J Anesth (2001) 15:78–82

Journal of
Anesthesia

Clonidine premedication prevents sympathetic hyperactivity but does not prevent hypothalamo-pituitary-adrenocortical responses in patients undergoing laparoscopic cholecystectomy

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Abstract
Purpose. The effects of oral administration of clonidine on sympathetic and endocrinological responses were investigated in patients undergoing elective laparoscopic cholecystectomy.
Methods. Twenty adult patients were allocated randomly to the clonidine group ($n = 10$) or the control group ($n = 10$). The control and clonidine groups received placebo on clonidine 4μg·kg^{-1} orally 2 h before the induction of anesthesia. All patients underwent laparoscopic cholecystectomy under isoflurane anesthesia. The hemodynamic variables were observed perioperatively. Plasma concentrations of cortisol, ACTH, noradrenaline, adrenaline, and dopamine were determined before administration of clonidine or placebo, 2 h after the beginning of the operation, and 3 h after the end of the operation.
Results. Systolic and diastolic blood pressures were lower in the clonidine group than in the control group immediately after endotracheal intubation and extubation ($P < 0.05$). Patients in the clonidine group showed lower plasma concentrations of noradrenaline 2 h after the beginning of the operation than patients in the control group ($P < 0.01$). However, the plasma concentrations of the other hormones did not differ between groups.
Conclusion. Clonidine premedication prevents sympathetic hyperactivity but does not suppress hypothalamo-pituitary-adrenocortical responses in patients undergoing laparoscopic cholecystectomy.

Key words Clonidine · Laparoscopic cholecystectomy · Cortisol · ACTH · Noradrenaline

Introduction

Clonidine, an α_2-selective adrenergic agonist, causes hypotension, sedation, and bradycardia. Preliminary evidence suggests that clonidine may be useful in patients undergoing anesthesia, because it may decrease the requirement for anesthetic agents and provide hemodynamic stability [1]. Other potential benefits of clonidine in anesthesia include sedation and anxiolysis [2], drying of secretions [3], and analgesia [4]. Other investigators have suggested a possible effect of clonidine in controlling excessive stress responses during surgical procedures [5–9]. In the present study, we investigated the effects of clonidine on sympathetic activities and hypothalamo-pituitary-adrenocortical (H-P-A) axis responses to surgical stress in patients undergoing laparoscopic cholecystectomy.

Received: June 6, 2000 / Accepted: December 11, 2000

Materials and methods

After approval from the local Ethics Committee and informed consent from the patients had been obtained, 20 adult patients, ASA class I or II, scheduled for laparoscopic cholecystectomy were included in this study. Patients who had cardiovascular or endocrine diseases were excluded. Patients were allocated randomly to the control group ($n = 10$) or the clonidine group ($n = 10$). The control and clonidine groups received placebo or clonidine 4μg·kg^{-1} orally 2 h before the induction of anesthesia. A clonidine tablet was crushed into pieces and weighed. Anesthesia was induced with propofol 2mg·kg^{-1} intravenously. Vecuronium 0.1mg·kg^{-1} was then administered, and endotracheal intubation was performed. The patient's lungs were mechanically ventilated, and anesthesia was maintained with nitrous oxide, oxygen, and isoflurane. End-tidal CO_2 was maintained within 35–40 mmHg. The concentration of isoflurane was adapted to maintain hemodynamic stability by an experienced anesthesiologist (the author) throughout anesthesia; the changes in mean blood pressure were maintained within ±20% of that before administration of clonidine. Blood specimens were withdrawn before administration of clonidine or placebo, 2 h after the beginning of the op-

eration, and 3 h after the end of the operation. The plasma concentrations of cortisol, ACTH, noradrenaline, adrenaline, and dopamine were determined. Systolic and diastolic blood pressure (BP) and heart rate (HR) were measured before administration of clonidine or placebo, at the time of entrance into the operating room, immediately after endotracheal intubation, 30 min after the beginning of the operation, and immediately and 20 min after tracheal extubation. In the operating room, BP, HR, and end-tidal concentrations of CO_2 and isoflurane were measured with Sola 7000 (Marquet Electronics Company, Madison, WI, USA).

The plasma concentration of cortisol was measured with a Gamma Coat Cortisol kit (Dade Behring, Tokyo, Japan), ACTH with an Allegro ACTH kit (Nihon Mediphysics, Hyogo, Japan), and noradrenaline, adrenaline, and dopamine with a complete automatic catecholamine analysis meter (HCL-8030, Tosoh, Tokyo, Japan).

Statistical analysis was performed by Statview. Values are shown as means ± SD. Differences within groups were analyzed by repeated-measures analysis of variance and Bonferroni/Dunn as post hoc test, and differences between groups by the Mann-Whitney U test. $P < 0.05$ was accepted as significant.

Results

The patients in the two groups were similar with respect to mean age, body weight, duration of surgery and anesthesia, fluid administration, and diuresis. The concentration of isoflurane was significantly lower in the clonidine group (1.27 ± 0.35%) than in the control group (1.82 ± 0.42%)($P < 0.01$), but there were no significant differences in minimum alveolar concentration (MAC)·h (Table 1).

The plasma concentration of noradrenaline was lower in the clonidine group than in the control group 2 h after the beginning of the operation (Table 2) ($P < 0.01$). There were no significant differences between the two groups at any time in plasma concentrations of cortisol, ACTH, adrenaline, or dopamine. The plasma concentrations of cortisol, ACTH, noradrenaline, adrenaline, and dopamine were significantly elevated 2 h after the beginning of the operation as compared with those before administration of clonidine or placebo in both groups, except plasma concentration of noradrenaline in the clonidine group. The plasma concentration of cortisol was higher 3 h after the end of the operation than before administration of clonidine or placebo in both groups (Table 2).

Table 1. Patient data

Characteristic	Control group	Clonidine group
No. of patients (male/female)	10 (5/5)	10 (5/5)
Age (yr)	51.3 ± 13.8	48.4 ± 10.3
Weight (kg)	63.5 ± 13.8	59.8 ± 5.3
Operation time (min)	144.5 ± 49.0	131.9 ± 40.9
Anesthesia time (min)	201.5 ± 52.1	195.8 ± 43.0
Urine volume ($ml \cdot kg^{-1} \cdot h^{-1}$)	0.49 ± 0.41	0.65 ± 0.32
Fluid administration ($ml \cdot kg^{-1} \cdot h^{-1}$)	7.3 ± 3.0	8.4 ± 1.8
Concentration of isoflurane (%)	1.82 ± 0.42	1.27 ± 0.35**
MAC·h of isoflurane	3.47 ± 1.63	2.49 ± 1.36

Concentrations of isoflurane were significantly lower in the clonidine group, but there were no significant differences with regard to minimum alveolar concentration (MAC)·h
** $P < 0.01$ versus control group. Values are shown as means ± SD

Table 2. Changes in hormone levels

Hormone	Group	Before administration of clonidine or placebo	2 h after the beginning of the operation	3 h after the end of the operation
Cortisol ($\mu g \cdot dl^{-1}$)	Control	7.85 ± 5.2	25.93 ± 3.5††	18.91 ± 5.9††
	Clonidine	8.12 ± 3.2	24.33 ± 7.1††	15.86 ± 7.6††
ACTH ($pg \cdot ml^{-1}$)	Control	18.6 ± 7.3	349 ± 178.9††	41.8 ± 43.3
	Clonidine	23.2 ± 7.2	413 ± 292.7††	42.6 ± 37.9
Noradrenaline ($pg \cdot ml^{-1}$)	Control	220.8 ± 70.2	376.4 ± 214.7†	201.4 ± 108.3
	Clonidine	235.9 ± 105.2	186.6 ± 77.9**	185.0 ± 68.2
Adrenaline ($pg \cdot ml^{-1}$)	Control	31.1 ± 14.2	62.2 ± 52.1††	48.3 ± 25.2
	Clonidine	25.9 ± 10.7	44.5 ± 27.9††	40.7 ± 33.8
Dopamine ($pg \cdot ml^{-1}$)	Control	10.6 ± 5.0	27.5 ± 10.2††	13.6 ± 8.1
	Clonidine	12.5 ± 3.4	28.3 ± 8.8††	12.4 ± 4.2

† $P < 0.05$ †† $P < 0.01$ compared with values before administration of clonidine or placebo within groups
** $P < 0.01$ versus control group. Values are shown as means ± SD

There were no significant differences in HR between the two groups at any time. HR values were significantly higher immediately after endotracheal intubation and extubation, and 30 min after the beginning of the operation, compared with those before administration of the placebo in the control group ($P < 0.01$). There were no significant differences over time in the clonidine group. Systolic and diastolic BPs were significantly lower in the clonidine group than in the control group at the time of entrance into the operating room ($P < 0.01$), immediately after endotracheal intubation and extubation, and 20 min after extubation (systolic, $P < 0.01$; diastolic, $P < 0.05$) (Fig. 1).

Discussion

Systolic and diastolic blood pressures were lower in the clonidine group than in the control group immediately after endotracheal intubation and extubation ($P < 0.05$). Patients in the clonidine group showed lower concentrations of plasma noradrenaline 2 h after the beginning of the operation than patients in the control group ($P < 0.01$). However, the plasma concentrations of the other hormones did not differ between groups.

The physiologic responses of patients who undergo surgical invasion are known to appear through autonomic, hormonal, and local cell systems [9–13]. Catecholamines are under autonomic nervous system control, and the plasma noradrenaline level reflects the sympathetic discharges being liberated from mammalian postganglionic nerves. The endocrine responses are primarily under H-P-A axis control, releasing ACTH, cortisol, and so on [10,11]. Glaser et al. reported marked elevations of plasma adrenaline and noradrenaline concentrations during laparoscopic cholecystectomy [12]. In the present study, significant elevations were observed in plasma cortisol, ACTH, adrenaline, noradrenaline, and dopamine concentrations in the control group during surgery, indicating fairly invasive stimulation by the operations.

α_2-Adrenoreceptors exist in the central sympathetic nervous system and sympathetic postganglionic nerves.

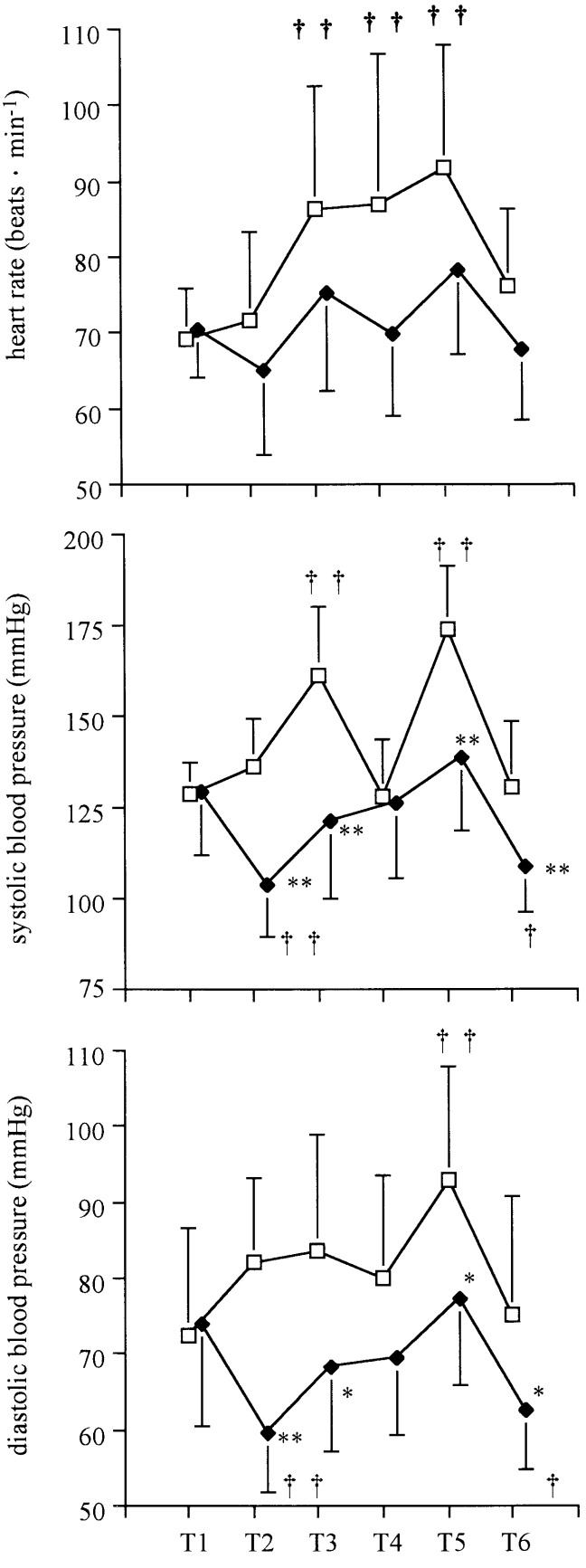

Fig. 1. Time course of heart rate, systolic blood pressure, and diastolic blood pressure. *T1*, Before administration of clonidine or placebo; *T2*, time of entrance into the operating room; *T3*, immediately after endotracheal intubation; *T4*, 3 min after the beginning of the operation; *T5*, immediately after extubation; *T6*, 20 min after extubation ** $P < 0.01$ * $P < 0.05$ versus control group. †† $P < 0.01$ † $P < 0.05$ versus T1 in each group. *Open squares*, control group; *closed diamonds*, clonidine group. Values are shown as means ± SD

We observed significantly lower levels of noradrenaline in the clonidine group. The results indicate a depressed activity of the sympathetic nervous system. Clonidine acts on central α_2-adrenoreceptors and decreases plasma concentrations of cortisol and ACTH in healthy adults [14]. Dorothee et al. showed that oral administration of clonidine suppressed the elevation of plasma cortisol concentration during the operation in patients undergoing neurosurgery [5]. Masala et al. reported that intravenous drip administration of clonidine suppressed the responses of sympathetic systems and the elevation of plasma cortisol concentration in surgery for chronic sinusitis [6]. 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 [7] and breast [8] surgery. In this study, the elevations of plasma concentrations of cortisol and ACTH were not inhibited. Considering past studies, it seems that administration of clonidine cannot inhibit the responses of the H-P-A axis to surgical stress, except in minor surgery.

In this study, blood specimens were not withdrawn after administration of clonidine or placebo before the operation because the author wanted to study the effect of clonidine on surgical stress, and for reasons of humanity and economy.

Although the bradycardic effect of α_2-adrenergic agonists is known [15], severe bradycardia requiring atropine was not observed in this study. Clonidine exerts a hypotensive action by affecting central α_2-adrenergic receptors [16]. In this study, oral administration of clonidine attenuated cardiovascular responses, such as HR, BP, and concentrations of noradrenaline, in laparoscopic cholecystectomy. Some anesthetic management agents can modulate these responses of hormones [17,18]. For instance, midazolam affects these responses [9,19,20]. The author used only inhalation anesthesia and did it more simply. Furthermore, clonidine has been known to decrease the MAC of isoflurane [21]. In this study, the concentration of isoflurane was significantly lower in the clonidine group, although there was no significant difference between the two groups in MAC·h.

In conclusion, oral administration of clonidine prevents sympathetic hyperactivity but does not suppress hypothalamo-pituitary-adrenocortical responses in patients undergoing laparoscopic cholecystectomy.

Acknowledgments. The author is greatly indebted to Professor Ryo Ogawa (Department of Anesthesiology, Nippon Medical School) for his support and advice related to this study. The author also wishes to thank Associate Professor Atsuhiro Sakamoto and other staff members (Department of Anesthesiology, Nippon Medical School) for their valuable suggestions.

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