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Oral clonidine premedication does not alter the efficacy of epidural test doses in adult patients anesthetized with isoflurane*

MAKOTO TANAKA[1,2], TOSHIAKI NISHIKAWA[2], SHINJI TAKAHASHI[1], and NAOKI MATSUMIYA[1]

[1]Department of Anesthesia / Critical Care Medicine, Tsuchiura Kyodo General Hospital, 11-7 Manabeshinnmachi, Tsuchiura, Ibaraki 300, Japan
[2]Department of Anesthesiology, Institute of Clinical Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305, Japan

Abstract: Clonidine premedication has been increasingly used in clinical anesthesia. Though clonidine was found to alter pressor responses to various sympathomimetics, its effect on epidural test dose efficacy to detect intravascular injection has never been evaluated. Eighty healthy patients were randomly assigned to one of four groups, each of which was anesthetized with 1% end-tidal isoflurane and 67% nitrous oxide in oxygen after endotracheal intubation. The control-epinephrine group (n = 20) given no clonidine premedication received 3 ml of 1.5% lidocaine with 15 μg epinephrine (1:200000) intravenously to simulate an intravenously administered epidural test dose. The control-saline group (n = 20) given no clonidine premedication received 3 ml of normal saline intravenously. The clonidine-epinephrine and clonidine-saline groups (n = 20 each) were identical to the control groups, but were premedicated with oral clonidine, approximately 5 μg·kg^{-1}, 90 min before induction of general anesthesia. Heart rate (HR) and systolic blood pressure (SBP) were measured by a blinded observer at 20-s intervals for 4 min after intravenous injections of the test dose or saline. Following intravenous test dose injection, there were no significant differences between the control-epinephrine and the clonidine-epinephrine groups in mean maximum increments of both HR (28 ± 3 *vs* 30 ± 3 bpm, [mean ± standard error], respectively) and SBP (46 ± 6 *vs* 45 ± 4 mmHg, respectively). Six patients in the control-epinephrine and 4 in the clonidine-epinephrine group developed negative HR responses (HR increment <20 bpm). Since HR and SBP were essentially unchanged in the two groups receiving saline, sensitivities (negative predictive values) based on the HR criterion (positive if ≥20 bpm increase in HR) were 80% and 70% (83% and 77%) with and without clonidine premedication, respectively (P > 0.05 between groups). However, when a modified HR criterion (positive if ≥10 bpm increase in HR) was used, sensitivities, specificities, and positive and negative predictive values were all 100% with or without clonidine. On the other hand, all of 20 patients in the control-epinephrine and the clonidine-epinephrine groups exhibited positive SBP responses (SBP increment ≥ 15 mmHg). Therefore, based on the SBP criterion, sensitivities, specificities, and positive and negative predictive values were all found to be 100% regardless of the presence of clonidine. We conclude that oral clonidine 5 μg·kg^{-1} premedication alters neither (a) hemodynamic responses to the intravenously administered epidural test dose containing 15 μg epinephrine, nor (b) the efficacy for detecting intravascular injection based on either criterion in adult patients under stable isoflurane anesthesia.

Key words: Epidural, Test dose, Clonidine

Introduction

Clonidine, a selective α_2-adrenergic agonist [1], is commonly used as an anesthetic adjuvant. It induces preoperative sedation, reduces the intraoperative anesthetic requirement, and potentiates the postoperative analgesic regimen [2]. Clonidine has been shown to augment the pressor effects of peripherally acting sympathomimetics such as ephedrine [3,4], norepinephrine [5], and phenylephrine [5]. Though the mechanism is not completely understood, the α-adrenoceptor-mediated vasoconstriction response to sympathomimetics appears to be enhanced in clonidine-treated patients [5]. If preoperative clonidine augments the hypertensive response to intravenous (IV) epinephrine by a similar mechanism, a greater increase in arterial blood pressure would in turn cause a greater degree of baroreflex-mediated slowing of heart rate (HR) counteracting the β-receptor-mediated tachycardic response, since arterial baroreflex sensitivity is not altered by clonidine in humans [6]. This may imply the inferior efficacy of epidural test doses containing epinephrine to

Address correspondence to: M. Tanaka at the Institute of Clinical Medicine, University of Tsukuba
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detect intravascular injection in clonidine-treated patients. However, the effects of clonidine premedication on hemodynamic responses to, and efficacy of, intravenously administered epidural test doses have never been addressed in the literature.

Continuous epidural analgesia is increasingly being used to reduce perioperative complications [7,8] as well as for preemptive analgesia [9]. General anesthesia with endotracheal intubation is frequently combined with epidural analgesia. Under these circumstances, accidental intravascular migration of the epidural catheter can only be detected by hemodynamic alterations by injecting an epidural test dose containing epinephrine. Therefore, the present prospective, randomized study was designed to determine the effects of oral clonidine premedication on hemodynamic response to and efficacy of intravenously injected test doses in adult patients under stable isoflurane anesthesia.

Materials and methods

The study protocol was approved by our Institutional Research Committee, and written informed consent was obtained from each patient. A total of 80 nonpregnant, ASA physical status I patients scheduled to undergo general anesthesia for elective surgery were studied. They were randomly assigned to one of four groups according to the combination of premedication and a study solution administered intravenously. The control-saline group ($n = 20$) received famotidine 20 mg orally 90 min before induction of general anesthesia, and was given 3 ml normal saline intravenously instead of an epidural test dose. The control-epinephrine group ($n = 20$) was identical to the control-saline group except that they received 1.5% lidocaine 3 ml with 15 μg epinephrine (1:200000) solution instead of normal saline. The clonidine-saline and clonidine-epinephrine groups ($n = 20$ each) were identical to the control groups, but received oral clonidine approximately 5 $\mu g \cdot kg^{-1}$ (Boehringer, Ingolsheim, Germany; each tablet contains 75 μg) in addition to famotidine as premedication.

Resting blood pressure (BP) and HR were measured noninvasively in the morning usually 1 day before surgery. On arrival at the operating room after 8 h fasting, preinduction BP and HR were obtained noninvasively. An arterial cannula was placed in the radial artery after local anesthetic infiltration. Lactated Ringer's solution was infused at a constant rate of approximately 15 $ml \cdot kg^{-1} \cdot h^{-1}$ throughout the study period. Following induction of general anesthesia with thiamylal 5 $mg \cdot kg^{-1}$ intravenously, endotracheal intubation was facilitated with vecuronium 0.2 $mg \cdot kg^{-1}$ intravenously. Anesthesia was then maintained with end-tidal 1% isoflurane and 67% nitrous oxide in oxygen, while ventilation was controlled using a tidal volume 10 $ml \cdot kg^{-1}$ and a respiratory rate 7–9 breaths·min^{-1} to maintain end-tidal carbon dioxide tension between 30 and 35 mmHg (5250 RGM, Ohmeda, Louisville, KY, USA). When the hemodynamic variables had stabilized for at least 5 min and a steady 1% end-tidal isoflurane concentration had been obtained (without changes in end-tidal isoflurane concentration at constant inspiratory concentration for 5 min), either normal saline or the epidural test dose was injected intravenously over 3 s. HR and systolic blood pressure (SBP) were recorded for 4 min after IV injections of the study drug, and maximum HR and SBP values were noted. Typically, we began hemodynamic measurements 25–30 min after anesthesia induction. The study solutions were prepared and coded by the hospital pharmacy using computer randomization. Investigators observing hemodynamic changes were blinded to the patients' treatment group. Upon completion of the study and all data collection, these codes were opened by one of the authors (M.T.). All hemodynamic measurements were performed before initiation of the patient's scheduled surgery in the supine position.

Preinduction BP measurements on arrival at the operating room were made using an automated BP cuff. Baseline and subsequent BP measurements after the test dose or saline injections were made using an appropriate transducer connected to the arterial cannula. A standard lead II electrocardiogram (Life Scope 12, Nihon Koden, Tokyo, Japan) was monitored continuously throughout the study period, and any arrhythmia was noted. HR was determined from electrocardiography as an average of every 5 s for a HR less than 96 bpm, or as an average from RR intervals of consecutive 8 beats for a HR more than 96 bpm.

Increases in HR $\geq$ 20 bpm and SBP $\geq$ 15 mmHg were prospectively defined as clinically significant (HR and SBP criteria, respectively) according to the study by Guinard et al. in which the criteria were determined with unmedicated, nonpregnant, awake volunteers [10]. In addition, a modified criterion (positive if $\geq$10 bpm increase in HR) determined in anesthetized adult patients was also tested [11]. Sensitivities and specificities of a positive test in HR and SBP along with positive predictive (+PV) and negative predictive values (−PV) were calculated using standard formulae: sensitivity, the number of true positives divided by the number of true positives plus false-negatives; specificity, the number of true negatives divided by the number of true negatives plus false-positives; +PV, the number of true positives divided by the number of true positives plus false-positives; −PV, the number of true negatives divided by the number of true negatives plus false-negatives. All data are expressed as mean ± standard error (SEM). The patients' demographic, hemodynamic, and arterial blood gas data as well as blood glucose values were

compared between groups using the chi-squared test or two-way analysis of variance (ANOVA) followed by unpaired Student's *t*-test with Bonferroni's correction. Paired hemodynamic data in each group were analyzed by repeated-measure ANOVA followed by paired Student's *t*-test with Bonferroni's correction. A P value less than 0.05 was considered the minimum level of statistical significance.

Results

There were no significant differences among the four groups in terms of age, weight, height, gender ratio, resting SBP, resting diastolic blood pressure (DBP), and resting HR (Table 1). The clonidine doses administered in the clonidine-saline and the clonidine-epinephrine groups were 4.72 ± 0.10 and 4.91 ± 0.12 $\mu g \cdot kg^{-1}$, respectively. Effects of preoperative clonidine medication were noted in the preinduction BP and HR values. The preinduction SBP and DBP values of the clonidine-saline and the clonidine-epinephrine groups were significantly lower than those of the control-saline and the control-epinephrine groups (Table 1, $P < 0.05$). The preinduction HR of the clonidine-epinephrine group was significantly lower than those of both control groups, while that of the clonidine-saline group was significantly lower than that of the control-saline group (Table 1, $P < 0.05$). However, these differences in hemodynamic variables due to clonidine medication disappeared following the introduction of general anesthetics. No significant differences among the four groups were seen in the baseline SBP, DBP, and HR immediately before the epidural test dose or saline injections.

IV injections of the epidural test dose containing epinephrine caused significant increases in both HR and SBP, while the hemodynamic variables remained essentially unchanged following saline injections (1 ± 1 bpm and 3 ± 4 mmHg in both groups, respectively). Significant increases in HR from the baseline values were seen in the control-epinephrine and the clonidine-epinephrine groups at intervals of 40–80 and 40–100 s following the injections, respectively (Fig. 1). Likewise, SBPs were significantly elevated above the baseline values in both epinephrine groups between 40 and 220 s (Fig. 2). However, there were no significant differences between the control-epinephrine and the clonidine-epinephrine groups in HR and SBP changes following IV test doses (Figs. 1, 2) as well as in the mean maximum increments of HR (26 ± 2 and 30 ± 3 bpm, respectively) and SBP (49 ± 5 and 45 ± 4 mmHg, respectively).

Fourteen of 20 patients in the control-epinephrine group and 16 patients in the clonidine-epinephrine group developed maximum HR increments ≥20 bpm, while all patients in both saline groups resulted in a

Table 1. Patients' demographic data, clonidine doses, and resting, preinduction, and baseline blood pressure and heart rate

	Control		Clonidine	
Group	Saline (n = 20)	Epinephrine (n = 20)	Saline (n = 20)	Epinephrine (n = 20)
Age (years)	40 ± 3	41 ± 4	38 ± 3	40 ± 3
Weight (kg)	58 ± 1	59 ± 1	58 ± 2	58 ± 1
Height (cm)	157 ± 1	159 ± 2	161 ± 1	160 ± 3
Male/female	4/16	6/14	9/11	7/13
Clonidine dose ($\mu g \cdot kg^{-1}$)	—	—	4.72 ± 0.10	4.91 ± 0.12
Resting				
SBP	123 ± 2	122 ± 3	121 ± 4	119 ± 3
DBP	71 ± 2	69 ± 2	74 ± 3	72 ± 2
HR	73 ± 3	74 ± 4	75 ± 2	71 ± 2
Preinduction				
SBP	131 ± 4	129 ± 3	110 ± 2*	106 ± 3*
DBP	76 ± 3	75 ± 3	63 ± 2*	62 ± 2*
HR	77 ± 4	74 ± 4	66 ± 2†	62 ± 3*
Baseline				
SBP	104 ± 4	99 ± 3	99 ± 3	98 ± 3
DBP	58 ± 2	58 ± 1	53 ± 2	56 ± 2
HR	70 ± 2	72 ± 3	72 ± 3	70 ± 2

Data are mean ± SEM or numbers.
SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); HR, heart rate (bpm).
*$P < 0.05$ versus the control-saline and the control-epinephrine groups.
†$P < 0.05$ versus the control-saline group.

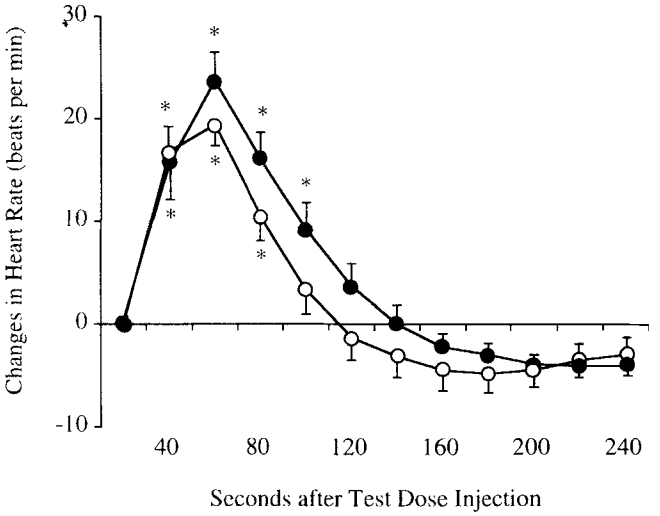

Fig. 1. Changes in heart rate after intravenous injection of an epidural test dose containing 15 μg epinephrine with (*solid circles*: $n = 20$) and without (*open circles*: $n = 20$) clonidine premedication 5 μg·kg^{-1}. Since heart rates were essentially unchanged after 3 ml saline injection, these data are not presented. Data are mean ± SEM. *$P < 0.05$ compared with the baseline values before test dose injections

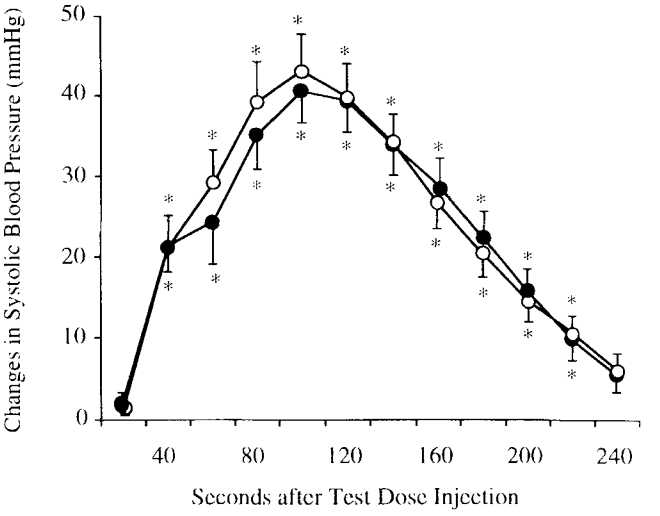

Fig. 2. Changes in systolic blood pressure after intravenous injection of an epidural test dose containing 15 μg epinephrine with (*solid circles*: $n = 20$) and without (*open circles*: $n = 20$) clonidine premedication 5 μg·kg^{-1}. Since systolic blood pressures were essentially unchanged after 3 ml saline injection, these data are not presented. Data are mean ± SEM. *$P < 0.05$ compared with the baseline values before test dose injections

Table 2. Sensitivity, specificity, and positive and negative predictive values of epidural test doses containing 15 μg epinephrine based on peak heart rate and systolic blood pressure in adult patients during isoflurane and nitrous oxide anesthesia with or without clonidine 5 μg·kg^{-1} medication

Group	Control group	Clonidine group	*P* value
Conventional heart rate criterion (positive if ≥20 bpm heart rate increase)			
Sensitivity	70% (14/20)	80% (16/20)	0.78
Specificity	100% (20/20)	100% (20/20)	—
Positive predictive value	100% (14/14)	100% (16/16)	—
Negative predictive value	77% (20/26)	83% (20/24)	0.85
Modified heart rate criterion (positive if ≥10 bpm heart rate increase)			
Sensitivity	100% (20/20)	100% (20/20)	—
Specificity	100% (20/20)	100% (20/20)	—
Positive predictive value	100% (20/20)	100% (20/20)	—
Negative predictive value	100% (20/20)	100% (20/20)	—
Systolic blood pressure criterion (positive if ≥15 mmHg systolic blood pressure increase)			
Sensitivity	100% (20/20)	100% (20/20)	—
Specificity	100% (20/20)	100% (20/20)	—
Positive predictive value	100% (20/20)	100% (20/20)	—
Negative predictive value	100% (20/20)	100% (20/20)	—

Data are percentages (numbers).

maximum HR increases <20 bpm (Table 2). Therefore, sensitivities and −PVs based on the conventional HR criterion were found to be 70% and 77% without clonidine premedication, and 80% and 83% with clonidine premedication, respectively (Table 2). However, based on the modified HR criterion, in which HR increase ≥10 bpm is regarded as a positive response determined in isoflurane-anesthetized adult patients [11], sensitivities, specificities, +PVs, and −PVs were all 100% with or without clonidine premedication (Table 2). On the other hand, all of 20 patients in both epinephrine groups and none in both saline groups developed maximum SBP increments ≥15 mmHg (SBP criterion), resulting in sensitivities, specificities, +PVs, and −PVs all 100% irrespective of the premedication (Table 2).

Significant correlations were not found in either epinephrine group between the maximum changes in HR

or SBP versus age, body weight, epinephrine dose in milligram per kilogram, baseline HR, or baseline SBP. No arrhythmia was observed in any patient throughout the study period.

Discussion

Our study demonstrated that neither hemodynamic responses to nor efficacy of the intravenously administered epidural test dose containing 15 μg epinephrine were affected by preoperative oral clonidine premedication 5 μg·kg^{-1}. Regardless of the presence of clonidine, it was shown that neither sensitivities nor −PVs of the test dose were of a clinically acceptable level based on the conventional HR criterion determined with awake, unmedicated volunteers, but the modified HR criterion was applicable. These results indicate that isoflurane rather than clonidine premedication was a major determinant of HR response to the IV test dose under the conditions of our study. The attenuated HR responses to the IV test dose during general anesthesia, as opposed to that in awake patients, is attributed to the presence of simultaneously administered isoflurane, since volatile anesthetics are known to reduce the normal electromechanical activity of human atrial fibers [12] as well as the maximum sinus rate response to epinephrine in a noncompetitive manner [13]. However, testing regimens based on the SBP criterion have produced 100% sensitivity and specificity. These results indicate that intravascular migration of the epidural catheter could also be diagnosed using peak SBP response in adult patients under an epidural-general anesthesia combination using isoflurane.

Following Moore and Batra's report of detectable HR increases after local anesthesia with 15 μg epinephrine [14], a combination of this kind to detect intravascular migration of the epidural catheter has become acceptable anesthetic practice. Guinard et al. [10] demonstrated that an increase in HR ≥ 20 bpm was 100% sensitive and specific for intravascular injection in healthy, unmedicated, nonpregnant adult volunteers. These efficacies, however, may not be applicable under certain conditions such as in the elderly [15,16] or in patients taking a β-adrenergic blocker [10]. The results of our present study are compatible with those of a more recent report [17], in which only 10 of 15 healthy patients under isoflurane anesthesia developed HR increases ≥20 bpm upon an IV test dose containing 15 μg epinephrine, resulting in 67% sensitivity. Also in that report, the modified HR criterion and SBP criterion were found to be 100% sensitive and specific. In adult patients anesthetized with isoflurane, isoproterenol is found to be more sensitive [18]. Furthermore, whether or not a larger dose of epinephrine would yield better efficacy remains controversial [11,19]. Until a more reliable methodology for the testing regimen is established, reinforcing doses of epidural local anesthetic solutions should be given slowly to avoid complications from accidental intravascular injection.

Oral clonidine premedication, 5 μg·kg^{-1}, enhances pressor responses, but not HR responses to IV ephedrine [3], norepinephrine [4], on phenylephrine [4], in both awake and anesthetized humans. Even though the underlying mechanisms have not been completely elucidated, a recent study demonstrated augmented pressor response to ephedrine without elevations in plasma catecholamine levels, suggesting an amplified α-adrenoceptor-mediated vasoconstriction caused by clonidine pretreatment [4,5]. Since arterial baroreflex sensitivity is not altered by clonidine in humans [6], we hypothesized that the hypertensive response to epinephrine is similarly augmented; thus, the intravenously administered test dose would cause a greater degree of reflex slowing of HR which would counteract the β-receptor-mediated increase in HR, resulting in inferior efficacy of the test dose on the HR criterion in clonidine-treated patients. However, our study confirmed that the hemodynamic response to and efficacy of the IV test dose were not modified by clonidine premedication (Figs. 1, 2; Table 2). This finding could be attributed to the fact that, compared with ephedrine, norepinephrine, and phenylephrine, epinephrine in small doses possesses a relatively greater β-adrenergic property [20], the characteristics of which may have been unaffected by preoperative clonidine. Another possible explanation would be that effects of additional isoflurane had confounded our results. In order to elucidate the effect of clonidine premedication per se rather than the combination of both clonidine and isoflurane, a further study needs to be performed without a general anesthetic.

The power of the study in relation to the sample size may limit the interpretation of the present results. Based on Bayes's theorem, true +PV and −PV are dependent to some degree on the prevalence of the outcome in question as well as the sample size [21]. In our study, a nomogram depicting the effect of the incidence of intravascular catheterization (0.7% according to a recent report [22]) on −PV based on the HR criterion gives 66% without clonidine, and 77% with clonidine, while 100% −PV was obtained based on the SBP criterion in both groups. These results also indicate that the modified HR criterion and SBP criterion are more reliable to detect intravascular injection in adult patients under isoflurane anesthesia.

In conclusion, oral clonidine premedication 5 μg·kg^{-1} affects neither hemodynamic responses to, nor efficacies for, detecting intravascular injection of epidural test doses containing 15 μg epinephrine. Based on the con-

ventional HR criterion, the epidural test dose remains an imperfect marker for intravascular injection in adult patients under isoflurane and nitrous oxide anesthesia, but the modified HR criterion and SBP criterion provide 100% sensitivity, specificity, +PV, and −PV regardless of the presence of clonidine premedication.

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