International Journal of Advances in Medicine
Bhalerao PM et al. Int J Adv Med. 2017 Jun;4(3):788-792
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20172273

Original Research Article

Intravenous clonidine for suppression of haemodynamic response to laparoscopy- a prospective randomised, placebo controlled, single centre study

Pradnya M. Bhalerao[1]*, Shalini K. Thombre[2], Upendra S. Kapse[3], Kunal V. Targe[4]

[1]Department of Anaesthesia, Government Medical College, Miraj, Maharashtra, India
[2]Department of Emergency Medicine, Dr. DY Patil Medical College, Hospital and Research Centre; DY Patil Vidyapeeth, Pimpri, Pune, Maharashtra, India
[3]Department of Anaesthesiology, BJ Government Medical College, Pune, Maharashtra, India
[4]Anaesthesiologist, NHS, Lincoln, UK

Received: 18 March 2017
Accepted: 18 April 2017

***Correspondence:**
Dr. Pradnya M. Bhalerao,
E-mail: dr.pradnyabhalerao@gmail.com

ABSTRACT

Background: Laparoscopic surgeries, including cholecystectomy are being performed on a large scale owing to the improved tissue healing and minimal hospital stay. However the haemodynamic response to pneumoperitoneum could pose a problem in these patients. The primary objective of this study was to evaluate the effectiveness of 1µg/kg intravenous clonidine in suppression of this hemodynamic response. The secondary objective was to assess the postoperative analgesia and sedation.
Methods: 60 patients posted for laparoscopic cholecystectomy were divided into two groups. 30 patients received intravenous midazolam 0.03mg/kg and pentazocine 0.3mg/kg and the other 30 received intravenous clonidine 1µg/kg 15 minutes prior induction.
Results: Intraoperative mean pulse rate was 90.82±4.81 beats per minute in control group. In clonidine group it was 74.76±9.88 beats per minute ($p<0.05$ significant). Similarly the mean systolic blood pressure was 137.87±4.89 and 125.79±6.44 respectively ($p<0.05$-significant). The duration of postoperative analgesia was 334.83±24.65 and 116.05±19.17 minutes respectively ($p<0.05$).
Conclusions: Premedication with intravenous clonidine, has been found to be relatively safe as well as an effective method that provides stable haemodynamics and protection against stress response induced by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy.

Keywords: Clonidine, neuroendocrine response, laparoscopy

INTRODUCTION

Laparoscopic cholecystectomy has revolutionized and become the "gold standard" for cholelithiasis surgery. It offers many benefits when compared to the conventional technique. However, this procedure, owing to the pneumopertoneum produces significant haemodynamic changes, especially in elderly and haemodynamically compromised patients.[1,2] Pneumoperitoneum affects several homeostatic systems leading to alteration in acid-base balance, cardiovascular, pulmonary physiology and stress response. The extent of cardiovascular changes associated with pneumoperitoneum includes an increase in mean arterial pressure, decrease in cardiac output and increase in systemic vascular resistance which in turn may compromise tissue perfusion. Various pharmacological agents have been used to prevent haemodynamic changes associated with pneumoperi-

toneum. Clonidine, an α-2 agonist, has centrally acting sympatholytic activity which can help reduce the cardiovascular adverse effects of carbon dioxide pneumoperitoneum and provide intraoperative and postoperative analgesia. It reduces the release of catecholamines and almost completely blocks the release of norepinephrine, thus reducing systemic vascular resistance and achieving haemodyanamic stability. Clonidine also acts as an analgesic intraoperatively and post operatively.[3,4]

Thus, this study was conducted with the primary objective to evaluate the efficacy of intravenous clonidine in laparoscopic surgeries in context with its effect on the haemodynamic response to pneumoperitoneum. The secondary objective was to assess the post operative analgesia and sedation

METHODS

This study is a prospective, randomized, placebo-controlled, single centre study. The study was conducted at a tertiary care level institute. The study protocol was submitted to the Institutional Ethics committee and approval was obtained. A written informed consent was obtained from each patient.

Total number of sixty cases, undergoing laparoscopic surgeries of upto three hours of duration were randomly divided into two groups of thirty cases each, group A and group B. Randomization was done in the block of two as per a computer-generated code. Baseline investigations such as haemoglobin, blood sugar level, blood urea level, serum creatinine and serum electrolytes of both the groups were recorded and were comparable. General anaesthesia was planned for both the groups.

The control group, (N=30) was pre-medicated 15 minutes prior to induction of anaesthesia with injection midazolam 0.03mg/kg intravenously as a sedative and injection pentazocine 0.3mg/kg intravenously as an analgesic.

The study group (N=30) was given injection clonidine 1µg/kg intravenously 15 minutes prior to induction of anaesthesia. No other sedative or analgesic was given in the study group.

Injection glycopyrrolate 5µg/kg intramuscularly, injection ondansetron 0.08mg/kg intravenously were given in both the group along with the above mentioned premedication 15 minutes prior to induction of anaesthesia. Induction of anesthesia was done using injection pentothal sodium 5mg/kg and injection vecuronium 0.08mg/kg intravenously. Anaesthesia was maintained intra-operatively using oxygen, nitrous oxide and isoflurane. Pneumoperitoneum was created by insufflation of carbon dioxide and operation table was tilted about 15° reverse Trendelenburg position. Intra-abdominal pressure (IAP) was kept below 15mmHg throughout the surgical procedure. After pneumoperitoneum, necessary changes in ventilator setting (tidal volume, respiratory rate) were made to maintain normocapnia.

At the end of the surgery neuromuscular paralysis was reversed with injection glycopyrrolate 10µg/kg intravenously and injection neostigmine 0.05mg/kg intravenously.

The parameters studied intraoperatively were systolic blood pressure, pulse rate and oxygen saturation (SpO_2). These parameters were recorded just prior to induction of anaesthesia, after endotracheal intubation, for every 5 minutes till 15 minutes after intubation and then every 15 minutes till the end of the surgery and then subsequently for every 15 minutes in post-operative unit.

Other parameters studied were end tidal CO_2, post-operative sedation score and post-operative analgesia. The duration of post-operative analgesia was determined by the time after which the patient demands for some kind of analgesia which we have termed as "rescue analgesia". The intensity of pain was assessed by using 10 point visual analogue scale (VAS). Patients were monitored in the post-operative care unit for sedation and post-operative analgesia. Level of sedation (sedation score) was assessed by sedation scale:

- Awake and agitated
- Awake and comfortable
- Asleep but arousable
- Asleep with sluggish response to persistent call or touch
- No response to call or touch.

Statistical analysis

Preliminary sample size estimation using previous studies showed that approximately 30 patients should be included in each group, assuming alpha error of 0.05 (95% confidence interval) in order to obtain power of study >80%. For the analysis of qualitative data, either chi-square test or Fischer analysis was used, whereas quantitative data was analyzed using paired or unpaired t test. $P<0.05$ was considered significant, $P>0.05$ not significant and $P<0.001$ highly significant. Data analysis was done using SPSS (statistical package for social science) version 17.0 (SPSS inc., Chicago II, USA).

RESULTS

Out of 60 patients, 27 were male and 33 were female. Sex distribution in the two groups was comparable. The average age of patients in group A i.e. the control group was 48.38 years ±11.58 while that in group B i.e. clonidine group was 45.77 years ±16.59. Average weight in control group was 57.16 kg ±5.53 SD, whereas average weight in clonidine group was 55 kg ±11.24SD (Table 1).

There was no statistically significant difference in average age and weight of the two groups.

Table 1: Demographic characteristics.

Parameter	Group A (Mean±SD)	Group B (Mean±SD)
Avg. age (years)	48.38±11.58	45.77±16.59
M/F	15/15	12/18
Avg. weight	57.16±5.53	55±11.24

The pre-operative baseline parameters i.e. pre-operative heart rate and blood pressure were comparable in control as well as clonidine group.

Table 2: Comparison of intraoperative pulse rate in two groups.

Group A (avg. intraop HR/min) [Mean±SD]	Group B (avg. intraop HR/min) [Mean±SD]
90.82±4.81	74.76±9.88**

*p<0.05, **p<0.001.

Intraoperative mean pulse rate was 90.82±4.81 beats per minute in control group. In clonidine group it was 74.76±9.88 beats per minute. Statistically significant variation was observed (p<0.001).

Table 3: Comparison of intraoperative blood pressure in two groups.

Group A (avg. Intraop BPmmHg)	Group B (avg. intraop BPmmHg)
137.87±4.89	125.79±6.44**

[Mean±SD] Unit: mmHg; *p<0.05, **p<0.001.

Changes in the systolic blood pressure when compared in the control and clonidine groups of patients were found to be statistically significant (p<0.001).

Table 4: Comparison of postoperative pulse rate in two groups.

Group A (avg. postop HR) [Mean±SD]	Group B (avg. postop HR) [Mean±SD]
92.67±5.74	78.03±6.97**

*p<0.05, **p<0.001.

Mean post-operative pulse rate was 92.67±5.74 beats per minute in control group. In clonidine group it was from78.03±6.97 beats per minute (p<0.001).

Table 5: Comparison of postoperative blood pressure in two groups.

Group A (avg. intraop BP) [Mean±SD] mmHg	Group B (avg. intraop BP) [Mean±SD] mmHg
139.08±2.63	128.88±5.82**

p<0.05, **p<0.001.

Changes in the post-operative systolic blood pressure when compared in the control and clonidine groups of patients were found to be statistically significant (p<0.05).

Table 6: Time for rescue analgesia.

	Group A	Group B
Time in minutes [Mean±SD]	116.05±19.17	334.83±24.65**

p<0.05, **p<0.001

Normocapnia was maintained throughout the procedure. $EtCO_2$ varied from 31.94±0.78mmHg in control group and 31.91±0.55mmHg in clonidine group.

The time required for rescue analgesia in the control group was 116.05±19.17 minutes whereas time required for rescue analgesia in the clonidine group was 334.83±24.65 minutes which is stastically significant (p<0.001) (Table 6).

Table 7: Comparison of sedation in two groups.

	Group A	Group B
Time in minutes [Mean±SD]	36±5.15	35.33±5.07

p>0.05-not significant; Post-operative sedation was comparable in both the control and clonidine.

There was no significant difference in post-operative sedation between the two groups.

DISCUSSION

Pneumoperitoneum during laparoscopy has been found to produce significant haemodynamic changes such as an increase in mean arterial pressure, decrease in cardiac output and increase in systemic vascular resistance which in turn compromise tissue perfusion, which can be detrimental especially in the elderly and haemodynamically compromised patients.[1]

A variety of pharmacological agents have been used to prevent these detrimental effects of pneumoperitoneum.

Clonidine, an imidazoline derivative is a selective α-2 adrenergic agonist. It is a potent antihypertensive drug which produces a fall in the heart rate and blood pressure with decrease in systemic vascular resistance (SVR) and cardiac output.

It has other desirable actions like anxiolysis, sedation, analgesia, probable antiemesis and prevention of shivering. It is a potent hypotensive agent. Clonidine inhibits catecholamine and vasopressin-mediated increase in SVR caused by pneumoperitoneum.

Dose of clonidine varied from 2 to 5μg.kg^{-1} in different studies. Higher dose of oral clonidine (5 μg.kg^{-1}) is usually required for potentiating postoperative analgesia by

intrathecal morphine.[4,5] A small oral dose of clonidine decreased the incidence of perioperative myocardial ischemic episodes without affecting haemodynamic stability. Aho et al used 3µg.kg^{-1} and 4.5µg.kg^{-1} clonidine intramuscularly for suppression of haemodynamic response to pneumoperitoneum.[6] Rise in blood pressure and heart rate was less in both the groups but 4.5µg.kg^{-1} of drug produced a greater fall in mean arterial pressure before induction.

Joris et al used very high dose of clonidine (8µg.kg $^{-1}$) for reducing the level of catecholamine and vasopressin following pneumoperitoneum.[7]

Malek et al used 150µg of clonidine as intravenous infusion and intramuscularly while Sung et al and Yu et al used 150µg of oral clonidine as premedication for maintenance of haemodynamic stability during pneumoperitoneum.[3,8,9]

A similar study was conducted in which oral clonidine 150µg/kg was given as a premedication in one group of patients undergoing laparoscopic cholecystectomy and the other group was given a placebo.[10] In this study it was found that significant rise in heart rate was observed following pneumoperitoneum in placebo group as compared to clonidine group (99.23±14.02 versus 81.26±8.40 beats per minute). Similarly, rise in systolic arterial pressure (143.63±19.60 versus 119.6±10.06mmHg), diastolic arterial pressure (99.23±14.02 versus 81.26±8.40mmHg) and mean arterial pressure (114.13±16.57 versus 93.83±8.107mmHg) was noted in placebo group following pneumoperitoneum. Nitroglycerine drip was started in 33.3% patients in placebo group to control intraoperative hypertension.[9]

In the present study clonidine was used in the dose of 1µg/kg 15 minutes prior to induction of anaesthesia. The preoperative heart rate in control and clonidine group was noted which were 78.03±6.76 beats/minute and 80.76±7.89 beats/minute respectively. The systolic blood pressure was noted in both control group and clonidine group which were 132.71±4.28 mm of Hg and 128.76±8.59mm of Hg. The pre-operative heart rate and systolic blood pressure were comparable in both the group.

The intra-operative mean pulse rate was 90.82±4.81 beats/minute in control group. In clonidine group it was 74.76±9.88 beats/minute A statistical comparison in two groups of patients showed significant variation throughout the intraoperative period except for the baseline value when no significant difference was observed (Table 2).

The drug has been found to preserve heart rate variability during laparoscopic surgeries.[10] The average intra-operative systolic blood pressure in the control and clonidine group were recorded which were 137.87±4.89mm of Hg and 125.79±6.44 mm of Hg respectively (Table 3). Changes in the systolic blood pressure when compared in the control and clonidine groups of patients was found to be statistically significant excepting the base line values where no significant difference was found. The other selective α-2 receptor antagonist, dexmeditomedine has been studied with a favourable benefit in terms of hemodynamic response to laparoscopy.[11]

Normocapnia was maintained throughout the procedure. $EtCO_2$ varied from31.94±0.78 mmHg in control group and 31.91±0.55 mmHg in clonidine group.

The post-operative sedation was noted in both the groups according the sedation scale mentioned above. The post-operative sedation in control group lasted for 36±5.15 minutes and in clonidine group lasted for 35.33±5.07 minutes after which patients were awake and comfortable. Post-operative sedation was comparable in both the control and clonidine group (Table 6).

Clonidine was also studied for its efficacy in providing post-operative analgesia which was determined by the time duration required for rescue analgesia. 1µg/kg of intravenous clonidine also provided good post-operative analgesia as compared to the control group. The duration of post-operative analgesia in clonidine group (334.83±24.65 minutes) was much longer than that of control group (116.05±19.17 minutes) which was statistically significant (Table 7).

Clonidine has been used to suppress the hemodynamic response to intubation.[12,13] We did not study this aspect in detail. The efficacy of the drug in a compromised cardiovascular system too was not studied.

CONCLUSION

In conclusion, premedication with 1µg/kg intravenous clonidine, has been found to be relatively safe as well as an effective method that provides stable haemodynamics and protection against stress response induced by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. It also provides intra-operative and post-operative analgesia with minimal or no post-operative sedation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Jean LJ. Anaesthesia for Laparoscopic surgery. In: Miller RD, ed. Anesthesia. 7th ed. New York: Churchill Livingstone; 2010;2185-2202.
2. 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.
3. Sung CS, Lin SH, Chan KH, Chang WK, Chow LH, Lee TY. Effect of oral clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Sin. 2000;38:23-9.
4. Laisalmi M, Koivusalo AM, Valta P, Tikkanen I, Lindgren L. Clonidine provides opioid sparing effect, stable haemodynamics and renal integrity during laparoscopic cholecystectomy. Surg Endosc. 2001;15:1331-5.
5. Goyagi T, Nishikawa T. Oral Clonidine premedication causes the quality of postoperative analgesics by intrathecal morphine. Anesth Analg. 1996;82:1192-6.
6. Aho M, Scheinin M, Lehtinen AM. Intramuscularly administered dexmedetomidine attenuates haemodynamic and stress responses to gynaecologic laparoscopy. Anesth Analg. 1992;75:932-9.
7. Joris J, Chiche JD, Lamy M. Clonidine reduces the haemodynamic changes induced by pneumoperitoneum during laparoscopic cholecystectomy. Br J Anaesth. 1995;74:A-124.
8. 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;78:286-91.
9. Yu HP, Hseu SS, Yien HW. Oral clonidine premedication preserves heart rate variability for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 2003;47:185-90.
10. Das M, Ray M, Mukherjee G. Haemodynamic changes during laparoscopic cholecystectomy: Effect of clonidine premedication. Indian J Anaesth. 2007;51:205
11. Hazra R, Manjunatha SM, Manuar MDB, Basu R, Chakraborty S. Comparison of the effects of intravenously administered dexmedetomidine with clonidine on hemodynamic responses during laparoscopic cholecystectomy. Anaesth Pain Intens Care. 2014;18(1):25-30
12. Raval DL, Mehta MK. Oral clonidine pre medication for attenuation of haemodynamic response to laryngoscopy and intubation. Indian J Anaesth. 2002;46:124-9.
13. Zalunardo MP, Zollinger A, Spahn DR, Seifert B, Radjaipour M, Gautschi K, et al. Effects of intravenous and oral clonidine on hemodynamic and plasma-catecholamine response due to endotracheal intubation. J Clin Anesth. 1997;9:143-7.

Cite this article as: Bhalerao PM, Thombre SK, Kapse US, Targe KV. Intravenous clonidine for suppression of haemodynamic response to laparoscopy-a prospective randomised, placebo controlled, single centre study. Int J Adv Med 2017;4:788-92.