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Research Article

Oral clonidine: a simple yet effective and safe premedicant for hemodynamic stability during laparoscopic surgery and a calm post-operative period

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ABSTRACT

Background: Laparoscopy is the essence of modern surgery but the carbon dioxide pneumoperitoneum used therein significantly impairs patient's cardiopulmonary function. Clonidine, by its central sympatholysis, reduces perioperative hemodynamic instability and also has multiple added advantages in post-operative period.

Methods: In this prospective, randomized, double-blind, placebo-controlled study on 60 ASA I/II patients, clonidine 150 μg for weight <55 kg and 200 μg for weight >55 kg was administered per oral to 30 patients (clonidine group) 90 minutes before induction of general anaesthesia and intra-operative haemodynamics were monitored at specific time periods and compared with the placebo group patients (n=30) who received oral vitamin C. We also noted pre-operative anxiety score, post-operative sedation and pain scores and the presence of nausea-vomiting, shivering and dry mouth at the end of first and sixth postoperative hours.

Results: Clonidine group patients remained haemodynamically stable throughout the intra-operative period. In clonidine group, less number of patients required fentanyl for tachycardia (1 vs 11) and NTG for hypertension (none vs 7). Similarly the pain and anxiety scores were significantly less in clonidine group patients. At the end of first postoperative hour incidence of pain, shivering and vomiting in placebo group was 33%, 36% and 20% respectively whereas in clonidine group incidence was 6%, 0 and 0. At the end of 6 post-operative hours, incidence of pain and vomiting was 73% and 36% in placebo group whereas it was 10% and 0 in clonidine group.

Conclusions: Oral clonidine in the present dose is able to maintain stable intra-operative haemodynamics and achieve a calm post-operative period during laparoscopic surgeries in ASA I/II patients.

Keywords: Oral clonidine, Premedication, Laparoscopy, Pneumoperitoneum, Haemodynamics

INTRODUCTION

Laparoscopic surgery is the quintessence of modern surgical practice due to its cosmetic scar, early ambulation, less mortality (less than 0.1%) and less compromised postoperative respiratory and gastro-intestinal functions.[1]

Carbon dioxide pneumoperitoneum (PNP), the hallmark of laparoscopic surgery and patient positioning lead to significant haemodynamic changes in laparoscopic surgeries. Postoperative nausea and vomiting is also a major drawback of laparoscopic surgery.[2]

Various drugs like opioids, ß blockers, nitroglycerine, magnesium sulphate etc.[3-5] have been tried to attenuate the PNP-associated haemodynamic instability but with limited success.

So we decided to study clonidine, a α_2 adrenoceptor agonist agent, which brings about a reduction in central sympathetic outflow and additionally also has anxiolytic, sedative, antisialogogue, analgesic and anti-emetic effects as a premedicant.[6,7]

Thus this prospective, randomized, double-blind, placebo-controlled study was conducted on 60 ASA I-II

patients posted for elective laparoscopic surgical procedures with the following aims:

- To investigate the effect of oral clonidine premedication on intra-operative haemodynamics.
- To note the other desirable effects of clonidine premedication in the pre-operative period including effect on pre-operative anxiety and post-operative sedation, nausea-vomiting (PONV), shivering and pain.

METHODS

After getting approval from the institutional ethical committee and written informed consent from patients, this study was conducted in a tertiary care medical college hospital.

60 ASA I/II patients of either sex, in age group 18-60 years, scheduled for elective laparoscopic surgeries were included in the study. A written informed consent was obtained from each patient. Patients were excluded from the study if they had ischaemic heart disease, valvular heart disease, atrioventricular block, hypertension, diabetes mellitus, chronic obstructive airway disorder, obesity, anticipated difficult airway or allergy to any of the drugs in the study or if they were on any antihypertensive treatment

Sample size of 30 patients per group was derived using Cohen's formula. We assumed an α error of 0.05 and power of study 80% after permitting β error of 0.2. Mean and standard deviation were calculated for all the quantitative variables using graph-pad prism statistical software. These 60 patients were randomly allocated using a computer generated randomization table into one of the following two groups:-

Group P (n=30) - These patients received oral vitamin C tablet as placebo premedication.

Group C (n=30) - These patients received oral clonidine premedication according to body weight [weight <55 kg-150 µg; weight >55 kg-200 µg].

We used tablet Arkamin (100 µg/ tablet), manufactured by Unichem laboratories, India for pre-medicating all the patients in clonidine group. Appropriate investigations were done in all the 60 patients. All the patients in both the groups received tablet diazepam 5mg and tablet ranitidine 150 mg on the night prior to surgery and were kept nil-by-month overnight. On the day of surgery, after noting "baseline vitals", depending upon the group, either tablet clonidine (150/200 µg) or tablet vitamin C was administered per orally to the patients, 90 minutes before surgery by a non-participating anaesthesiologist. Anxiety scores[8] of the patients were noted at 90 minutes after administration of oral premedication. The degree of anxiety was graded as follows:

Anxiety score:

 0. Patient quiet and comfortable.
 1. Patient uneasy.
 2. Patient worried or anxious.
 3. Patient very worried or very upset.
 4. Patient frightened or terrified.

After taking patients inside the O.T., monitors were attached including 5-lead ECG, NIBP and SpO_2 monitors and vitals were noted and labeled as 'pre-induction vitals'. Intravenous (IV) access was established using a wide bore IV cannula and preloading was done with 5 ml.kg^{-1} of Ringer lactate. Patients were premeditated with IV ranitidine hydrochloride 50 mg and IV glycopyrrolate 0.2 mg and sedation was achieved with IV midazolam 0.02 mg.kg^{-1} and IV fentanyl citrate 2 µg.kg^{-1}. After preoxygenation with 100% oxygen on mask for three minutes, patients were induced with IV propofol 2 mg.kg^{1} and endotracheal intubation by appropriate sized cuffed polyvinylchloride endotrachaeal tube was facilitated using IV vecuronium bromide 0.15 mg.kg^{-1}. Patients were ventilated for 3 minutes on mask with oxygen and nitrous oxide in ratio of 40:60 along with 1.2% isoflurane and then trachea was intubated. After securing the tube, anaesthesia was maintained with oxygen and nitrous oxide in ratio of 40:60 along with 1.2% isoflurane using circle absorber. Intra-operatively, intermittent doses of IV vecuronium bromide 0.02 mg.kg^{-1} were used for muscle relaxation. All patients received intramuscular diclofenac sodium 75 mg immediately after endotracheal intubation. Carbon dioxide was used for creation of pneumoperitoneum and intra-abdominal pressure (IAP) was not allowed to exceed 14 mm Hg throughout the surgery. The tidal volume and respiratory rate were altered so as to keep the end tidal carbon dioxide (etCO$_2$) concentrations between 35-45 mmHg throughout the procedure. Intra-operative monitoring of haemodynamic parameters was done using Phillips multipara monitor and vitals were noted at particular time intervals as given below:-

Heart rate, blood pressure (systolic, diastolic and mean) and SpO_2 were noted at:

- Pre-induction
- 2 minutes after induction of anaesthesia
- 2 minutes after endotracheal intubation
- After peritoneal insufflations at 1, 2, 3, 15, 30, 60 minutes
- After exsufflation and
- At extubation

Approximately 15-20 minutes prior to reversal, IV ondansetron 0.1 mg.kg^{-1} was given to all patients & local infiltration of surgical site was done with 10 ml of 0.25% bupivacaine. At the end of surgery, residual neuromuscular blockade was reversed with IV neostigmine 0.05 mg.kg^{-1} and IV glycopyrrolate 0.01

mg.kg^{-1}and trachea was extubated after achieving satisfactory extubation criteria.

Intra-operative complications and their treatments were defined as follows:

1. Bradycardia- Heat rate <50/min-IV Atropine 0.6 mg,
2. Tachycardia- Heat rate >100 min-IV Fentanyl 1 µg.kg^{-1}
3. Hypotension- systolic BP <30% of baseline value- if persistent after reduction in inhalational anesthetic concentration-IV, mephentermine 6 mg (Repeated if required)-If hypotension was associated with heart rate <60/ min-IV, atropine 0.3 mg
4. Hypertension-systolic BP >160 mm Hg and/or diastolic BP >110 Hg-intravenous NTG infusion-0.5-1 µg.kg^{-1}min^{-1}, increased if needed.

Postoperatively, HR, SBP, DBP, MAP, SpO$_2$ and any occurrence of complications or adverse events were monitored for next one hour. At completion of first post-operative hour, we noted the presence or absence of nausea-vomiting, shivering, dry mouth or any other untoward effect. Degree of pain was graded as follows:

Pain score:

0- No pain
1- Mild pain
2- Moderate pain
3- Severe pain.

Sedation was graded as per Ramsay sedation scale[9] as follows:

Sedation score

1- Patient anxious, agitated, restless
2- Patient co-operative, tranquil
3- Patient responds to oral commands only
4- Patient asleep but easily arousable by tactile stimulus
5- Patient asleep and difficult to arouse by tactile stimulus
6- Patient deeply sedated, no response to stimulus

Rescue treatment was administered before shifting the patients to wards in form of IV metoclopramide 10 mg (if vomiting present) and IV pentazocine 0.5 mg.kg^{-1} (pain score $\geq$ 2). At the end of six post-operative hours, patients were visited in wards and vitals were noted along with pain and sedation scores, and presence or absence of nausea or vomiting.

An intra-group comparison was made using paired Student's t-test and comparison between two groups at a time (inter-group comparison) was done using the unpaired t-test. P<0.05 was considered statistically significant.

RESULTS

Demographic equi-distribution in both the groups can be ascertained by looking at Table 1.

Table 1: Comparison of demographic data between two groups.

Characteristic	Grp P (n=30)	Grp C (n=30)	'p'
Age (years)			
M±SD	31.13±10.70	31.8±11	0.43(NS)
Sex			
Male	15 (50%)	12 (40%)	0.87(NS)
Female	15 (50%)	18 (60%)	
Weight (kg)			
M±SD	46±6.15	45.9±6.1	0.11(NS)
Height (cm)			
M±SD	152.7±21.54	156.4± 5.21	0.35(NS)
ASA status			
I	30 (100%)	30 (100%)	1(NS)
Duration of pneumoperitonem (min)	51.03±26.71	65.96± 32.86	0.06(NS)
Duration of anaesthesia (min)	74.66±30.9	89.67± 34.69	0.08(NS)

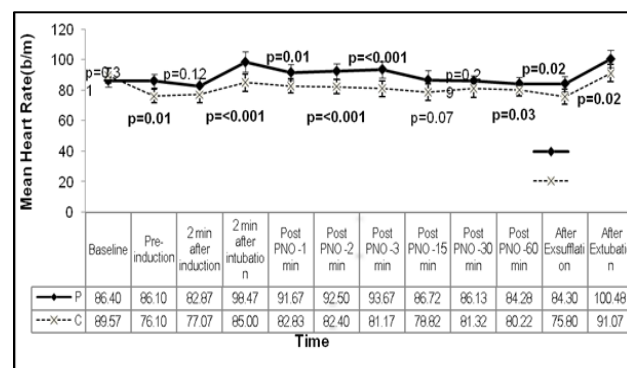M-mean, SD-standard deviation, NS-Not significant

Figure 1: Comparison of mean heart rate between groups P & C at various time intervals.

The mean heart rate in placebo group rose steadily from baseline and had a steep rise at 2 minutes after intubation (98.47), 3 minutes after insufflation (93.67) and at extubation (100.48). In clonidine group, heart rate never crossed the baseline value throughout intra-operative period (Figure 1). On intergroup comparison, difference in HR between the two groups was significant throughout intra-operative period (p<0.05) and highly significant (p<0.001) after intubation and insufflations.

The mean SBP in the placebo group rose steadily after insufflation to a peak at 3 minutes after insufflation (132.10) and again rose at extubation (137.14). The SBP

remained below the baseline value at all times throughout the surgery in clonidine group and difference between the two groups was highly significant (p<0.001) (Figure 2).
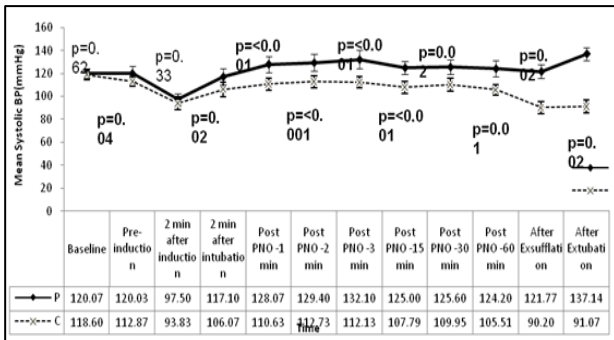

Figure 2: Comparison of systolic BP (SBP) between groups P & C at various time intervals.

The mean DBP in placebo group rose from baseline value of 77.93 to 93.87 at 2 minutes after PNP and to 94.86 at extubation. This rise in DBP did not occur in clonidine group and difference between the two groups was highly significant (p<0.001) throughout the surgery and at extubation (Figure 3).
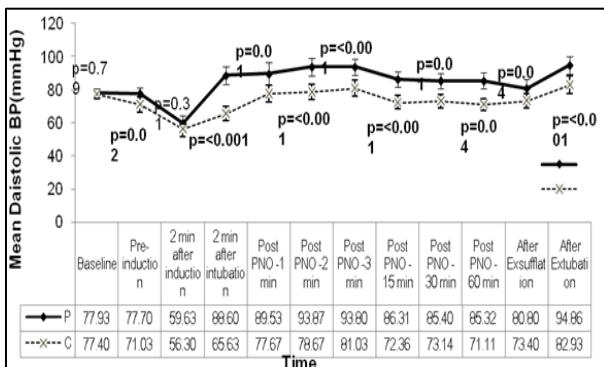

Figure 3: Comparison of mean diastolic BP between groups P & C at various time intervals.

Similarly, the mean MAP in placebo group ranged from 69.9 to 96.26 and that in clonidine group ranged from 67.79 to 86.63 (Figure 4). Difference in the mean MAP between the two groups was statistically highly significant except at baseline.

Clonidine significantly reduced the pre-operative anxiety score of the patients (0.22 vs. 1.62) and the difference in mean anxiety scores was highly significant (p<0.001).

Intra-operatively, 11 patients in the placebo group had tachycardia and were administered fentanyl whereas only 1 patient in the clonidine group had tachycardia. Only one patient in the clonidine group had intra-operative bradycardia which was easily corrected with atropine.
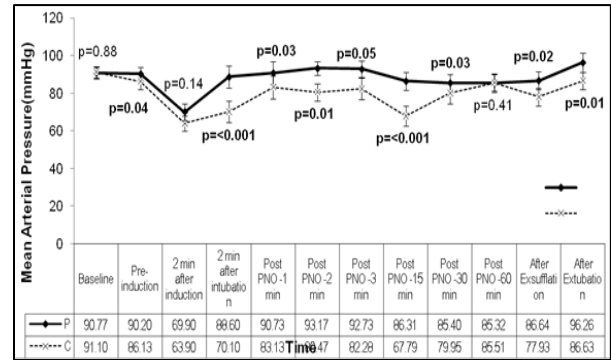

Figure 4: Comparison of mean MAP between groups P & C at various time intervals.

Similarly, 7 patients in the placebo group had intra-operative hypertension and were started on NTG infusion while none of the patients in clonidine group had hypertension (7 vs. 0). None of the 60 patients had hypotension or arrhythmia in the intra-operative period.

Post-operative pain score at the end of first hour was significantly high in the placebo group than clonidine group (1.48 vs. 0.07) and difference was highly significant (p<0.001). The patients of clonidine group were more sedated than those from placebo group as seen from the sedation scores 0.72 vs. 0.03 at the end of first postoperative hour.

At the end of first post-operative hour, patients in clonidine group were relatively free from complications with only 2 patients complaining of pain and none of the patients having vomiting. In contrast, 10 patients (33%) had pain and 6 (20%) had vomiting in the placebo group. These differences were significant statistically with p<0.05. Shivering was seen only in the placebo group patients and not seen at all in the clonidine group (11 vs. 0) (Table 2).

Table 2: Complications at the end of first postoperative hour.

Complication	Group P	Group C	P value
Pain	10 (33%)	2 (6%)	<0.05 (S)
Shivering	11 (36%)	0	-
Vomiting	6 (20%)	0	-
Total	27	2	

S: Significant

At the end of six post-operative hours, when patients were assessed in wards, 22 (73%) of patients in placebo group had pain whereas only 3 (10%) patients in clonidine group had pain. Similarly, 11 (36%) patients in placebo group had vomiting while none of the patients in clonidine group complained of vomiting. Dry mouth was seen in only 3 patients of clonidine group (vs. none in the placebo group), but this number was not statistically significant. No other complications were seen in patients of either group.

DISCUSSION

Pneumoperitoneum created during laparoscopic surgery induces certain drastic changes in the patients' haemodynamics. These include an increase in MAP, decrease in CO and increase in SVR which manifest as hypertension, tachycardia and may also compromise tissue perfusion and affect the acid-base homeostasis. This necessitates the use of anaesthetic interventions for maintaining haemodynamic parameters in acceptable range in order to maintain blood supply to vital organs. Techniques like use of low intra-abdominal pressure and gasless laparoscopies using abdominal elevators have been used with limited success.[10,11]

We chose clonidine, an alpha-2 adrenergic agonist, with an easy oral administration, excellent absorption, prolonged action and good safety profile as a premedicant for laparoscopy. The central sympatholysis induced by clonidine takes care of the tachycardia and hypertension seen after peritoneal insufflation. Additional properties like analgesia, sedation, anxiolysis, antiemesis and anti-shivering actions make it a near-ideal agent for laparoscopies where PONV is a problem. Thus it not only helps in the intra-operative period but also has effect on preoperative anxiety and postoperative pain, shivering and emesis.

Studies using clonidine in different doses (2-6 µg/kg) have been conducted but additional advantages like suppression of vasopressin release were not seen with higher doses.[12] With an average weight of 50 kg in the study population, we decided a dose of 150 micrograms for body weight less than 55 kg and 200 micrograms for body weight more than 55 kg respectively in our study so as to utilize a dose of approximately 3 micrograms per kg.

In our study, clonidine reduced the pre-operative anxiety scores of the patients and the difference between clonidine and placebo groups i.e. 0.22 vs. 1.62 was highly significant. Rawal et al also found highly significant difference in preoperative anxiety scores between clonidine group patients (4 µg/kg clonidine) and placebo group patients.[8]

A comparatively higher sedation score in clonidine group patients can be viewed as an advantage as all the patients were sleeping comfortably and none of them had any respiratory depression. Thus all the clonidine-premedicated patients remained calm and quiet in peri-operative period.

The first stimulus for sympathoadrenal response i.e. laryngoscopy and intubation was associated with a steep rise in HR, SBP, DBP and MAP in the placebo group. This rise in HR and BP did not occur in clonidine group patients. Our findings matched the findings of Rawal, et al who used a dose of 4 µg/kg clonidine for attenuation of haemodynamic response to laryngoscopy and intubation.[8]

Ishizaki, et al observed a significant fall in cardiac output at 16 mmHg intra-abdominal pressure (IAP), but hemodynamic alteration was not observed at 12 mmHg IAP.[13] In our study; the IAP was kept below 14 mm Hg in all cases. Following PNP, ventilation was adjusted to maintain normocapnia. In spite of maintaining normocapnia and the intra-abdominal pressure below 14 mmHg, a significant rise in HR, SBP, DBP, and MAP was observed in placebo group. The HR and BP in clonidine group patients remained below the baseline values even after PNP as indicated by the straighter lines in the Figure 1-4. Thus in this study, 3 µg/kg of oral clonidine could achieve hemodynamic stability during laryngoscopy and intubation as well as during pneumoperitoneum. Similar findings were reported by Yu et al, Joris et al, Bhandari et al, Malek et al, Das et al, Chandrashekaraiah, et al and Sung, et al.[12,14-19]

A decrease in sympathetic tone by central action and pre-synaptically mediated inhibition of norepinephrine and vagomimetic action at nucleus tractus solitarius by clonidine is responsible for bradycardia. Clonidine related bradycardia is more commonly associated with clonidine poisoning or overdose and rarely occurs after clonidine administration in prescribed doses.[12] In our study, only one patient in clonidine group developed bradycardia but she responded well to single dose of atropine of 0.6 mg. Singh, et al and Bhandari, et al also reported cases of bradycardia in clonidine group but the values were not significant and patients responded to single dose of iv atropine.[12,20]

Intraoperative tachycardia requiring treatment with IV fentanyl citrate was observed in 36% patients in placebo group whereas it was seen in only one patient in clonidine group. NTG infusion was employed for control of insufflation-induced hypertension in 23% patients in placebo group whereas none of the patients in clonidine group developed hypertension. Bhandari, et al also required NTG in 28% patients in control group.[12] None of our patients had intra-operative arrhythmia.

As seen during intubation, extubation was also associated with steep rise in HR and BP in the placebo group patients but this rise did not occur in any patient of clonidine group.

At the end of first postoperative hour, more number of patients in placebo group had pain (33% vs 6%). Vomiting (20% vs nil) was seen predominantly in placebo group patients as compared to clonidine group. Clonidine increases gastrointestinal motility by decreasing sympathetic and increasing parasympathetic outflow from the central nervous system, thus reduces incidence of post-operative nausea and vomiting.[21]

Shivering was seen in 36% patients of placebo group and none in clonidine group. This finding corroborates the finding of Nicolaou, et al who stated that clonidine could be used as an effective perioperative anti-shivering agent

as it inhibits the cold thermoregulatory response due to an effect on central integration control and output from the thermoregulatory center.[22]

Patients in the clonidine group were more sedated but they were arousable to oral commands. Das, et al reported the incidence of nausea-vomiting, hypertension, shivering and shoulder pain to be respectively 35.70%, 35.70%, 10.7% and 14.3% in the placebo group, while only 6.89% patients suffered from nausea vomiting in clonidine group.[17] The findings of Bhandari, et al were no different from those of our study.[12]

Studies with IV clonidine are being performed and drug has shown good results for maintenance of haemodynamic stability during laparoscopic surgery.[23] But in our study, oral clonidine was used because of ease of its administration.

Also, recently introduced clonidine congener with higher selectivity for α_2 adrenoceptors - 'dexmedetomidine' has also shown promising results for attenuation of the sympathetic response to laryngoscopy and intubation.[24] But we selected oral clonidine due to good bioavailability after oral administration, easy administration, excellent sympatholysis and multiple advantages in the peri-operative period, with prolonged effect (long $t_{1/2}$) lasting upto 6-8 hours post-operatively.

CONCLUSION

Thus carbon dioxide pneumoperitoneum created during laparoscopic surgery is associated with wide fluctuations in haemodynamics. To tackle these, an additional anaesthetic modality needs to be used. Excellent absorption, ease of administration, central sympatholysis with favourable effects on HR and BP and multiple favourable additional effects on PONV, pain, shivering etc. make oral clonidine a safe and effective premedicant for use in laparoscopy. Based on our study we conclude that 150-200 µg clonidine (3 µg/kg) orally can be safely used for premedication in ASA-I/II patients for laparoscopy as it has a good safety profile. But further studies are needed for confirming its safety in elderly patients and patients with compromised cardiovascular function.

Study strength

In this study, in addition to maintenance of stable haemodynamics, we have attempted to focus on the additional multiple desirable properties of clonidine which keep the patients comfortable in the first six hours after surgery which is the period of maximum vexation for the patients. Also the dose used (3 µg/kg) is optimum in the sense that it is able to attenuate the sympathetic response to PNP without side effects like bradycardia or hypotension in either the intra-operative or the post-operative periods.

Limitations

Invasive blood pressure monitoring was not done in our study due to unavailability of the required setup. Additionally, we did not record postoperative total analgesic requirement. Also our study was conducted on ASA-I and II class patients. So further studies on elderly and compromised cardiac function patients are required to recommend its use in such high risk patients.

REFERENCES

1. Osborne DA, Alexander G, Boe B, Zervos EE. Laparoscopic cholecystectomy: past, present and future. Surg Technol Int. 2006;15:81-5.
2. Thune A, Appalgren L, Haglind E. Prevention of post-operative nausea and vomiting after laparoscopic cholecystectomy. Eur J Surg. 1995;161:265-8.
3. Koivusalo AM, Scheinin M, Tikkanen I, Yli-Suomu T, Ristkari S, Laakso J et al. Effects of esmolol on hemodynamic responses to CO_2 pneumoperitoneum for laparoscopic surgery. Acta Anaesthesiol Scand. 2008:510-7.
4. Feig BW, Berger DH, Doughtery TB. Pharmacological interventions can reestablish baseline hemodynamic parameters during laparoscopy. Surgery. 1994;116:733-7.
5. Jee D, Lee D, Yun S, Lee C. Magnesium sulphate attenuates arterial pressure increases during laparoscopic cholecystectomy. Br J Anaesth. 2009;103(4):484-9.
6. Kamibayashi T, Maze M. Clinical uses of α-2 adrenergic agonist. Anaesthesiol. 2000;93:1345-9.
7. Hall JE, Uhrich TD, Ebert TJ. Sedative, analgesic and cognitive effects of clonidine infusions in humans. BJA. 2001;86:05-11.
8. Raval DL, Mehta MK. Oral clonidine pre medication for attenuation of haemodynamic response to laryngoscopy and intubation. IJA. 2002;46(2):124-9.
9. Schulte-Tamburen AM, Scheier J, Briegel J, Schwender D, Peter K. Comparison of five sedation scoring systems by means of auditory evoked potentials. Intensive Care Med. 1999;25(4):377-82.
10. Dexter SPL, Vucevic M, Gibson J, McMahon MJ. Hemodynamic consequences of high- and low-pressure capnoperitoneum during laparoscopic cholecystectomy Surg Endosc. 1999;13(4):376-81.

11. Gurusamy KS, Samraj K, Davidson BR. Abdominal lift for laparoscopic cholecystectomy. Cochrane database Syst Rev. 2008;16(2):CD006574.
12. Bhandari D, Tidke S, Sharma V, Dongre H, Garg D, Dhande P. Hemodynamic changes associated with laparoscopic cholecystectomy: Effect of oral clonidine premedication. IOSRPHR. 2012;2(4):72-7.
13. Ishizaki Y, Bandae Y, Shimomaura K, Abe H, Ohotoma Y, Idezuki Y. Safe intra-abdominal pressure of CO_2 pneumoperitoneum during laparoscopic surgery. Surgery. 1993;114:549-54.
14. Yu HP, Hseu SS, Yien HW, Teng YH, Chan KH. Oral clonidine premedication preserves heart rate variability for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 2003;47(2):185-90.
15. Joris J, Chiche JD, Lamy M. Clonidine reduced hemodynamic changes induced by pneumoperitoneum during laparoscopic cholecystectomy. BJA. 1995;74:A124.
16. Malek J, Knor J, Kurzova A, Lopourova M. Adverse hemodynamic changes during laparoscopic cholecystectomy and their possible suppression with clonidine premedication. Comparison with intravenous and intramuscular premedication. Rozhl Chir. 1999;78(6):286-91.
17. Das M, Ray M, Mukherjee G. Haemodynamic changes during laparoscopic cholecystectomy: effect of clonidine premedication. IJA. 2007;51(3):205-10.
18. Chandrashekaraiah MM, Upadya M, Jayachandran SP, Wali M. Effects of clonidine premedication on hemodynamic changes during laparoscopic cholecystectomy- a randomized control study. Applied Cardiopulm Pathophysiol. 2011;15:91-8.
19. Sung CS, Lin SH, Chan KH, Chang WK, Chow LH, Lee TY. Effect of oral clonidine premedication on perioperative haemodynamic response & postoperative analgesic requirement for patients undergoing laparoscopic Cholecystectomy. Acta. Anesthesiol Sin. 2000;38:23-9.
20. Singh S, Arora K. Effect of oral clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. IJA. 2011;55:26-30.
21. Javaherfroosh F, Pipelzadeh MR, Namazi M. Clonidine reduces post-operative nausea and vomiting in laparoscopic gynecological surgery. Pak J Med Sci. 2009;25:782-5.
22. Nicolaou G, Chen AA, Johnston CE, Kenny GP, Bristow GK, Giesdbrecht GG. Clonidine decreases vasoconstriction and shivering threshold without affecting the sweating threshold. Can J Anaesth. 1997;44:636-44.
23. Tripathi DC, Shah KS, Dubey SR, Doshi SM, Raval PV. Hemodynamic stress response during laparoscopic cholecystectomy: Effect of two different doses of intravenous clonidine premedication. J Anaesthesiol Clin Pharmacol. 2011;27(4):475-80.
24. Keniya VM, Ladi S, Naphade R. Dexmedetomidine attenuates sympathoadrenal response to tracheal intubation and reduces perioperative anaesthetic requirement. IJA. 2011;55(4):352-7.