

# Effect of intravenous clonidine as premedication on haemodynamic responses during laparoscopic cholecystectomy

## Abstract

The cervical epidural blockade is a procedure that little is done through fear, ignorance and lack of training in medical units residences. Anatomy is not very different from other neuraxial areas, which gives a similar especially lumbar approach. Complications are rare, knowing the changes in various systems; it is possible to perform in expert hands as surely a lumbar epidural block from the technical point of view. Convenient serious studies and compare different techniques of regional anesthesia to assess risk, comfort and cost.

**Keywords:** laparoscopy, pneumoperitoneum, clonidine, general anesthesia

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**Abbreviations:** PNP, pneumoperitoneum; SVR, systemic vascular resistances; PVR, pulmonary vascular resistances; HR, heart rate; PaO<sub>2</sub>, arterial saturation of oxygen; MBP, mean blood pressure; IV, intravenously; SpO<sub>2</sub>, peripheral oxygen saturation; VT, tidal volume; IPPV, intermittent positive pressure ventilation; EtCO<sub>2</sub>, end tidal carbon dioxide; ECG, electrocardiography; VAS, visual analogue score; OAS, observer assessment of alertness/sedation score; mean +/- SD, mean value +/- standard deviation; S, significant (P<0.05); NS, not significant (P>0.05)

## Introduction

Laparoscopy has made significant revolution in the field of surgery. The advantages of cosmetically superior scar, less post-operative pain, less morbidity and early discharge makes the laparoscopic cholecystectomy more acceptable and the procedure of choice for gall stone diseases. However, the pneumoperitoneum (PNP) affects several homeostatic systems leading to alteration in acid-base balance, cardiovascular, pulmonary physiology and stress responses. These are characterized by an increase in arterial pressure and systemic (SVR) and pulmonary vascular resistances (PVR) early after the beginning of intra-abdominal insufflation, with no significant changes in heart rate (HR). A 10% to 30% decrease in cardiac output has also been reported in most studies.<sup>1-3</sup> Pulmonary function changes are characterized by reduced compliance without large alterations in arterial saturation of oxygen (PaO<sub>2</sub>), but tissue oxygenation can be adversely affected due to reduced O<sub>2</sub> delivery.<sup>2</sup> A major difficulty is in maintaining normocarbia due to decreased pulmonary compliance secondary to upward movement of the diaphragm with PNP and the changes in CO<sub>2</sub> homeostasis following absorption of insufflated CO<sub>2</sub> that contribute to the hemodynamic changes.<sup>2-4</sup> To prevent them various modes of anaesthesia like epidural/spinal/combined epidural and general anesthesia techniques using drugs such as opioids, esmolol, Na. Nitroprusside, Nitroglycerin and  $\alpha$ 2-adrenergic agonists are reported. The  $\alpha$ 2-adrenoceptor agonists like clonidine have several beneficial actions during the perioperative period. They exert a central sympatholytic action with sedation, anxiolysis, analgesia and improve haemodynamic stability in response to intubation and surgical stress. Furthermore they reduce the anesthetic/opioid requirements thus

may offer benefits in the prophylaxis and treatment of perioperative myocardial ischaemia.<sup>5</sup>

We aimed to study the effects of intravenous clonidine in attenuation of the stress responses resulting in haemodynamic instability during laparoscopic cholecystectomy in 60 ASA grade I/II patients.

## Material & methods

This randomized double blind prospective study was carried out in 60 ASA grade I/II patients of either sex between 18 to 60 years of age, scheduled for elective laparoscopic cholecystectomy. Approval of local institutional ethical committee and written informed consent obtained. A thorough evaluation, standard fasting guidelines were followed. Patients with known hypertension, ischemic heart diseases, aortic stenosis, atrio ventricular blocks, and any past history of heart failure were excluded from the study. Patients concomitantly taking clonidine, methyldopa, beta-blockers, and calcium channel blockers were also excluded. All patients received 5 mg of diazepam tablet orally on the night before surgery. The patients were randomly allocated by computer generated number assigned to two groups. Group C (clonidine group) received Inj. clonidine 1.5 mcg/kg body weight intravenously (IV) in ringer lactate 500 ml as infusion 30 minutes before induction of anesthesia, whereas patients in group B (control group) received plain ringer lactate as infusion of pre-hydration. The observer was totally blind about the groups or medications received by the patients.

On arrival in the operation theatre, baseline parameters such as heart rate (HR), Systemic arterial blood pressure and peripheral oxygen saturation (SpO<sub>2</sub>) were noted down. Pre-medicated with injection glycopyrrolate 0.2 mg, ranitidine 50 mg, ondansetron 4 mg and fentanyl citrate 1.5  $\mu$ g/kg intravenously and pre-oxygenation started. The baseline parameters before induction were then noted. Electrodes and leads of the peripheral nerve stimulator were connected. The ulnar nerve at the wrist was used in patients according to described standard procedures. Patients were induced with induction dose of Inj. propofol 2 mg/kg and endotracheal intubation was facilitated by Inj. succinylcholine 1.5 mg/kg. Anaesthesia was maintained by 50% oxygen in nitrous oxide, 0.6-1% isoflurane and Vecuronium bromide

0.1 mg/kg. The tidal volume (Vt) and ventilator frequency was adjusted and intermittent positive pressure ventilation (IPPV) was continued by mechanical ventilator to maintain end tidal carbon dioxide between 30-40 mm Hg. Nasogastric tube was placed, aspirated in all the patients to prevent gastric distension. Pneumoperitoneum (PNP) was created by insufflation of CO<sub>2</sub> in supine position and then operation table was tilted to 10-15 degrees in reverse trendelenberg position with left lateral tilt. Intra abdominal pressure (IAP) was not allowed to exceed more than 15 mm Hg throughout the surgical procedure. After PNP necessary changes in the ventilator setting (tidal volume, respiratory rate) were made to maintain desired end tidal carbon dioxide levels. Throughout the procedure, concentration of isoflurane was kept in the range of 0.6-1%. Any fall in heart rate <60 was treated with Inj. atropine 0.6 mg IV and rise in mean arterial pressure (MAP) more than 20% from baseline was treated with nitroglycerine 1-5 mcg/kg/min IV with infusion. Systemic arterial pressure (systolic, diastolic and mean), heart rate, peripheral oxygen saturation (SpO<sub>2</sub>), end tidal carbon dioxide concentrations (EtCO<sub>2</sub>), electrocardiography (ECG) with ST segment analysis was done at the following points of time during surgery.

- a. Baseline, before premedication.
- b. Prior to induction.
- c. Three minutes after endotracheal intubation.
- d. Before pneumoperitoneum.
- e. Fifteen minutes after pneumoperitoneum.
- f. Thirty minutes after pneumoperitoneum.
- g. Ten minutes after release of CO<sub>2</sub>.
- h. Ten minutes after extubation.

At the end of surgery residual neuromuscular block was reversed by appropriate dosages of neostigmine and glycopyrrolate intravenously, when third response on TOF stimulation and/or ratio of 0.9 had appeared. Trachea was extubated and patient was transferred to post-operative recovery room and observed for the next six hours for any evidence of complications or adverse events. Degree of sedation, intensity of pain was assessed in the immediate postoperative period every thirty minutes after the surgery for six hours by the observer with the help of observer assessment of alertness/sedation score (OAS 5=fully alert, 4=light, 3=moderate, 2=deeply sedated, 1=deep sleep/unconscious) [6] and 10 point visual analogue scale (VAS). The patients were later shifted to the wards when they were awake (OAS has reached >3) with no adverse events and vitals were stable. The time of first rescue analgesic was noted when VAS > 4 and provided with Inj. diclofenac 75 mg IV. The total dose required in 24 hours postoperative period noted. As per the Institutional protocol the patients were followed until discharged on third day, later they revisited on seventh day and followed telephonically whenever required.

Group size was determined by the power analysis based on standard deviation data from previously published reports. To compare the study group, parametric data (like age, sex, weight) was analyzed by paired Student's t-test and non-parametric data was compared by chi square test with Yates continuity correction. Data is presented as mean, unless otherwise stated. Figures in the brackets indicated the Standard Deviation. The level of statistical significance used was P<0.05. The statistical analysis was done using programme STATA 12 special edition (Data analysis and statistical software) Texas, USA.

## Results

The demographic profile of the patients in two groups is shown in Table 1. Upon statistical comparison of haemodynamic parameters significant variation was observed throughout the intra-operative period. Mean heart rate varied from  $77.3 \pm 10.43$  to  $111.23 \pm 13.67$ /min in group B and in group C. It varied from  $77.66 \pm 9.43$  to  $83.53 \pm 8.35$ /min (P=0.00), Figure 1. Only one patient in group C required inj. Atropine for the treatment of bradycardia HR of 50/min after reversal and needed single dose of inj. Atropine 0.6 mg, who responded promptly. Figure 2 shows mean blood pressure (MBP) record that varied from  $91.3 \pm 10.05$  mmHg before premedication to  $104.56 \pm 7.31$  mmHg after intubation in group B and was higher during PNP. In group C, it varied from  $91.4 \pm 11.55$  mmHg before premedication to  $92.46 \pm 6.20$  mmHg after intubation and was lower as compared to in group B patients during PNP. Changes in both the groups were statistically significant (P=0.00) at all-time except at baseline, where the values were comparable. Table 2 shows intra-operative events. The mean intra-abdominal pressure was around 12 mmHg (P= 0.1127, >0.05) and duration of PNP was around 53 min (P=0.957, <0.05). 7 (23.33%) patients required intra-operative IV nitroglycerine infusion for control of hypertension in group B whereas no patient required it in group C (P = 0.01, <0.05). The perioperative SpO<sub>2</sub> and EtCO<sub>2</sub> were within normal range with no statistical significance in variation. The average duration of surgery was 82 minutes. Table 3 displays the various post-operative events. Postoperatively increased number of patients in group C were more sedated (OAS score 2 & 3 = 12), as compared to group B (OAS score 2 & 3= 4). The average VAS score of patients in group B was significantly more  $6.56 \pm 1.69$  as compared to  $4.66 \pm 1.76$  in patients of group C when compared on a 10 point scale. (P= 0.00, < 0.05). The average requirement of injection diclofenac sodium within 24 hrs of patients in group B was  $2.33 \pm 0.8023$  as compared to  $1.5 \pm 0.6789$  in patients of group C (P= 0.0001, <0.05) . Postoperative nausea, vomiting (PONV) occurred in 3 (10%) patients in group B and 2 (6.67%) in group C. (P= 0.50, >0.05). Post-operative shivering occurred in 9 (30%) in group B, where as it 2 (6.67%) in group C (P= 0.02, <0.05) and the difference was statistically significant. The postoperative course was uneventful in all the patients who were discharged on third day and later followed on seventh post-operative day.

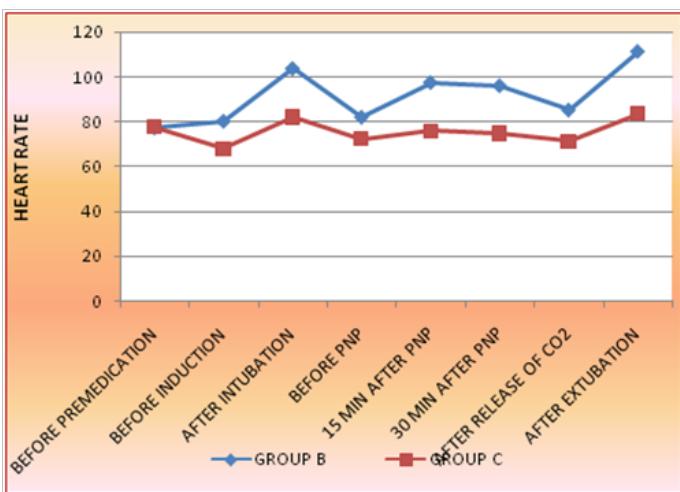
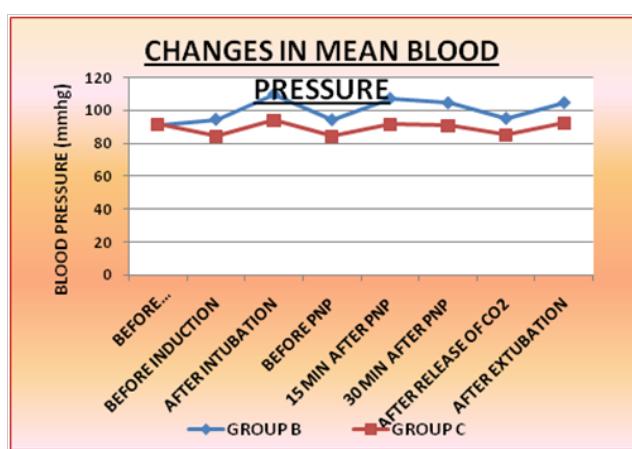


Figure 1 Changes in heart rate/min in both the groups.

(P=0.00, P<0.05, S = significant).



**Figure 2** Changes in mean blood pressure (MBP) in both the groups. (P=0.00, P<0.05, S=Significant).

## Discussion

Laparoscopic cholecystectomy with its unique advantages is now the 'gold standard' technique for gall bladder diseases, but PNP required for this surgery has its own disadvantages. The pathophysiological changes are because of the combination of mechanical and neuro-humoral factors. The factors being an increase in intra-abdominal pressure, effect of absorbed CO<sub>2</sub> caused by PNP and release of various hormonal factors because of the same.<sup>5,7</sup> More important is the releases of vasopressin and catecholamine's that are potentially deleterious in patients, such as elderly patients, or patients with limited cardio-pulmonary reserve.<sup>8</sup> The pathophysiological effects of PNP on the cardiovascular system may further compromise the cardiac function in such high risk group.<sup>1-3</sup> To prevent these adverse hemodynamic effects many surgical interventions such as abdominal wall lift method (Laprotensers) providing gasless field

for visualization, low intra-abdominal pressure techniques, or use of helium/argon gas instead of CO<sub>2</sub> are tried and well-studied.<sup>9-11</sup>

Clonidine, an imidazoline derivative is a selective alpha 2 adrenergic agonist. It is a potent antihypertensive drug. It produces a fall in the heart rate and blood pressure associated with decreased SVR and cardiac output. Clonidine is known to have longer recovery profile as it has a half life of 9-12 hours suitable for anesthesia for major surgical procedures and not recommended for ambulatory anesthesia. Recent  $\alpha_2$ -adrenoceptor agonists with short duration of action (dexmedetomidine and mivazerol) are adapted for the administration of anaesthesia for short stay procedures and to patients at high risk for coronary artery disease during surgery. The  $\alpha_2$ -adrenoceptor agonists have an analgesic action at several sites of the peripheral and central nervous system. It also causes prolongation of epidurally or intrathecally administered local anesthetics and opioids.<sup>12</sup> Laurito CE et al.<sup>13</sup> studied the effectiveness of oral clonidine as a sedative/anxiolytic and as a drug to blunt the hemodynamic responses to laryngoscopy. Clonidine has been used in various doses (from 2 to 8 mg/kg) to attenuate haemodynamic responses to PNP in laparoscopic cholecystectomy. Malek et al.<sup>14</sup> used 150  $\mu$ g of clonidine as IV infusion and intramuscularly while Sung et al.<sup>15</sup> and Yu et al.<sup>16</sup> used 150  $\mu$ g of oral clonidine as premedication for maintenance of haemodynamic stability during PNP. They found that clonidine provided reasonably well haemodynamic stability at these doses without adverse effects. In our study we used inj. Clonidine 1.5 mg/kg intravenously 30 minutes prior to laparoscopic cholecystectomy to study the hemodynamic response under general anaesthesia using 0.6-1% Isoflurane. M Das et al.<sup>17</sup> in their study also used 150 mg of clonidine orally 90 minutes prior to surgery and found that clonidine at this dose effectively blunts hemodynamic response to laparoscopic cholecystectomy without any increase incidence of side effects. Adverse effects on hemodynamics, ventilation and circulations are well studied.<sup>18,19</sup> Tripathy DC et al.<sup>20</sup> studied two doses 1 mcg/kg and 2 mcg/kg of IV clonidine with tramadol 1.5 mg/kg for stress responses and observed attenuation of stress response to intubation/extubation and PNP was significantly better with 2 mcg/kg dose.

**Table 1** Demographic profile of the patients in two groups

	Group B (n=30)	Group C (n=30)	P value, S/NS
Sex (M/F)	21/9	19/11	P= 0.50, NS
Age (yrs)	38.60 $\pm$ 12.29	39.26 $\pm$ 8.66	P = 0.55, NS
Weight (Kg)	55.36 $\pm$ 8.00	53.06 $\pm$ 6.98	P=0.24, NS
ASA Class I/II	21:9	23:7	P=0.50, NS

Values are mean +/- SD, S-Significant (P<0.05), NS-Not Significant (P>0.05).

**Table 2** Intra-operative events

	Group B (n=30)	Group C (n=30)	P Value, S/NS
Mean Intra-abdominal pressure (mmHg)	12.80 $\pm$ 0.45	12.98 $\pm$ 0.415	(P = 0.1127, NS, (P > 0.05)
Mean duration of pneumoperitoneum (min)	53.16 $\pm$ 19.06	53.46 $\pm$ 20.64	P=0.9536, NS, P>0.05
Intra-operative NTG required	7(23.33%)	0(0.00%)	P= 0.01 S, P <0.05
Duration of surgery (min)	82.46 $\pm$ 20.64	81.56 $\pm$ 20.80	P=0.8670, NS, P >0.05
EtCO <sub>2</sub> (mmHg) Mean $\pm$ SD	31.39 $\pm$ 2.25	32.32 $\pm$ 3.11	P= 0.1897 NS, P>0.05
SpO <sub>2</sub> Mean $\pm$ SD	98.81 $\pm$ 1.39	98.82 $\pm$ 1.37	P=0.08 NS, P>0.05

Values are mean +/- SD, S-Significant (P<0.05), NS –Not Significant (P>0.05).

**Table 3** Postoperative events

	Group B (n=30)	Group C (n=30)	P Value, S/NS
OAS score (2 & 3) (n)(4 & 5)	4.26	12.18	
PONV n (%)	3 (10%)	02 (6.67%)	P = 0.50 NS, P >0.05
Post-operative shivering	9 (30%)	02 (6.67%)	P = 0.02 S, p<0.05
Post-operative VAS Score (mean $\pm$ SD)	6.56 $\pm$ 1.69	4.66 $\pm$ 1.76	P = 0.00 S, P<0.05
Inj. Diclofenac sodium required in 24 hrs. (mean $\pm$ SD)	2.33 $\pm$ 0.8023	1.5 $\pm$ 0.6789	P = 0.0001 S, P<0.05

Values are mean+/SD, S-Significant (P<0.05), NS –Not Significant (P>0.05).

Chiruvella et al.<sup>21</sup> studied IV 1 mcg/kg of dexmedetomidine and clonidine for attenuation of stress responses during laparoscopic cholecystectomy and found dexmedetomidine more effective than clonidine however chances of hypotension and bradycardia were more with dexmedetomidine. Singh M et al.<sup>22</sup> studied 2 mcg/kg of IV clonidine with 2 mcg/kg intramuscular clonidine injection as premedication and found better haemodynamic stability (MBP,HR) in patients receiving clonidine by IV route and more patients required treatment for hypertension who received intramuscular clonidine as premedication. Based on studies by others with different doses and route we aimed to use 1.5 mcg/kg of IV clonidine with fentanyl 1.5 mcg/kg as premedication for general anaesthesia to observe the effects on stress responses and found to have significant haemodynamic stability in patients who received clonidine infusion as premedication, as observed by others.<sup>20-22</sup>

Due to attenuation of stress responses lesser need of use of drugs like esmolol, labetalol and nifedipine, clonidine thus also minimizes the requirement of intraoperative analgesics and inhalational agent almost by 30% which is observed on study by Sung et al.<sup>15</sup> We also observed lesser need of nitroglycerine infusion in patients of clonidine pre-medicated group. M Laisalmi et al.<sup>23</sup> in their study with 4.5 mcg/kg of clonidine on neuroendocrine response and renal parameters by measuring plasma renin activity (PRA), serum anti-diuretic hormone (ADH), urine N-Acetyl-beta-D-glucosaminidase and creatinine levels and oxygen tension of the urine peri-operatively. They concluded significant attenuation of rise of PRA, ADH indicating inactivation of catecholamine's with better renal parameters maintained as compared to control where significant rise observed in MBP, HR and PRA levels for 3 hours post-operatively and concluded it's beneficial effects that may be useful in patients with hypertension, cardiovascular and renal diseases. Joris et al.<sup>24</sup> in his study with 8 mcg/kg of clonidine noted significant reduction in the concentration of catecholamine's but not the vasopressin or plasma cortisol concentration. Sahajananda H et al.<sup>25</sup> used 8 mcg/kg Clonidine just before PNP and measured serum cortisol levels and found significant suppression of stress responses as well as peak cortisol concentration in clonidine group as compared to the placebo group. There is less incidence of adverse events like shivering, nausea, vomiting and lesser level of anxiety noted so also significantly less requirement of postoperative analgesic doses observed in our study as well as reported by others.<sup>15,17</sup> Thus use of clonidine premedication can be considered safe and cost effective for general anaesthesia for major laparoscopic surgery. However, certain limitations with our study are as follows-all above studies state the beneficial effects of clonidine on anxiety, haemodynamic and endocrine stress responses associated with intubation, pneumoperitoneum with carbon dioxide, extubation and pain reduction during perioperative periods but we have not measured the levels of catecholamine, cortisol or other stress related hormones. We need further study in patients of high risk group with cardio-respiratory or renal comorbidity in elderly patients to prove the safety of clonidine as premedication in ASA grade III/IV patients for laparoscopic cholecystectomy.

## Conclusion

IV clonidine in a dose of 1.5mcg/kg before induction can be recommended to maintain haemodynamic stability during laparoscopic cholecystectomy in ASA grade I/II patients. It is cost effective in terms of reduction in intraoperative anesthetic and postoperative analgesic requirement.

## Acknowledgments

None.

## Conflicts of Interest

None.

## References

1. Joris J. *Anesthetic management of laparoscopy*. Miller RD (Ed.) Anesthesia Churchill Livingstone, USA, 1994. p. 2011–2029.
2. Wahba RWM, Beique F, Kleiman SJ. Cardiopulmonary function and laparoscopic choleystectomy. *Can J Anaesth.* 1994;42(1):51–63.
3. Sharma KC, Brandstetter RD, Brensilver JM, et al. Cardiopulmonary physiology and pathophysiology as a consequence of laparoscopic surgery. *Chest.* 1996;110(3):810–815.
4. Joris JL, Noirot DP, Legrand MJ, et al. Hemodynamic changes during laparoscopic cholecystectomy. *Anesth Analg.* 1993;76(5):1067–1071.
5. Boussofara M, Mtaallah MH, Nefaa MN, et al. Clonidine and anesthesia. *Tunis Med.* 2004;82(3):249–257.
6. Hillier SC, Mazurek MS. *Monitored anesthesia care*. In: Barash PG, et al., editors. Clinical Anaesthesia. 6<sup>th</sup> edn Lippincott Williams Wilkins, USA. 2009. p. 820–828.
7. O'Leary E, Hubbard K, Tormey W, et al. Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position. *Br J Anaesth.* 71997;6(5):640–644.
8. Solis-Herruzo JA, Moreno D, Gonzalez A, et al. Effect of intra-thoracic pressure on plasma arginine vasopressin levels. *Gastroenterology.* 1991;101(3):607–617.
9. Saunders CJ, Gunther RA, Wolfe BM, et al. Effector of hemodynamics during laparoscopy: CO<sub>2</sub> absorption or intra-abdominal pressure? *J Surg Res.* 1995;59(4):497–503.
10. Tido Junghans, Bartholomas Bohm, kerstin Grundel, et al. Effects of pneumoperitoneum with carbon dioxide, Argon or Helium on hemodynamic and respiratory function. *Arch Surg.* 1997;132(3):272–278.
11. Menes T, Spivak H. Laparoscopy: searching for the proper insufflation gas. *Surg Endosc.* 2000;14(11):1050–1056.
12. Maze M, Tranquilli W. Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia. *Anesthesiology.* 1991;74(3):581–605.
13. Laurito CE, Baughman VL, Becker GL, et al. The effectiveness of oral clonidine as a sedative/anxiolytic and as a drug to blunt the hemodynamic responses to laryngoscopy. *J Clin Anesth.* 1991;3(3):186–193.
14. Yu HP, Hsue SS, Yien HW, et al. Oral clonidine premedication preserves heart rate variability for patients undergoing laparoscopic cholecystectomy. *Acta Anaesthesiol Scand.* 2003;47(2):185–190.
15. Sung CS, Lin SH, Chan KH, et al. Effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. *Acta Anaesthesiol Sin.* 2000;38(1):23–29.
16. Mutzbauer TS, Obwegeser JA, Gratz KW. Clonidine in oral medicine, literature review and our experience. *Schweiz Monatsschr Zahnmed.* 2005;115(3):214–218.
17. Mrinmoy Das, Manjushree Ray, Gauri Mukherjee. Hemodynamic changes during laparoscopic cholecystectomy: effect of oral clonidine premedication. *Indian J Anaesth.* 2007;51(3):205–210.
18. Duale C, Bazin JE, Ferrier C, et al. Hemodynamic effects of laparoscopic cholecystectomy in patients with coronary disease. *Br J Anaesth.* 1994;72(Suppl): 17.
19. Dhoste K, Lacoste L, Karayan J, et al. Hemodynamic and ventilatory changes during laparoscopic cholecystectomy in elderly ASA III patients. *Can J Anaesth.* 1996;43(8):783–788.

20. Tripathy DC, Shah KS, Dubey SR, et al. Hemodynamic stress response during laparoscopic cholecystectomy: Effect of two different doses of intravenous clonidine premedication. *Anaesthetol Clin Pharmacol*. 2011;27(4):475–480.
21. Sunil Ch, Balaji D, Venkata S, et al. Comparative Study of Clonidine versus Dexmedetomidine for Hemodynamic Stability during Laparoscopic Cholecystectomy. *International Journal of Scientific Study*. 2014;2(7):186–190.
22. Meena S, Arin Choudhary, Manpreet K, et al. The comparative evaluation of intravenous with intramuscular clonidine for suppression of hemodynamic changes in laparoscopic cholecystectomy. *Saudi J Anaesth*. 2013;7(2):181–186.
23. Laisalmi M, Koivusalo AM, Valta P, et al. Clonidine provides opioid-sparing effect, stable haemodynamics and renal integrity during laparoscopic cholecystectomy. *Surg Endosc*. 2001;15:1331–1335.
24. Joris JL, Chiche JD, Canivet JL, et al. Hemodynamic changes induced by laparoscopy and their endocrine correlates: Effects of clonidine. *J Am Coll Cardiol*. 1998;32(5):1389–1396.
25. Sahajananda H, Rao S. Effects of clonidine on haemodynamics and on plasma cortisol level during laparoscopic cholecystectomies. *Indian J Anaesth*. 2015;59(1):53–56.