EFFECT OF ORAL CLONIDINE PREMEDICATION ON HEMODYNAMIC STRESS RESPONSE TO LARYNGOSCOPY AND TRACHEAL INTUBATION

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ABSTRACT

Introduction

Different techniques have been tried to blunt undesirable hemodynamic effects like tachycardia, hypertension and dysarrhythmias during and after laryngoscopy and tracheal intubation.

Objective

To find out the effect of oral clonidine premedication on hemodynamic stress response to laryngoscopy and tracheal intubation.

Methodology

It was a prospective, randomized, double-blind comparative study conducted in patients undergoing laparoscopic cholecystectomy. Either oral clonidine 300 mcg (n=30) or placebo (n=30) was given one hour before the surgery. Depth of anesthesia was monitored and maintained at 40-60 level using bispectral index (BIS) monitor. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MABP) and oxygen saturation (SpO_2) at baseline, one hour after premedication, on operation theatre (OT) table, just before and after one, two and five minutes after laryngoscopy and intubation were compared in Clonidine and placebo group using Paired t test and Chi-square test. SPSS was used for statistical analysis at P-value<0.05

Result

Hemodynamic variables like HR, SBP, DBP and MBP were significantly lower in the clonidine group compared to placebo just before and after the first five minutes of laryngoscopy and tracheal intubation (P<0.05). Propofol requirement for induction of anesthesia was less in the clonidine group (95±31.8 mg vs 75.3±28.5 mg, p=0.014) compared to the placebo group. Adverse effects like hypotension and bradycardia were comparable in the groups. Time taken for extubation, time to follow verbal commands and time to orientation after surgery were similar in the both groups (P>0.05).

Conclusion

Oral clonidine premedication was effective in blunting undesirable hemodynamic stress response to laryngoscopy and tracheal intubation compared to the placebo.

KEYWORDS

Clonidine, Hypertension, Intubation, Laryngoscopy, Tachycardia

INTRODUCTION

Direct laryngoscopy and tracheal intubation are noxious stimuli that can result in surge of catecholamines and provoke adverse responses in the cardiovascular systems that includes tachycardia, hypertension and dysrhythmias.[1-5] These hemodynamic changes are transitory, variable, unpredictable and are usually well tolerated by healthy individuals; however, they are undesirable in patients with coronary artery disease, systemic hypertension, myocardial insufficiency and intracranial hypertension.[6-8] These changes in such patients can lead to development of intraoperative myocardial infarction, acute left ventricular failure and pulmonary edema, dysrhythmias and cerebrovascular accidents.[9]

Many techniques have been tried to attenuate these adverse hemodynamic responses to the direct laryngoscopy and tracheal intubation; but so far, none is ideal. There are very few studies on different doses of oral clonidine premedication on hemodynamic response to tracheal intubation with conflicting results.[10,11] None of the studies have used bispectral index (BIS) monitor to guide the adequate depth of anesthesia during laryngoscopy and tracheal intubation. The objectives of the study were (a) to find out the effect of oral clonidine premedication on hemodynamic response to laryngoscopy and tracheal intubation guided with BIS monitor and (b) to investigate the adverse effects of oral clonidine premedication.

METHODOLOGY

A prospective, double-blinded, randomized comparative study was conducted at routine operation theatre of B.P. Koirala institute of Health Sciences (BPKIHS) in patients undergoing laparoscopic cholecystectomy under total intravenous general anesthesia during January-December, 2018. According to previous study conducted by Singh and Arora 2011, mean (x_1, x_2) and standard deviation (SD_1, SD_2) of mean arterial blood pressure in cases and controls were 101.9, 10.4 and 114.8, 14.08 respectively.[10] At probability of power 95%, alpha error of 5% and 20% drop out the follow up, a sample size of 30 patients in each group was calculated using STATA 11 software (Stata Corp., College Station, TX).

Symptomatic gall stone disease patients 18-60 years of age with American Association of Anaesthesiology Physical Status (ASA PS) I and II and the disease diagnosed by ultrasonography and scheduled for laparoscopic cholecystectomy were enrolled.[12] Exclusion criteria were patient refusal to participate in the study, airway abnormalities and expected difficult intubation, intubation time > 30 seconds, known allergy to clonidine, severe sinus bradycardia (<50 beats per minute) or sick-sinus syndrome, second and third-degree atrioventricular (AV) block, severe hypotension (systolic blood pressure < 90 mm Hg), shock and severe hepatic, renal, endocrine and cardiac impairment. The consecutive patients undergoing laparoscopic cholecystectomy under general anesthesia were enrolled.

A self-designed proforma was used to collect the relevant data. It consisted of age, sex, weight, ASA PS, duration of surgery, time to laryngoscopy and intubation, induction dose of propofol, hemodynamic parameters [heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MABP)], time to tracheal extubation, time to follow commands, time to orientation and cardiovascular adverse effects (arrhythmia, hypotension, hypertension, bradycardia). Ethical clearance of the study was obtained by the Institutional Review Committee, BPKIHS (IRC/466/015).

After an overnight fasting, the patients were explained about the study objectives and written informed consent was obtained. Then, they were randomly allocated to either group A or group B by opening the sequentially numbered white opaque sealed envelope which were opened 30 minutes before the premedication. Patients in group A received Pantoprazole 40mg and patients in group B received Clonidine 300 microgram with 20ml of water as premedication 60 minutes before the estimated anesthesia induction time. Peripheral venous access was secured with 18G intravenous cannula. Then, patients were shifted to the operation table. Before the induction of anesthesia, routine monitoring (ECG, non-invasive blood pressure and pulse oximetry) were started. The level of anesthesia was monitored with BIS. The BIS electrodes were placed on the forehead and connected to BIS monitoring system. 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/hr. Time and dose of Propofol infused for loss of verbal command were recorded. After confirming successful ventilation, intravenous 0.1 mg/kg of Vecuronium bromide was administered. The tracheal intubation was performed after 3 minute of intravenous Vecuronium administration. After confirming endotracheal intubation by auscultation and capnography, endotracheal tube was secured and attached to the anesthesia machine. The anesthesia was maintained with oxygen and Propofol infusion was adjusted to achieve a target BIS between 40 and 60. Vitals (heart rate, noninvasive arterial blood pressure and arterial oxygen saturation) were recorded at baseline, 60 minutes after premedication, just before tracheal intubation and after endotracheal intubation at interval of one, two, and five minutes and then every five minutes onwards till one minute after extubation of tracheal tube. End-tidal concentration of Carbondiaxide ($EtCO_2$) was recorded after intubation and at above intervals and was maintained between 30-40 mmHg by controlled mechanical ventilation.

After closure of the skin incision, Propofol infusion was stopped and this time was considered as a reference point for calculation of time to tracheal extubation, time to response to verbal commands and orientation time. Residual neuromuscular blockade was reversed with injection of neostigmine 0.05mg/kg and injection Glycopyrolate 0.01mg/kg and tracheal extubation was performed. At the end of the propofol infusion, the following times were recorded: (i) time to tracheal extubation; (ii) time to response to verbal commands

(spontaneous eye opening); (iii) orientation time (for the patient to give their name, date of birth and location).

The data were entered in Microsoft Excel 2010. Descriptive statistics like mean, standard deviation, frequency and percentage were calculated. As the data followed the normality, Analysis of variances and Independent paired t test were used to compare the mean between more than two groups and to compare the mean values between two groups respectively. Paired t test was used to compare the mean values before and after the study drug administration within the same group. Chi-square test was used to compare the categorical variables. All statistical analysis were conducted using Statistical Package of Social Sciences (version 17.0) at P-value < 0.05.

RESULTS

The patients in the two study groups were similar to each other with regards to age, sex, weight, ASA PS and duration of surgery as shown in Table 1.

Table 1: Age, sex, weight, ASA PS and Duration of Surgery in the control and Clonidine group

Variables	Control (mean±SD)	Clonidine (mean±SD)	P-value
Age (year)	34.2 ± 9.8	39.4 ± 12.2	0.071
Sex (M:F)	4:26	5:25	0.72
Weight (Kg)	61.1 ± 13.9	62.4 ± 10.9	0.681
ASA PS (I:II)	26:4	25:5	0.72
Duration of surgery (min)	51.8 ± 19.9	58 ± 22.2	0.262

Time taken for laryngoscopy and tracheal intubation was lower in the control group; however, it was statistically not significant (P-value>0.05) (Table 2). The induction dose of Propofol was significantly lower in the Clonidine group than the control group (P-value<0.05) (Table 2).

Table 2: Time taken for laryngoscopy and tracheal intubation and mean induction dose of Propofol in the control and Clonidine group

Variable	Control (n=30)	Clonidine (n=30)	P-value
Time to laryngoscopy and tracheal intubation (seconds)	8.5 ± 2.64	9.13 ± 3.49	0.432
Induction dose of Propofol (mg)	95 ± 31.81	75.33 ± 28.49	0.014*

*Statistically significant at P-value less than 0.05; Values are expressed as mean ± SD.

Hemodynamic parameters at different point of time in the control and Clonidine group are shown in Table 3. Heart rate was significantly lower in the clonidine group after premedication, just before intubation and after tracheal intubation at 1, 2 and 5 minutes (P-value<0.05). Systolic blood pressure (SBP) was significantly lower in the clonidine group after premedication, on OT table and after tracheal intubation at intervals of 1, 2 and 5 minutes (P-value<0.05). Similarly mean DBP was significantly lower in the clonidine group as compared to the control group after premedication, on OT table, pre-intubation and after tracheal intubation at intervals of 1, 2 and 5 minutes (P-value<0.05). MAP was significantly lower in the clonidine group as compared to the control group at all mentioned point of time (P-value<0.05) (Table 3).

Table 3: Hemodynamic parameters at different point of time in the control and Clonidine group

Hemodynamic parameters		Control (n=30)	Clonidine (n=30)	P-value
Heart rate (Mean±SD)	Baseline	78.63 ± 10.93	79.6 ± 10.09	0.72
	After premedication	81.00 ± 11.04	72.3 ± 9.64	0.002*
	OT table	81.03 ± 14.13	74.3 ± 12.4	0.05
	Pre-intubation	73.27 ± 13.74	64.57 ± 10.24	0.007*
	1 min after intubation	86.67 ± 16.48	76.9 ± 11.62	0.009*
	2 min after intubation	83.2 ± 13.82	73.33 ± 11.54	0.004*
	5 min after intubation	80.6 ± 12.99	70.33 ± 10.62	0.001*
Systolic blood pressure (Mean±SD)	Baseline	117.5 ± 15.46	119.8± 12.75	0.532
	After premedication	125.97 ± 18.38	111.27 ± 16.95	0.002*
	OT table	127.67 ± 17.56	117.17 ± 12.91	0.011*
	Pre-intubation	111.57 ± 15.08	105.87 ± 9.69	0.087
	1 min after intubation	139.03 ± 21.39	121.43 ± 18.29	0.001*
	2 min after intubation	133.27 ± 19.13	120.5 ± 16.25	0.007*
	5 min after intubation	127.9 ± 18.57	111.1 ± 13.69	0.006*
Diastolic blood pressure (Mean±SD)	Baseline	77.67 ± 11.41	74.97 ± 7.56	0.284
	After premedication	79.5 ± 11.55	70.67 ± 8.1	0.001*
	OT table	82.5 ± 11.5	70.07 ± 9.66	0.009*
	Pre-intubation	70.5 ± 12.24	64.9 ± 9.14	0.049*
	1 min after intubation	95.53 ± 18.41	80.03 ± 13.91	0.001*
	2 min after intubation	87.47 ± 14.35	77.00 ± 11.87	0.003*
	5 min after intubation	83.8 ± 11.5	75.43 ± 9.96	0.004*
Mean arterial blood pressure (Mean±SD)	Baseline	91.33 ± 14.00	88.47 ± 10.82	0.379
	After premedication	96.7 ± 14.68	85.27 ± 11.61	0.001*
	OT table	100.97 ± 13.51	91.87 ± 9.88	0.004*
	Pre-intubation	87.37 ± 12.56	79.37 ± 10.53	0.023*
	1 min after intubation	113.93 ± 19.2	97.43 ± 16.08	0.001*
	2 min after intubation	106.27 ± 15.34	95.23 ± 13.27	0.004*
	5 min after intubation	111.17 ± 12.83	92.57 ± 11.33	0.008*

*Statistically significant at P-value less than 0.05; Values are expressed as mean ± SD.

Mean HR, SBP, DBP and MAP were lower in the clonidine group; however, only HR was statistically significant (P-value<0.05) (Table 4).

Table 4: Post-tracheal extubation haemodynamic in control and Clonidine group

Variables	Control (mean±SD)	Clonidine (mean±SD)	P-value
HR (bpm)	84.23±16.3	80.53± 11.7	0.318*
SBP (mm Hg)	137.8±12.8	131.6± 11.6	0.055
DBP (mm Hg)	90.9± 10.3	82.5± 8.1	0.001
MAP (mmHg)	108.5± 12.8	101.9± 10.2	0.03

*Statistically significant at P-value less than 0.05; Values are expressed as mean ± SD.

Time taken to extubation, time to follow commands and time taken for full orientation after stoppage of Propofol infusion were lower in the control group; however, they were not significant (P-value>0.05) (Table 5).

Table 5: Time to tracheal extubation, time to follow commands and time to orientation in control and Clonidine group

Variables	Control (n=30)	Clonidine (n=30)	P-value
Time to tracheal extubation (min)	8.3 ± 4.08	9.03 ± 5.45	0.882
Time to follow commands (min)	9.13 ± 4.023	9.47 ± 5.18	1.00
Time to orientation (min)	13.33 ± 9.65	13.77 ± 7.54	0.635

Values are expressed as mean ± SD.

Hypotension and hypertension were more common in the control group whereas bradycardia was more common in the Clonidine group; however, it was statistically not significant (P-value>0.05). Arrhythmia was not observed in any group of the patients (Table 6).

Table 6: Cardiovascular adverse effects in control and Clonidine group

Adverse effects	Control (n=30)		Clonidine (n=30)		P-value
	n	%	n	%	
Arrhythmia	0	0	0	0	-
Hypotension	2	6.67	1	3.33	0.55
Hypertension	2	6.67	0	0	0.15
Bradycardia	2	6.67	3	10.0	0.50

DISCUSSION

Clonidine, being an alpha-2 adrenoreceptor agonist, exerts central sympatholytic effect.[13] Premedication with clonidine blunts the stress response to surgical stimuli, reduces the narcotic and anaesthetic doses, increases cardiac baroreceptor reflex sensitivity to increase in systolic blood pressure and thus stabilises blood pressure.[14] Due to these characteristics, clonidine might be useful in the anaesthetic management of patients undergoing laparoscopic surgeries. The findings of present study has supported use of clonidine in anaesthesia. It was interesting to find out that when oral clonidine was given as a premedication 60 minutes before the anaesthesia induction time, the dose of propofol for the induction of anaesthesia was significantly reduced. Titration of propofol with BIS monitoring during induction of anaesthesia decreased propofol use significantly. These findings indicated that the use of BIS monitoring may be valuable in guiding the administration of propofol for induction as well as maintenance of anaesthesia.[15,16] Gan et al had also showed that the BIS may be used to measure the pharmacodynamic effect of propofol and thereby facilitate its titration to improve recovery from anaesthesia. In their study group wherein BIS was not used, patients were consistently administered more propofol throughout the anaesthetic period.[16] Similarly Fehr et al also documented that clonidine decreased propofol requirements by 20% during anaesthesia based on BIS monitoring.[15] In another study by Agrawal et al, oral clonidine premedication led to reduction in the induction dosage of propofol.[17] Therefore, increase in anaesthetic depth given by clonidine premedication can be measured with bispectral EEG analysis that allows reducing propofol dose to achieve a specific depth of anaesthesia.

In the present study, oral clonidine 300 mcg was more effective in attenuating the haemodynamic response to laryngoscopy and tracheal intubation as compared to placebo which was in accordance with other studies.[18, 19] Hypotension and bradycardia were encountered with clonidine premedication in the present study which was similar to other reports.[20, 21] The study has some limitations. Variability in the laryngoscopy and tracheal intubation skill of anaesthesiologists, blood level of clonidine and stress hormone were not measured due to lack of facility and oral clonidine was not given according to the body weight due to lack of drug preparation. Being a single-center study, the findings may not be generalized.

CONCLUSION

Oral administration of a single dose of Clonidine 300 mcg as a premedication prior to the induction of general anaesthesia along with BIS monitoring helped attenuate the hemodynamic stress response following laryngoscopy and endotracheal intubation as compared to the placebo. It also reduced the induction dose of Propofol and thus reduces the cost of anaesthesia. BIS monitoring can be used in guiding the administration of Propofol for the induction as well as maintenance of general anaesthesia. Clonidine 300 mcg was also safe as it did not lead to serious perioperative adverse effects.

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CONFLICT OF INTEREST

No conflict of interest

FINANCIAL DISCLOSURE

None declared

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