Effects of intravenous clonidine on haemodynamics and on plasma cortisol level during laparoscopic cholecystectomies

INTRODUCTION

Both mechanical and neurohumoral factors contribute to the haemodynamic changes induced by carbon dioxide pneumoperitonium (PNP). Several mediators have been proposed.[1] Clonidine is a α-2 adrenoreceptor agonist and has been shown to reduce perioperative haemodynamic instability during laparoscopic surgeries. Other investigators have suggested a possible effect of clonidine in controlling excessive stress responses during surgical procedures.[2,3] In the present study, the effects of intravenous administration of clonidine on sympathetic and hormonal responses were investigated in patients undergoing elective laparoscopic cholecystectomy.

The aim of this study was to investigate the effects of intravenously (IV) administered 3 μg/kg clonidine as pre-anaesthetic medication on haemodynamics and plasma cortisol levels which is one of the markers of the stress response.

METHODS

After the approval by the Institutional Ethical

Committee, and written informed consent, 60 patients were enrolled for the study. In this prospective, comparative, 2-Arm (Group), double-blind controlled study, 60 American Society of Anaesthesiologists grades I and II adult patients of either sex aged 20-60 years, scheduled to undergo laparoscopic cholecystectomy were recruited. Exclusion criteria were lack of patient consent, bronchial asthma, patients suffering from hypertension, diabetes mellitus severe coronary insufficiency, recent myocardial infarction and concomitant use of monoamine oxidase inhibitors.

Patients were pre-medicated with injection midazolam 0.04 mg/kg and 0.004 μg of glycopyrrolate IV. All patients were pre-hydrated with 500 ml of lactated Ringer solution and were assigned to one of the two groups by closed envelope method, Group C (clonidine 3 μg/kg in 20 ml), and Group P (placebo - 20 ml normal saline). The observer was totally blinded to the groups or medications received by the patients. Pre-operative baseline readings of heart rate (HR) and mean arterial pressure (MAP) were noted. Loading dose of test drug diluted in 20 ml of normal saline or placebo, 20 ml of normal saline were administered IV. Thirty minutes after the end of the infusion of the test drug, anaesthesia was induced with titrating doses of 2.5% thiopentone sodium 5 mg/kg and intubated by a senior anaesthesiologist using vecuronium 0.1 mg/kg. Anaesthesia was maintained with 33% of oxygen in nitrous oxide, isoflurane and vecuronium. Injection fentanyl 1-2 μg/kg and injection paracetamol 1 g IV were used as analgesics. Ventilator parameters were adjusted to maintain end-tidal carbon dioxide level between 30 and 40 mm Hg. After carbon dioxide PNP, patients were positioned in 15° reverse Trendelenburg position. Intra-abdominal pressure was maintained around 15 mm Hg during the surgery. Throughout the procedure, any rise in the MAP > 20% from the baseline (MAP > 110) was treated with 0.5-5 μg/kg/min of nitroglycerine drip. If bradycardia occurred, it was treated with an injection atropine. Hypotension (MAP < 60 mm Hg) was managed with fluid challenges and/or IV mephentermine 6 mg bolus. At the end of surgery residual neuromuscular block was reversed with injection neostigmine 50 μg/kg and injection glycopyrrolate 10 μg/kg IV. After extubation patients were monitored in the post-anaesthesia care area.

Heart rate, MAP, were recorded at 1, 5 and 20 min after giving the test drug; 1, 3 and 5 min after intubation; 15 and 30 min after PNP and at 10 and15 min after release of carbon dioxide from the abdomen. After extubation, the same parameters were recorded at 10 min. Blood samples were drawn into pre-chilled K2-ethylenediaminetetraacetate tubes before induction of general anaesthesia (T1), 5 min (T2), 15 min (T3) after the beginning of laparoscopy and 1 h (T4) after the procedure. Blood samples were centrifuged, and plasma stored at −70°C. Cortisol analysis was carried out by Cobas e 411 Fully automated, immunoassay analyzer for random access processing of ECL-based immunoassays (Roche Diagnostics, USA). The statistical software, S 9.2, R environment ver. 2.11.1 were used for the analysis of the data. Haemodynamic variables were represented by mean ± S.D. Statistical significance in mean difference was done by using analysis of variance (ANOVA), student *t*' and Chi square tests as appropriate. A $P < 0.05$ was considered statistically significant.

RESULTS

Demographic profile of 60 patients was compared among the two groups of patients, and no significant difference was found [Table 1]. Mean HR varied from 71.91 ± 4.95 to 99.88 ± 2.83 bpm in Group P. In Group C, it varied from 63.78 ± 1.07 to 86.38 ± 6.28 bpm [Table 2]. Similarly, rise in MAP (106.85 ± 8.36 vs. 86.00 ± 0.57 mm Hg) was more in Group P 15 min following PNP and after intubation (109.26 ± 10.93 vs. 76.84 ± 4.32). Incidence of intraoperative hypertension was 34.3% in Group P (11 patients) that required treatment with IV infusion of 0.5 μg/kg/min injection nitroglycerine.

In our study, plasma cortisol levels were increased to a large extent after PNP and 2-3 times at the end of surgery in the control Group P compared with clonidine Group C [Table 2]. In our study, differences in plasma cortisol level in two groups (P and C) were statistically significant at all-time intervals.

DISCUSSION

Even after maintaining normocapnia and keeping intra-abdominal pressure below 15 mm Hg, a significant

Table 1: Demographic data given as mean±SD

	Group P	Group C	*P* value
Age in (years)	33.84±4.40	33.94±5.08	0.937
Weight (kgs)	57.69±6.39	57.66±5.46	0.983
Height (cms)	162.08±3.82	163.8±3.42	0.874
Sex (m:f)	10:20	11:19	0.5

SD: Standard deviation

Table 2: Comparison of MAP (mmHg) , HR (Beats/mt) and plasma cortisol(μg/dl) in two groups of patients studied

Time interval	(I) MAP (mmHg)		*P* value	(II) HR Beats/mt		*P* value	(III) Cortisol (μg/dl)		*P* value
Time (mts)	Group C (*n*=30)	Group P (*n*=30)		HR in Group C (*n*=30)	HR in Group P (*n*=30)		Group C *N*=30	Group P *N*=30	
Pre-op	101.91±5.77	99.81±5.12	0.13	79.59±5.59	84.38±5.94	0.457	4.58±0.63	6.08±1.63	*t*=4.954; *P*<0.001**
1 minute	92.22±1.58	92.91±3.99	0.369	74.72±5.75	78.41±5.91	0.014*			
5 minutes	88.44±3.51	91.85±4.35	0.001**	67.84±2.3	71.91±4.95	<0.001**			
20 minutes	72.91±3.74	89.17±10.48	<0.001**	63.78±1.07	74.63±7.61	<0.001**			
ETT 1	76.84±4.32	109.26±10.93	<0.001**	86.38±6.28	96.88±6.22	<0.001**	7.14±1.04	13.76±3.13	*F*=98.848; *P*<0.001**
ETT 3	81.19±4.84	100.36±8.70	<0.001**	74.22±1.07	86.22±8.13	<0.001**			
ETT 5	77.72±4.93	93.55±8.33	<0.001**	74.94±0.56	82.19±4.72	<0.001**			
B pneuma	74.06±4.48	88.81±9.58	<0.001**	74.91±0.39	80.81±6.69	<0.001**			
15 pneumo	86.00±0.57	106.85±8.36	<0.001**	74.25±1.11	99.88±2.83	<0.001**			
30 pneumo	86.47±1.46	100.02±6.91	<0.001**	75.72±1.59	92.13±3.47	<0.001**	11.14±4.14	19.64±3.35	*F*=63.080; *P*<0.001**
Exsufflati 10	78.63±3.26	88.75±8.09	<0.001**	68.00±5.30	83.66±4.37	<0.001**			
Exsufflati 15	79.50±3.57	83.77±6.51	0.002**	70.28±5.59	77.19±2.89	<0.001**			
After extb 10	104.81±3.13	103.28±5.47	0.174	85.90±6.33	93.41±4.87	<0.001**	16.73±5.52	29.92±6.29	*F*=63.863; *P*<0.001**

MAP: Mean arterial pressure, HR: Heart rate

rise in HR , and MAP was noticed in Group P compared to Group C. Clonidine decreases sympathetic tone centrally, inhibits norepinephrine pre-synaptically and also has the vagomimetic action at nucleus tractus solitarius.[1-4] These actions can also cause bradycardia.[5] Bradycardia was however not observed in both the treatments groups in our study. The general anaesthesia protocol chosen for this study provided a sufficient depth and prevented the adrenergic and cardiovascular response to incision. Hence, 3 μg/kg of IV clonidine premedication was useful in maintaining haemodynamic stability during laparoscopic cholecystectomy.

Clonidine acts on central α-adrenoreceptors and decreases plasma concentrations of cortisol and adrenocorticotropic hormone in healthy adults.[6] Masala *et al*. reported that IV drip administration of clonidine suppressed the responses of sympathetic systems and the elevation of plasma cortisol concentration in surgery for chronic sinusitis.[7] However, other studies showed that administration of clonidine depressed the responses of sympathetic systems, but could not blunt the elevation of plasma cortisol concentration in pelvic[8] and breast[9] surgery. Yotsui stated that considering past studies, administration of clonidine cannot inhibit the responses of the hypothalamic-pituitary-adrenal (HPA) axis to surgical stress, except in minor surgery.[10] Joris *et al*. used 8 μg/kg of clonidine, which significantly reduced the concentration of catecholamine but not vasopressin and plasma cortisol concentration.[1] Difference in species, route of administration, time intervals and doses may explain these discrepancies.

In our study, plasma cortisol level was increased to a large extent after PNP and 2-3 times at the end of surgery in the control group compared with clonidine group. The peak cortisol response reflects the surgical stress response and clonidine can attenuate the responses of the HPA axis to surgical stress.One drawback of this study was our inability to assess the plasma catecholamine levels.

CONCLUSION

Clonidine at a dose of 3 μg/kg administered IV before peritoneal insufflation with carbon dioxide attenuated the haemodynamic changes by reducing hormonal stress response and plasma cortisol concentration.

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