Original article

Effect of oral clonidine premedication on propofol consumption for patient undergoing laparoscopic cholecystectomy

JN Prasad , SN Singh, K Pokhrel , S Khatiwada
Department of Anaesthesiology and Critical Care, BP Koirala Institute of Health Sciences, Dharan, Nepal

Abstract

Background: Various goals of premedication includes anxiolysis, sedation, amnesia, analgesia, attenuation of autonomic reflexes, and reduction of anaesthetic dose requirement. Preanaesthetic oral clonidine has been shown to produce anxiolysis, sedation and attenuation of hemodynamic stress response to tracheal intubation. **Objective:** To investigate the clinical efficacy of oral clonidine on propofol consumption in patients undergoing laparoscopic cholecystectomy. **Methods:** This was a prospective, randomized, double-blind placebo controlled study conducted in ninety consecutive patients randomly divided into three equal groups (placebo, tab. clonidine 150 mcg and tab. clonidine 300 mcg) meeting inclusion and exclusion criteria who underwent laparoscopic cholecystectomy. Study drug was given 60 minutes before induction of anaesthesia. Anaesthesia was induced with intravenous pethidine 1mg/kg followed by propofol . The dose of propofol for loss of verbal command was recorded. Anaesthesia was maintained with propofol at the rate of 10 mg/kg/h for 10 minutes then to 8 mg/kg/h for 10 minutes and ultimately decreased to 6 mg/kg/h after tracheal intubation. The rate of propofol infusion was adjusted by 2mg/kg/h to obtain adequate depth of anaesthesia (maintaining hemodynamic parameters within 20% of baseline). **Results:** The propofol induction dose was less in clonidine 150 mcg (1.2±0.2 mg/kg) and clonidine 300 mcg (1.08±0.24 mg/kg) groups as compared to placebo group (1.4±0.3 mg/kg) (p=<0.001). The rate of propofol infusion in mg/kg/h and in mcg/kg/h was lower in clonidine 150 mcg (6.7±1.6 and 121.3±11.37) and clonidine 300 mcg (7±1.4 and 120.0±9.8) groups as compared to placebo (10±3.2 and 148.0±32.53) group (p =< 0.001). **Conclusion:** oral clonidine premedication reduces propofol requirement for induction and maintenance of anaesthesiain patients undergoing laparoscopic cholecystectomy.

Keywords: clonidine, laparoscopic cholecystectomy, propofol

Introduction

Satisfactory preoperative preparation and medication facilitate an uneventful perioperative course. Various goals of premedication include anxiolysis, sedation, amnesia, analgesia, attenuation of autonomic reflexes, and facilitation of smooth induction of anesthesia.[1] One of the important goal of premedication is to reduce the anaesthetic dose requirement. To achieve this goal many drugs have been studied.[2-5] One of them is clonidine, which is alpha-2 adrenergic receptor agonist. This class of receptor is widely distributed and exerts several actions related to anaesthesia. It has been demonstrated in animal studies that stimulation of alpha-2 receptors induces sedation, hypnosis, analgesia and inhibition of sympathetic neural activity.[6]

Address for correspondence
Jagat Narayan Prasad
Assistant Professor
Department of Anaesthesiology and Critical care
B.P.Koirala Institute of Health Sciences, Dharan
Email: prasadjagat@yahoo.com

Oral clonidine premedication reduces peripheral sympathetic discharge, induces sedation by inhibiting pontine locus cerulleus, attenuates hemodynamic response to noxious stimuli such as tracheal intubation[7,8,] and reduces postoperative pain and analgesic requirement in neuraxial block.[2,9] It also increases cardiac baroreflex sensitivity in hypertensive individuals and stabilize blood pressure.[10] Furthermore clonidine increases perioperative hemodynamic stability in patients undergoing laparoscopic cholecystectomy with enhancement of parasympathetic control of heart rate.[11, 12]

The effect of preanaesthetic medication on minimum anaesthetic concentration of propofol has been studied earlier. However, there are very few studies using oral clonidine premedication on rate of propofol requirement to maintain adequate depth of anesthesia. So the objective of this prospective randomized placebo control study was to investigate the effect of premedication with oral clonidine on propofol requirement to maintain adequate depth of anaesthesia for patients undergoing laparoscopic cholecystectomy.

Methods

The study was carried out in the department of anaesthesiolgy and critical care of a hospital of Eastern Nepal. Approval for study was gained from the institutional ethical committee. Ninety patients undergoing laparoscopic cholecystectomy were randomized to three groups of thirty each by opening the sequentially numbered white opaque sealed envelope. Group A received tab. pantoprazole 40 mg, group B received tab. Clonidine 150 mcg and group C received tab. Clonidine 300 mcg 60 minutes before estimated anaesthesia induction time. Both the patients and the investigator observing the outcome were unaware of the group assigned.

Patients aged 18-60 years booked to undergo laparoscopic cholecystectomy under general anaesthesia were screened and patients of ASA physical status I & II were included. Patients unwilling to give consent, or those with history of previous renal and liver disfunction, heart diseases (coronary artery disease, valvular heart disease and electro cardiogram abnormalities), diabetes mellitus, asthma, monoamine oxidase inhibitor intake, and smoker were excluded from the study.

After the patients arrived at patient holding area in the operation theatre, peripheral venous access was secured with 18G intravenous cannula. The study drug was administered according to the study group assigned 60 minutes before estimated anaesthesia induction time. Then, patients were shifted to operation theatre. ECG, non-invasive blood pressure (NIBP) and pulse oximetry were monitored. Preoxygenation was done with 100% oxygen for three minutes. General anesthesia was administered with loading dose of intravenous pethidine 1 mg /kg and propofol at the rate of 20 mg/kg/h. Time and dose of propofol infused for loss of verbal command were recorded. After confirming successful ventilation, 0.1 mg/kg of intravenous vecuronium bromide was administered. The tracheal intubation was performed after 3 min of intravenous vecuronium administration. After confirming endotracheal intubation by auscultation and capnography, endotracheal tube was secured and attached to anaesthesia machine.

Vitals (heart rate, noninvasive arterial blood pressure, and arterial oxygen saturation) were recorded at baseline, 60 min after premedication, at preinduction and after endotracheal intubation at interval of 1 min, 2 min, 5 min and then every 5 min onwards till oneminute after extubation of trachea. $ETCO_2$ was recorded after intubation and at the above intervals and ventilation with O_2 was continued. Anesthesia was maintained with continuous intravenous infusion of propofol at the rate of 10 mg/kg/h for 10 minutes then 8 mg/kg/h for 10 minutes and 6 mg/kg/h. Thereafter additional dose of vecuronium bromide was administered for muscle relaxation as needed. The rate of infusion of propofol was adjusted by 2 mg/kg/h till heart rate, arterial blood pressure was maintained within 20% of their baseline values. Same music was played to all patients throughout intraoperative period using ear phone. The end tidal CO_2 concentration was maintained

between 30-40 mmHg by controlled mechanical ventilation. The rate of propofol infusion was maintained at 6 mg/kg/hr at the start of closure of skin incision and was stopped when last suture applied. Residual neuromuscular blockade was reversed with inj. neostigmine 0.05mg/kg and inj. glycopyrolate 0.01mg/kg. The rate of propofol consumption in each case was calculated. Time taken from stoppage of propofol infusion to tracheal extubation was noted.

The following questionnaires were asked for perioperative memory after 24 h of operation.

- Do you remember my asking your name? Y/N
- Can you remember anything or events during sleep? Y/N
- Do you recall listening to music during surgery? Y/N
- Do you remember my asking you to open your eyes? Y/N

Statistical analysis

The collected data was entered in MS excel program. Data was analyzed using the Statistical Package for Social Science (version 17.0 for windows, SPSS). Statistical tests used were : Analysis of variances for comparison of mean values between more than two groups, independent paired t test to compare the mean values between two groups, paired t test to compare the mean values before and after the study drug administration within the same group and chi square test to compare the nonparametric variables like gender and sedation score.

Results

The three groups were similar in age, weight, and baseline anxiety score (p>0.05) (table 1). However, the mean duration of surgery was longer in the placebo group (p=<0.05).

Table 1: Patient characteristics. Mean (SD)

Parameters	Study group			p-value
	Group A Pantoprazol 40 mg (n=30)	Group B Clonidine 150 mcg (n=30)	Group C Clonidine 300 mcg (n=30)	
Age (Year)	36.93 ±9.15	36.73±10.56	35.63±11.35	p=0.873
Weight (Kg)	51.9±8.72	56.5±8.2	56.17±8.98	p=0.07
Baseline anxiety score	37±21.03	36.67±14.22	37.33±12.85	p=0.988
Duration of surgery (minutes)	69.83±28	56.5±15	59.83±13.86	p=0.035

Significantly greater doses of propofol were required in Group A than Group B and Group C, for induction of anaesthesia p<0.001 (Fig. 1). Induction dose of propofol was lower in Group C than Group B.

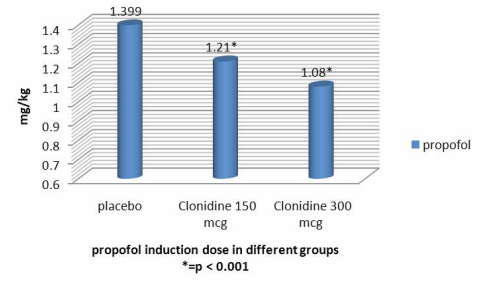

Figure 1: Propofol induction dose as mean in different groups

The rate of propofol infusion was lower in clonidine 150 mcg and clonidine mcg 300 groups than placebo grou (Fig. 2). The difference in the rate of propofol infusion was not statistically significant between clonidine 150 mcg and clonidine 300 mcg groups (p=>0.05). Intra-operative awareness was absent in all the three groups (table 2).

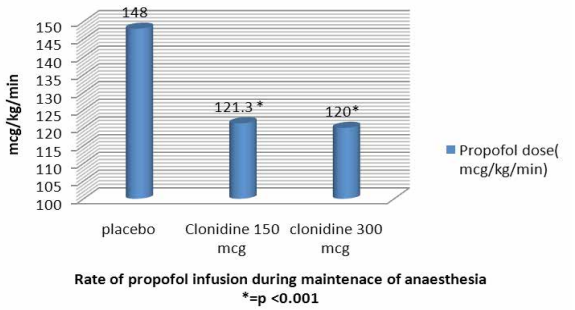

Fig.2: Rate of propofol infusion in different groups

Table 2: Questions asked postoperatively to assess intraoperative awareness.

Questionnaire	Placebo (n=30)	Clonidine 150 mcg (n=30)	Clonidine 300 mcg (n=30)
Do you remember my asking your name? Y/N	N	N	N
Can you remember anything or events during sleep? Y/N	N	N	N
Do you recall listening to music during surgery? Y/N	N	N	N
Do you remember my asking you to open your eyes? Y/N	N	N	N

Discussion

The present study, a double blind randomized controlled evaluation, was conducted to see the effect of oral clonidine premedication on propofol consumption for patients undergoing laparoscopic cholecystectomy.

Three study groups were similar with respect to age, sex and body weight. Long duration of surgery in the placebo group in our study was most probably due to relatively small sample size. In our study, propofol induction dose was around 22% lower in clonidine 150 mcg and 300 mcg groups as compared to the placebo group (p=<0.001). Rate of propofol infusion in mg/kg/h and in mcg/kg/min was 18% and 18.9% lower in clonidine 150 mcg and clonidine 300 mcg groups respectively as compared to placebo group (p=<0.001). With reduced rate of propofol infusion still there was no recall of intraoperative events in all groups. The total propofol requirement were 25.12% and 22.7% lower in clonidine 150 mcg and clonidine 300 mcg groups respectively as compared to placebo group (p=<0.001). The rate of reduction of propofol requirement between oral clonidine 150 mcg and clonidine 300 mcg were similar (p=0.656). In a study conducted by Imai et al[13], the total requirement of propofol were 14.38% and 41.16% lower in clonidine 75 mcg and clonidine 150 mcg respectively as compared to placebo group. The mean infusion rates of propofol in mg/kg/h in the present study were 21.11% and 37.77% lower in clonidine 150 mcg and clonidine 300 mcg respectively as compared to placebo group. Looking at oral clonidine dose wise, the rate of propofol reduction was more in study done by Imai et al[13]. The difference in the findings could be due to the fact that they conducted their study in minor surgery and the mean duration of anaesthesia in their study was longer than our study. Further, they also used nitrous oxide during maintainance of anaesthesia along with propofol infusion. Richards and co-workers[14] reported oral clonidine 600 mg to reduce the minimum anaesthetic concentration of propofol with prolonged recovery from anaesthesia. In our study, with a smaller dose of clonidine (150 mcg and 300 mcg) reduced the intraoperative total requirement of propofol. Propofol anaesthesia sometime induces hypotension and bradicardia. On top of it clonidine can produce further bradycardia and hypotension. Despite these facts in our study, however, preanaesthetic oral clonidine 150 mcg and 300 mcg neither produced bradycardia nor hypotension. Main limitation of our study is that oral clonidine was given in dose of 150 mcg and 300 mcg irrespective of body weight due to unavailability of different dose preparation of oral clonidine. Further, our sample size is relatively small.

Conclusion

Oral clonidine reduces induction dose and the rate of propofol infusion thus reduces the cost of anaesthesia. These findings suggest that preanaesthetic medication using clonidine is safe, cheap and efficacious.

Acknowledgments

We are very grateful to all our faculties and technical staffs for their constant support and encouragement. We extend our heartfelt thanks to all the participants of this study without whom the study would not have been completed.

References

1. Moyers JR, Hata TM. Preoperative evaluation and management. In: Barash PG, Cullen BF, Stolting Rk.(eds). Clinical anaesthesia. 5th edi.Philadelphia:Lippincott Williams & wilkins; 2006. p. 475-501.
2. Park J, Forrest J, Kolesar R, Bhola D, Beattie S, Chu C. Oral clonidine reduces postoperative PCA morphine requirements. Can J Anaesth 1996; 43:900–6.
3. Bloor BC, Flacke WE. Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. Anesth Analg 1982; 61:741–5.
4. Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. Anesthesiology 1986; 64:36–42.
5. Flacke JW, Bloor BC, Flacke WE, et al. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 1987; 67:11–9.
6. Deckert V, Lachaud V, Parini A, Elghozi JL. Contribution of alpha 2-adrenoceptors to the central cardiovascular effects of clonidine and S 8350 in anaesthetized rats. Clin Exp Pharm Physiol 1991; 18:401– 8.
7. Laurito CE, Baughman VL, Becker GL, DeSilva TW, Carranza CJ. The effectiveness of oral clonidine as a sedative/anxiolytic and as a drug to blunt the hemodynamic responses to laryngoscopy. J Clin Anesth 1991; 3:186 –93.
8. Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. Anesthesiology 1986; 64:36–42.
9. Goyagi T, Nishikawa T. Oral clonidine premedication enhances the quality of Postoperative analgesia by intrathecal morphine. Anesth Analg 1996;82:1192– 6.
10. Parlow JL, Begou G, Sagnard P, Cottet-Emard JM, Levron JC, Annat G, Cardiac baroreflex during the postoperative period in patients with hypertension: Effect of clonidine. Anesthesiology 1999; 90:681-92.
11. Ndiaye AL, Guyon F, *Knorr M*, Huch V, Veith M , Anorg Z. Adverse hemodynamic changes during LC and their possible suppression with clonidine premedication. comparison with intrvenuos intravascular premedication Rozal chir 1999:78(6):286-91.
12. DeBoer RW, Karemaker JM, Strackee J. Hemodynamic fluctuationsand baroreflex sensitivity in humans: a beat-to-beatmodel. Am J Physiol 1987: 253: 608—609.
13. Imai Y, Muammoto T, Murakami K, Sakai T, Kirita T, Sugimura M et al. The effects of preanesthetic oral clonidine on total requirement of propofol for general anesthesia. J. clin anesthesia 1998;10:660-665.
14. Richards MJ, Skues MA, Jarvis AP, Prys-Roberts C. Total i.v. anaesthesia with propofol and alfentanil: dose requirements for propofol and the effect of premedication with clonidine. Br JAnaesth 1990;65:157–63.