had either bradycardia or hypotension, but 1/25(4%) patients had hypertension which was present only in this group. Time to attain full recovery was comparable in all the three groups P, C and D (12.04±1.645, 12.72±1.838, 12.16±1.519 minutes respectively; ANOVA test, p-0.313).

Table-1: Comparison of baseline characteristics

Characteristics	Group P	Group C	Group D	ANOVA/Fisher's exact test
Age(years)	44.28±9.163	45.84±6.811	46.6±8.246	P-0.591
Weight(kg)	53±5.107	51.96±4.800	51.44±5.276	P-0.543
Duration of laryngoscopy(seconds)	8.92±1.956	8.88±1.424	9.36±1.912	P-0.574
Duration of surgery(minutes)	52.28±4.844	53.48±5.394	52.84±5.047	P-0.708
Sex(M/F)	7/18	6/19	5/20	P_A -0.752 P_B -0.705
ASA class(I/II)	13/12	11/14	12/13	P_A-0.883 P_B-0.772
Mallampatti class(I/II)	19/6	19/6	21/4	P_A 0.731 P_B 0.731

Table-2: Comparison of changes in mean arterial blood pressure (MAP)

Time	Group P	Group C	Group D	ANOVA test,P value	Tukey's HSD
Baseline	92.48±6.51	94.52± 5.75	93.76± 5.58	0.540	NA
At 5minutes	93.04±6.31	95.44± 5.57	95.96± 5.45	0.171	NA
At 10minutes	94.32±6.12	89.28± 5.72	84.72± 5. 40	<0.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.05
At induction	92.6±6.150	87.48± 5.68	83.24± 5.29	<0.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.05
At intubation	99.16±6.60	91.84± 5.32	87.04± 4.970	<0.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.05
At 5minutes of pneumoperitoneum	102.08±6.46	90.36± 5.18	86.44± 5.14	<0.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.05
At 15minutes of pneumoperitoneum	104± 6.48	89± 5.07	85.08± 5.32	<0.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.05
At 30minutes of pneumoperitoneum	100.64±6.44	88.44± 4.92	84.6± 5.26	<0.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.05
At 45minutes of pneumoperitoneum	101.92±6.55	88.96± 5.00	85.08± 5.12	<0.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.05
At desufflation	94.68±5.99	85.08± 5.50	81.16± 5.28	<0.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.05
At extubation	102.08±6.44	90.2± 5.00	85.84± 5.19	<0.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.05

Table-3: Comparison of changes in heart rate

Time	Group P	Group C	Group D	ANOVA test, P value	Tukey HSD
Baseline	82.88± 9.57	82.08±8.80	84.64±9.87	0.619	NA
At 5minutes	85.36± 9.95	79.04±7.72	78.24±8.78	0.0107	M1 vs M2 P<.05 M1 vs M3 P<.05 M2 vs M3 NS
At 10minutes	90.32±10.07	72.96±7.50	71.92±7.62	0.0000	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 NS
At induction	86.12±10.07	70.08±6.81	63.92±6.89	0.0000	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.05
At intubation	100.04±10.40	80.8± 8.29	67.68±6.62	0.000	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.01
At 5 minutes of pneumo-peritoneum	94.36±8.92	80.56±5.95	65.96±6.46	0.000	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.01
At 15 minutes of pneumo-peritoneum	98.76±9.10	75± 5.84	66.92±6.63	<.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.01
At 30 minutes of pneumo-peritoneum	101.52±9.22	71.8±5.65	66.92±6.63	<0.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 NS
At 45minutes of pneumo-peritoneum	100.48±8.62	67.92±5.60	65.8± 6.61	<0.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 NS
At desufflation	89.04±8.34	67.4±4.54	63.48±6.42	<.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 NS
At extubation	100.8 ±9.05	78.16±7.87	67.08±6.30	<.0001	M1 vs M2 P<.01 M1 vs M3 P<.01 M2 vs M3 P<.01

NS-non significant

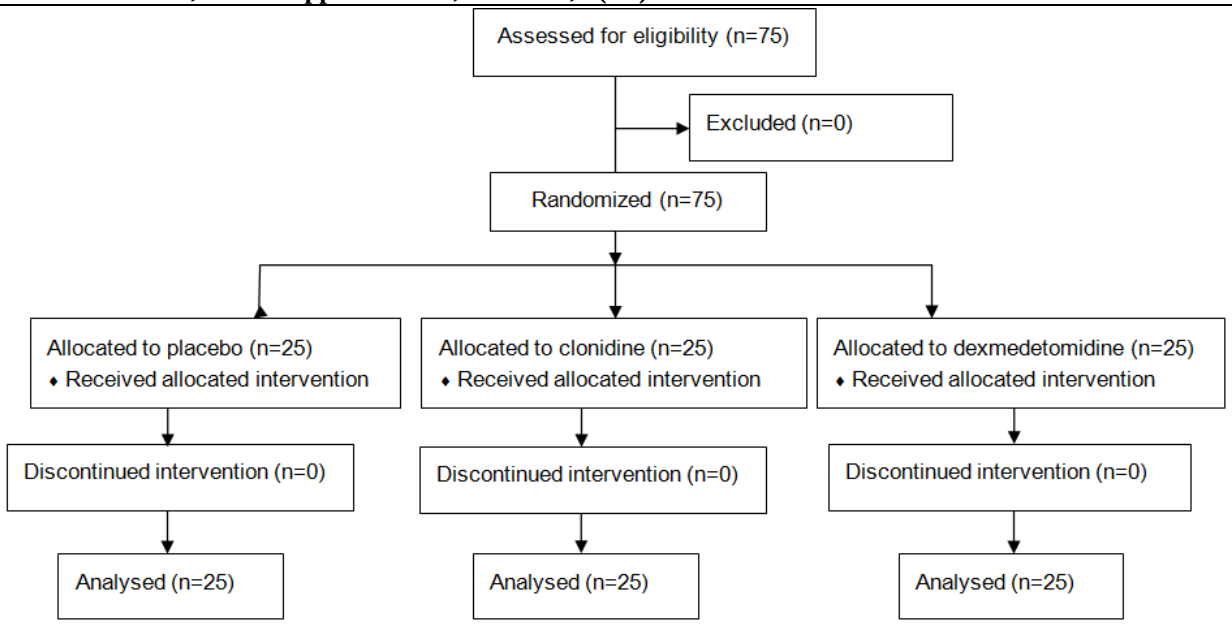

Fig-1: Flow of study

DISCUSSION

Hemodynamic changes produced by creation of pneumoperitonium during laparoscopic surgery, such as decrease in venous return can be partially attenuated by prior volume infusion but an increase in MAP and systemic vascular resistance require therapeutic interventions. To counteract these hemodynamic changes, various techniques like keeping a low intra-abdominal pressure during pneumoperitonium, gasless laparoscopy using abdominal elevators and various phramcological agents have been tried [10].

Amongst pharmacological agents, α2 agonists are the most preferred drugs. These drugs produce sedation, sympatholysis and analgesia through their actions on locus ceruleus, vasomotor centre and spinal cord respectively, and thereby maintain hemodynamic stability during surgical interventions. Sedation provided by these drugs is particularly advantageous in terms of easy and quick arousal, resembling a natural sleep.[11] Here we compared the hemodynamic stability (MAP and heart rate) provided by injection clonidine, injection dexmedetomidine and placebo in 75 adult patients (25 in each group) undergoing laparoscopic cholecystectomy, and found dexmedetomidine to be superior than clonidine. Placebo controlled randomized trial and adequate sample size were the major strengths of our study. For wider application, limitations included highly selected population (only cholecystectomy patients) and single centre trial.

In our study MAP and heart rate remained more stable in both clonidine and dexmedetomidine group in comparison to placebo. Hemodynamic stability provided by both clonidine and dexmedetomidine has been proved in previous studies also [1, 4, 9, 11-16]. Tripathi *et al*., demonstrated 2 µg/kg dose of clonidine to better than 1µg/kg for this purpose [17].

On comparing clonidine and dexmedetomidine the later provided better hemodynamic stability in the present study. The same findings have been observed previously also by Hazra et al and Kumar VA *et al*., [9, 12] But in contrast to our results adverse events like hypotension and bradycardia in dexmedetomidine were higher in the study of Hazra *et al*., This difference may be due to use of low dose of clonidine (1µgm/kg) in their study in comparison to our study (2µgm/kg).

On the contrary, Kumar S [10] and Anjum [13] found both dexmedetomidine and clonidine to be equally effective, whereas Bhanderi [18] found later to be more effective than former in reducing heart rate at the end of pneumoperitoneum and after reversal. These differences in findings can be explained by different regimens used by all the authors. Kumar S and Bhanderi used both the drugs only before induction while Anjum used both the drugs not only before induction but throughout operation as well. Dexmedetomidine being a short acting drug (elimination half time is 4 times less and distribution half time 2 times less) in comparison to clonidine, requires a continuous infusion to demonstrate sustainable effects [19].

In our study neither clonidine nor dexmedetomidine delayed the recovery. Similar to our results LiBY [20], and So-Young Kwon [21] also noted that dexmedetomidine does not prolong the recovery time. On the contrary Patel [22] concluded that dexmedetomidine delays recovery for first few hours after extubation. In their study at 10 minutes post extubation proportion of patients with modified Aldrete recovery score more than 8 was lower in dexmedetomidine group than placebo (4/30 vs 30/30, p-0.00), which equalized at 2 hours. But in comparison to

us and other previous studies, they didn't compare mean time of recovery. Our findings are also in concordance with the results of Vanderstappen [23] and Ray [24]; no delay in recovery time with clonidine. In contrast Mohammadi [25] noted delayed emergence time and Heinmiller [26] found prolonged stay time in PACU with clonidine. These contrasting results may be because of use of different recovery scales by different authors.

CONCLUSIONS

Both alpha-2 agonists; clonidine and dexmedetomidine are effective in attenuating hemodynamic responses of intubation and pneumoperitoneum, later being more effective. Side effects profile of clonidine and dexemedtomidine is comparable, and both the drugs do not delay recovery. Dexmedetomidine should be preferred over clonidine to maintain hemodynamic stability during intubation and pneumoperitoneum. For wider application, multi centre trials involving wide variety of patients are required.

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