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Anesthesia and Hypertension: The Effect of Clonidine on Perioperative Hemodynamics and Isoflurane Requirements

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Thirty patients (ASA physical status II–III) with a history of arterial hypertension, whose blood pressure (BP) control varied from normotension to moderate hypertension (diastolic BP < 110 mmHg), scheduled for elective surgery under general anesthesia, were randomly assigned to two groups. Group 1 was premedicated 90–120 min prior to induction with diazepam 0.15 $mg \cdot kg^{-1}$ po; group 2, in addition, received clonidine 5 $\mu g \cdot kg^{-1}$ po. Anesthetic depth was assessed by on-line aperiodic analysis of the electroencephalogram. Following lidocaine 1 $mg \cdot kg^{-1}$ and fentanyl 2 $\mu g \cdot kg^{-1}$ (group 1 only), anesthesia was induced with thiopental 3–4 $mg \cdot kg^{-1}$ and vecuronium 0.1 $mg \cdot kg^{-1}$ was used to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane in N_2O/O_2 and supplemented by fentanyl. In group 2, clonidine produced a rapid preoperative control of systolic and diastolic BP from 166 ± 32/95 ± 14 to 136 ± 80 ± 11 ($P < 0.01$), was more effective in blunting the reflex tachycardia associated with laryngoscopy and endotracheal intubation than lidocaine-fentanyl pretreatment. It significantly reduced the intraoperative lability (coefficient of variation) of systolic ($P < 0.01$) and diastolic BP and heart rate (HR) ($P < 0.05$), and resulted in significantly slower HR during recovery ($P < 0.01$). Anesthetic requirements for isoflurane were reduced 40% ($P < 0.01$) in group 2; narcotic supplementation was also significantly reduced ($P < 0.005$). The authors conclude that these effects of clonidine are explained by the inhibitory action of clonidine on central monoaminergic systems involved in cardiovascular control, modulation of sleep/wake cycle, cortical arousal, and of nociception. (Key words: Anesthesia: hypertension. Anesthetics, volatile: isoflurane. Pharmacology: clonidine. Premedication: clonidine. Sympathetic nervous system, alpha adrenergic agonist: clonidine.)

CLONIDINE, A CENTRALLY-ACTING antihypertensive agent known to reduce central sympathetic outflow and modulate presynaptic transmitters' release,[1] has been shown to suppress central noradrenergic hyperactivity induced by immobilization stress[2] in animals, to decrease the MAC of halothane[3] and the dose of narcotics required to prevent reflex cardiovascular response to laryngoscopy and intubation,[4] and to have potent analgesic properties in humans.[5] These characteristics suggest that clonidine might be a useful adjunct to the anesthetic management of patients with preexisting hypertension.

Accordingly, we studied the effects of clonidine premedication on: 1) attenuation of the cardiovascular response to laryngoscopy and intubation; 2) perioperative hemodynamic lability; and 3) isoflurane and narcotic requirements in the perioperative period.

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Methods

The present study was approved by the Institutional Review Board of the Texas Tech University Health Sciences Center; informed consent was obtained. Subject material consisted of 30 treated hypertensive patients (14 men, 16 women) scheduled for elective abdominal, head and neck, and orthopedic surgical procedures.

In this study, the level of BP control with drug therapy varied from normotension to mild to moderate hypertension; however, no patient with severe hypertension (diastolic BP > 110 mmHg) was included in the present investigation. No patient had signs or symptoms of accelerated or malignant hypertension, congestive heart failure, or chronic airway obstruction. Ischemic heart disease (IHD), defined as history of myocardial infarction and/or ischemic changes in the ECG, was present in five patients, but no patient had experienced a myocardial infarction within 2 yr of the proposed surgery nor presented with angina pectoris. Patients' characteristics and drug therapy are reported in tables 1 and 2, respectively. Using a random-number table, the patients were assigned to one of two groups according to pre-anesthetic regimen. Fifteen subjects (group 1) received premedication with diazepam po 0.15 $mg \cdot kg^{-1}$ 90 min before surgery. Fifteen other subjects (group 2) received the above premedication plus clonidine po 5 $\mu g \cdot kg^{-1}$ at the same time. All antihypertensive medications were continued up to the time of surgery; the last dose of the appropriate diuretic was given the day prior to the scheduled operation.

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TABLE 1. Patients' Characteristics (Mean ± SD, with Range in Parenthesis)

	Group 1	Group 2
Age (yr)	48 ± 13 (30–64)	49 ± 15 (29–65)
Sex		
Male	N = 6	N = 8
Female	N = 9	N = 7
Weight (kg)	80 ± 23 (58–110)	77 ± 14 (60–98)
ASA physical status		
II	N = 7	N = 9
III	N = 8	N = 6
Associated disease		
Diabetes Mellitus	5	4
IHD/PVD/CVD	3/3/11	2/2/1
SLE	1	1
Rheumatoid Arthritis	2	3
Obesity	3	4
Other	2	1
Type of surgery		
Extremities (Orthopedics)	6	5
Abdominal	4	6
Head and Neck	5	4
Duration (min)	135 ± 100 (40–240)	146 ± 72 (60–250)
IV Fluid		
Crystalloid (ml)	1955 ± 1675	1530 ± 970
Colloid (ml)	350 ± 130	300 ± 150
Blood loss (ml)	750 ± 450	650 ± 480

IHD = ischemic heart disease; PVD = peripheral vascular disease; CVD = cerebrovascular disease; SLE: systemic lupus erythematosus.

ANESTHETIC PROTOCOL

Electrocardiographic lead V_5 and II were monitored throughout the operative period. Systemic BP was monitored by automated oscillographic method (Dinamap®) in 12 patients (six in each group) and by intrarterial cannulation in 18 patients (nine in each group); central venous pressure (CVP) was monitored in ten patients (six in group 1, four in group 2). Pharyngeal temperature was maintained between 35.5 and 37.5° C. Expiratory concentration of anesthetic gases was sampled every 3 min, analyzed by mass spectrometry (MGA 1100, Perkin Elmer), and displayed on a monitor; a hard copy, summarizing all operative values, was obtained. Controlled mechanical ventilation with a tidal volume of 10 $ml \cdot kg^{-1}$ was adjusted to maintain the end-tidal CO_2 between 30 and 35 mmHg. On-line computerized aperiodic analysis of the EEG signal (Lifescan™ Neurometrics, San Diego, CA) was employed to support the clinical assessment of anesthetic depth, since conventional clinical criteria based upon stability of hemodynamic variables may not be reliable in hypertensive patients treated with vasodilators, beta-adrenergic blocking drugs, and muscle relaxants. Increasing concentration of isoflurane/N_2O anesthesia produced a progressive shift of the EEG spectral frequencies towards delta (0.5–3 Hz) and low theta (4–6 Hz) activities and an increase in their amplitude, along with a significant reduction of high alpha and low beta activity (10–14 Hz).[6]

Before induction of anesthesia, lidocaine 1 $mg \cdot kg^{-1}$ iv and fentanyl 2 $\mu g \cdot kg^{-1}$ were administered to the control group only, and all patients received 500 ml of crystalloids over 10 min. After preoxygenation for 3 min, anesthesia was induced over 90 s with sodium thiopental 3–4 $mg \cdot kg^{-1}$. Muscle relaxation was produced by the administration of vecuronium 0.1 $mg \cdot kg^{-1}$ preceded 2 min earlier by a "priming dose" of 0.01 $mg \cdot kg^{-1}$. Following tracheal intubation, anesthesia was maintained with isoflurane delivered in 50% N_2O/O_2 mixture. During the operation, BP was measured and recorded every 5 min, or more frequently when rapid changes occurred. HR was continuously acquired and stored (HP 78534B MONITOR/TERMINAL), and a hard copy of the tabular summary of intraoperative values was obtained. The hemodynamic end point of the anesthetic management was maintenance of BP and HR within 20% of pre-induction values.

TABLE 2. Antihypertensive Therapy (Mean ± SD, with Range in Parenthesis)

	Group 1 (Control)			Group 2 (Clonidine)		
Drugs						
Furosemide ($mg \cdot day^{-1}$)		40	N = 1		80	N = 1
Hydrochlorothiazide ($mg \cdot day^{-1}$)	(25–50)	42 ± 13	N = 6	(25–50)	45 ± 11	N = 5
Propranolol ($mg \cdot day^{-1}$)	(80–160)	120 ± 31	N = 11	(60–160)	115 ± 34	N = 12
Hydralazine ($mg \cdot day^{-1}$)	(75–150)	112.5 ± 53	N = 2	(50–150)	87.5 ± 43	N = 4
Prazosin ($mg \cdot day^{-1}$)	(1–3)	1.75 ± 95	N = 4	(1–3)	1.7 ± 1.15	N = 3
Nifedipine ($mg \cdot day^{-1}$)	(60–120)	90 ± 42	N = 2	(80–120)	100 ± 28	N = 2
Regimens						
Diuretic + beta blocker		N = 7			N = 6	
Vasodilator + beta blocker		N = 4			N = 6	
Vasodilator only		N = 4			N = 3	

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Tachycardia was defined as an increase in HR of 20% or greater of pre-induction values; hypertension and hypotension were defined as intraoperative or recovery room changes in systolic BP more than 30% compared to pre-induction levels. Intraoperative fluid challenges were defined as 250 ml of iv fluid over a 5-min period or 1000 ml in no more than 20 min for the purpose of increasing BP.

When hypotension occurred, isoflurane concentration was reduced by 0.25% increments and/or fluid challenges were administered until BP returned to within 15% of the pre-induction values. At this point, if the EEG showed a shift towards higher frequencies or clinically lighter anesthesia was detected, fentanyl in 50 μg increments was administered in order to maintain or restore EEG pattern previously described and obtain hemodynamic stability.

Hypertension was treated by increasing isoflurane by 0.25% increments every 3–5 min and/or by administering 50 μg increments of fentanyl, depending on whether it was associated with tachycardia. Measurements of the blood pressure and heart rate were taken and recorded at the following times: 1) the evening prior to and the morning of surgery (values were averaged) before the administration of the preanesthetic medication; 2) prior to induction of anesthesia, approximately 90–120 min after premedication; 3) after induction of anesthesia (before endotracheal intubation); 4) within 3 min after endotracheal intubation; 5) every 5 min during the operative period; and 6) upon arrival in recovery room (every 5 min for 5 measurements).

During the postoperative course, the patients were observed for 24 h by one of the investigators, and the charts reviewed after they were discharged from the hospital.

Statistical Analysis

Patients' characteristics were analyzed by chi-square for discrete variable, and by two-sample *t* test for continuous variables.

Analysis of variance repeated measures studies, Scheffé and Tukey's methods were performed, and the Bonferroni's inequality correction for *t* test was applied to the hemodynamic data for selected pairs of simultaneous multiple comparisons. The differences between pre-anesthetic values and values between each of the six conditions was considered significant when P was less than 0.05.[7]

The two sample *t* test and the Wilcoxon's two-sample rank sum test (when the large standard deviation indicated highly skewed distribution, *i.e.*, fluids, fentanyl, and morphine requirements) were applied to the drug requirements between the two groups and to the number of interventions required to maintain hemodynamic variables within target levels. A value of $P < 0.05$ was considered significant.

Intraoperative SBP and DBP and HR represent the average of measurements taken every 5 min during the entire duration of surgical period beginning 5 min after the post-intubation measurement. Two sample *t* tests were applied to the standard deviation (SD) of each patient intraoperative mean value to obtain coefficient of variation, an index which reflects the lability of the variable in question for the individual patient included in each group. This was expressed as percent of the mean value ($SD/X \cdot 100$).

N_2O and isoflurane concentrations are expressed as the mean time averaged end expiratory concentrations. They were obtained by calculating the sum of the areas determined by the time-concentration plot derived from the mass spectrometry measurements, and were normalized by the total duration in minutes of the anesthesia time from post-intubation to admission to the recovery room.

Results

There were no significant differences between the two groups with respect to sex distribution, weight, age, associated disease, hypertensive drug therapy, preoperative HR, type and duration of surgery, or intravenously administered fluids. Preoperative systolic and diastolic BP was $166 \pm 32/95 \pm 16$ mmHg in group 2 and $149 \pm 15/86 \pm 15$ mmHg in group 1. These differences, while not statistically significant, reflect the fact that seven moderately hypertensive patients were assigned to group 2 and only three to group 1.

Clonidine consistently produced dryness of the mouth and marked sedation. No signs of excessive sympathetic drive (*i.e.*, hypertension, tachycardia, irritability) that could be attributed to clonidine withdrawal were observed in group 2 within the first 24 postoperative hours.

Hemodynamics

In the present study, intraoperative fluctuations of BP and HR to less than 20% of preinduction value were observed in both groups, regardless of the preoperative BP control.

The addition of clonidine to the anesthetic regimen decreased the number of interventions (*i.e.*, vasopressor and fluid administration for the purpose of increasing BP, narcotic supplementation, adjustment of anesthetic gas concentration) required to maintain hemodynamic variables within target levels from 12 ± 5 in group 1 to 6 ± 2 in group 2 ($P < 0.01$). Hemodynamic results are shown in figures 1 and 2 and tables 3 and 4. Reduction

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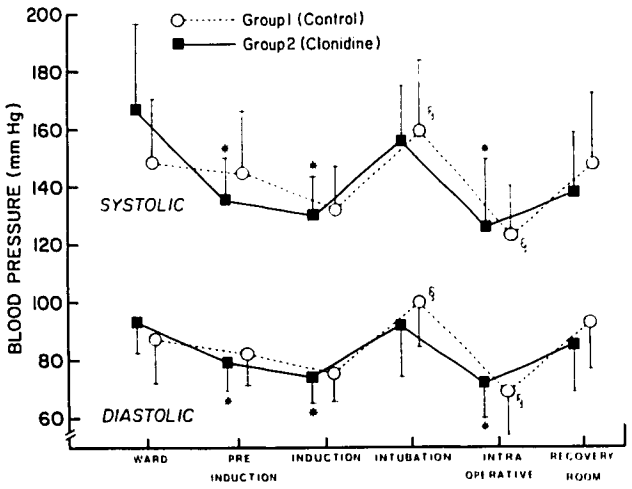

FIG. 1. Blood pressure (±SD) during the study period (see text). *P < 0.05 when each condition is compared with WARD values within the clonidine group; §P < 0.05 when the values of both groups at a given measurement are compared with preceding and following condition; †P < 0.01 between groups at a given measurement.

of BP values from 166 ± 32/95 ± 14 to 136 ± 16/80 ± 11 mmHg (P < 0.05) was observed in group 2 within 90–120 min of clonidine administration.

Clonidine also blunted the cardiovascular response to intubation more effectively than the lidocaine-fentanyl pretreatment administered to group 1. While the BP rose approximately 20% in both groups, the HR rose 25% in group 1 and only 10% in group 2 (P < 0.01). Three patients in group 1 experienced tachycardia in

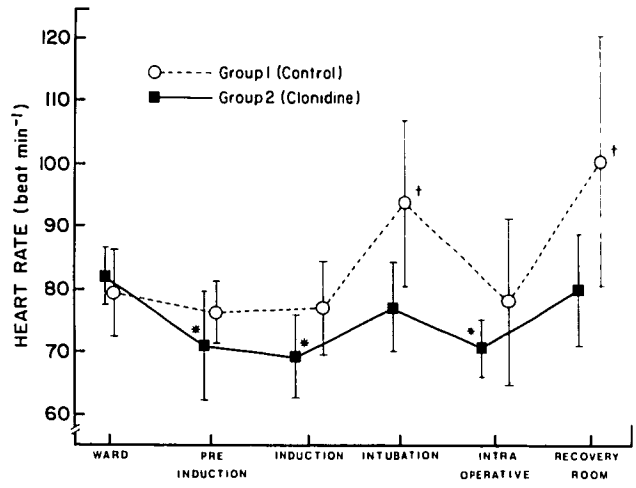

FIG. 2. Heart rate values (±SD) during the study period (see text). *P < 0.05 when each condition is compared with WARD values within the clonidine group; §P < 0.05 when the values of both groups at a given measure are compared with preceding and following condition; †P < 0.01 between groups at a given measurement.

TABLE 3. Intraoperative Variability of Hemodynamic Variables

	Group 1	Group 2	P
BP			
Syst	22%	11%	P < 0.01
Diast	13%	9%	P < 0.05
HR	17%	8%	P < 0.05

Coefficient of variation of heart rate and systolic and diastolic pressures as % of time averaged mean values (SD/X · 100).

excess of 110 bpm, and, in two, the ECG showed ST depression greater than 2 mm that responded to propranolol administration (1–2 mg iv). Phenylephrine (75 μg iv bolus) was given when systolic BP fell more than 30% of pre-induction value to three patients in group 1 and to one patient in group 2 (N.S.). Heart rate was consistently lower in the clonidine group compared with group 1 throughout the operative period (71 ± 5 *vs.* 78 ± 15) (P < 0.05) and in the post-anesthetic period (79 ± 10 *vs.* 101 ± 23) (P < 0.01). Similar mean systolic and diastolic blood pressures were observed in the two groups in the intraoperative period. By contrast, the coefficient of variation for HR and systolic and diastolic BP (an index of variability of these variables for the individual patient) were reduced by one-half (P < 0.05) in the clonidine group as compared with the control group, as reported in table 3.

ANESTHETIC REQUIREMENT

The induction dose of thiopental, the intraoperative average N_2O concentration administered, and the morphine requirement in the recovery period were similar in both groups. Anesthetic requirements are reported in table 5. The end-expiratory concentration of isoflurane required was reduced 40% (P < 0.01) in the clonidine-treated patients (group 2) compared to group 1 (*i.e.*, 0.61 ± 0.2 and 1.03 ± 0.16%, respectively); intraoperative fentanyl dose also was significantly reduced: 0.9 ± 1.2 $\mu g \cdot kg^{-1}$ in group 2 and 3.5 ± 4.5 $\mu g \cdot kg^{-1}$ in group 1 (P < 0.005).

Intraoperatively, hemodynamic stability and lack of adrenergic response to surgical stimulation were consistently associated with a bimodal distribution of the EEG spectral activity with one peak around 3–6 Hz and a second at 10–12 Hz; the 95% activity edge (an indicator of the overall trend in both frequency and amplitude of the cerebral electrical activity) was encompassed within the 10–12 Hz power band.[8] Therefore, this pattern associated with signs of adequate clinical anesthetic depth was chosen to evaluate anesthetic requirement. Supplementation of anesthesia with fentanyl while reducing isoflurane concentration to obtain hemodynamic stability did not alter the EEG pattern described above;

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TABLE 4. Hemodynamic Parameters (Mean ± SD)

	Ward		Pre-induction		Post-induction		Intubation		Intra operative		Post-anesthetic Recovery Room	
	1	2	1	2	1	2	1	2	1	2	1	2
SBP (mmHg)	149 ± 15	166 ± 32	145 ± 18	136* ± 16	134 ± 12	130 ± 12	159† ± 24	157† ± 20	123† ± 10	125† ± 11	148 ± 28	137 ± 27
DBP (mmHg)	86 ± 15	95‡ ± 14	82 ± 14	80* ± 11	76 ± 12	74* ± 10	99† ± 16	94† ± 19	69† ± 13	71† ± 9	93 ± 12	85 ± 13
HR bpm	80 ± 8	82 ± 5	76 ± 6	71* ± 10	76 ± 10	70* ± 10	96‡ ± 15	78 ± 8	78 ± 15	71* ± 5	101* ± 23	79 ± 10

Group 1 = control; Group 2 = clonidine treated.

* Denotes $P < 0.05$ when each condition is compared with ward values within the clonidine group.

† Denotes $P < 0.05$ when values of both groups (at a given measurement) are compared with preceding and following condition.

‡ Denotes $P < 0.01$ between groups (at a given measurement).

lighter planes of anesthesia, however, as assessed clinically, were reflected by a shift of the activity edge of the EEG toward higher frequencies.

Discussion

In the present study, we maintained hemodynamic stability in both groups regardless of the preoperative BP values. Clonidine, however further reduced intraoperative hemodynamic lability and the number of interventions designed to maintain hemodynamic variables within a narrow predetermined range, and decreased anesthetic requirements.

HEMODYNAMICS

Clonidine, an alpha$_2$-adrenoceptor agonist, interacts with the catecholaminergic neuronal system which modulates tonic and phasic (reflex) blood pressure control,[9] and reduces the release of norepinephrine from nerve endings both centrally and peripherally.[8] The net effect results in a reduction of BP and HR likely due to a reduction of sympathetic outflow. In our study, clonidine pretreatment resulted in a reduction of preoperative systolic and diastolic blood pressures, 18 and 16%, respectively ($P < 0.01$). This observation is consistent with previous reports,[10,11] and suggests a simple and safe way to obtain, within a 90–120-min period, rapid control of BP without significant depression of myocardial contractility.[12] Clonidine blocked the cardiovascular response to laryngoscopy and intubation more effectively than did lidocaine (1 $mg \cdot kg^{-1}$) and fentanyl (2 $\mu g \cdot kg^{-1}$) pretreatment in group 1; however, it is possible that larger doses of fentanyl would have produced similar results. Post-intubation HR increased 25% in group 1 compared to 10% in group 2 ($P < 0.01$). This was associated with transient electrocardiographic ischemic changes in two patients in group 1 whose HR exceeded 110 bpm. Prevention of tachycardia in response to laryngoscopy and intubation and the slowing of the HR induced by clonidine share a complex underlying mechanism. It consists of at least three different components. Centrally, the activation of alpha$_2$-adrenoceptors causes both a reduction in peripheral sympathetic tone and an increase of vagally induced reflex bradycardia;[13] peripherally, stimulation of presynaptic alpha-adrenoceptors leads to diminished release of norepinephrine from the nerve endings toward the vasculature and to a reduction in peripheral sympathetic tone towards the heart.[14] Clonidine may, therefore, represent an effective and specific regimen to blunt this cardiovascular response which may result in myocardial ischemia and dysfunction in susceptible patients.[15] This result is also in keeping with previous findings in patients with ischemic heart disease, where clonidine premedication did not decrease pump performance during anesthetic induction with a high dose of fentanyl.[4]

The absence of a double-blind design represents a limitation of the present study, since observers' bias could have been introduced with respect to anesthetics administered, as well as to intraoperative management of the blood pressure and pulse rate. However, despite this inherent weakness, we believe the results support

TABLE 5. Drugs Requirements (Mean ± SD)

	Intraoperative				Postanesthesia Recovery Room
	Isoflurane (End Expiratory %)	Fentanyl (μg)	Thiopental (mg)	N_2O (%)	Morphine (mg)
Group 1	1.03 ± .16	250 ± 345	353 ± 93	51 ± 3.5	7.0 ± 7.7
Group 2	0.62 ± .2	61 ± 99	302 ± 112	49 ± 5	9 ± 5
P	$P < 0.01$	$P < 0.005$	NS	NS	NS

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the usefulness of clonidine. Intraoperative mean values for systolic and diastolic blood pressure and heart rate of the two groups were similar (table 4); however, the clonidine group showed a reduced hemodynamic lability as indicated by a significantly smaller coefficient of variation of these variables (table 3), despite a 50% reduction of the number of interventions ($P < 0.01$) designed to maintain BP and HR within a narrow predetermined range. In the postoperative period, while high blood pressure was most likely to occur in group 2 patients in view of the higher ward BP,[16,17] mean systolic and diastolic pressures were not different from pre-induction values. Premedication with clonidine may, therefore, represent a safe and effective way to achieve preoperative BP control in patients with mild to moderate hypertension, since the hypertensive control obtained appears to improve perioperative hemodynamic stability and to ease the anesthetic management.

While this approach may avoid the inconvenience and the cost of postponement of scheduled surgery in patients incidentally discovered to have mild to moderate hypertension, patients with severe hypertension (diastolic BP > 110 mmHg) should have proper medical evaluation and adequate BP control prior to elective surgery.

Concern may be expressed regarding the risk of hypertension following withdrawal of clonidine or of delayed hypotension in view of its long elimination half-life (12 h).[18] We observed neither during the first 24 postoperative hours; and, in a previous human study, no clinical nor biochemical evidence for an overshoot of sympathetic activity was observed after a single oral dose of clonidine similar to that used in the present study.[19] Similarly, the time to maximum effect (1.5–3 h) and the degree of BP reduction observed are in agreement with the pharmacokinetics and the concentration-effect relationship of orally administered clonidine.[18,19]

Beta-adrenergic blocking drugs were part of the preoperative antihypertensive regimen in 11 patients in each group; however, the addition of clonidine significantly improved hemodynamic stability of group 2. Both clonidine and beta-adrenergic blocking drugs have been found to reduce BP and HR at rest and during exercise, but only clonidine significantly reduces catecholamines at rest and during exercise.[10,20] This different reaction of the sympathetic nervous system with regard to its sympathoneural and sympathoadrenal components during stress may explain the improved hemodynamic stability of group 2. HR has been shown to correlate with plasma norepinephrine levels[21]; thus, the consistently slower HR in the clonidine-treated group and the reduced blood pressure lability are likely a consequence of the inhibition of the sympathetic outflow.[10] This is supported by recent work where clonidine resulted in inhibition of central noradrenergic catechol metabolic hyperactivity induced by immobilization stress.[2]

There are additional similarities shared by alpha$_2$-adrenergic agonist and beta-adrenergic blocking drugs. These include antianginal effects,[22] improvement of myocardial O_2 supply/demand ratio, and perioperative hemodynamic stability.[4,16,23] However, in other respects, such as the analgesic properties and the lack of adverse effect on the bronchomotor tone,[24] clonidine appears to be a superior drug and could find specific indication in hypertensive patients with severe airways obstruction and ischemic heart disease where beta-blockers are contraindicated.[25]

Previous work has demonstrated that the adrenergic response to surgery can be blocked or significantly reduced by higher anesthetic concentration or by increasing the narcotic dose.[26] The present study suggests that this can be achieved with a lower anesthetic concentration and smaller narcotic dose when clonidine is also administered. The 50% reduction of the number of interventions to maintain the fluctuations of hemodynamic variables within a narrow predetermined range and the decreased coefficient of variation observed in group 2, despite similar mean values of BP and HR of the two groups during the operative period, suggests that better hemodynamic control was obtained not only for the group as a whole, but also for each individual patient. The stabilizing effect of clonidine on the hemodynamics of these hypertensive patients is most likely explained by its specific inhibitory action on catecholaminergic lower brain stem structures.[9] These adrenergic neurons, very sensitive to clonidine,[27] have been shown to exert tonic and phasic influences to maintain and adjust arterial tone *via* monosynaptic projections to sympathetic preganglionic neurons.[9,28]

Clonidine therefore decreases the resting tone of the sympathetic nervous system by interfering with tonic influences on excitatory cardiovascular neurons, but still permits the conduction of reflex information to the inhibitory cardiovascular neurons without influencing the final efferent sympathetic vasomotor neurons of the medulla.[29] The site and mechanism of action of clonidine, therefore, explain why, in humans, the drug does not produce severe orthostatic hypotension, does not abolish baroreceptor response, but lowers the set point and increases the sensitivity of the baroreceptor reflex.[30] This also likely explains the better control of HR observed perioperatively in group 2, and suggests the safety of its clinical use.

In addition to the direct effect of clonidine on the sympathetic outflow, the reduction of anesthetic requirement must have been a contributing factor to the reduced hemodynamic lability observed in group 2. In

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fact, the reduction of isoflurane concentration would reduce the dose-dependent decrease in vascular resistance,[31] and preserve baroreflex response which has been found to be blocked even at modest levels of anesthesia with isoflurane.[32]

Anesthetic Requirements

Intraoperatively, a similar clinical depth of anesthesia was observed in the two groups despite a 40% reduction of the isoflurane requirements. The anesthetic dose of isoflurane used in group 1 is in close agreement with the typical concentrations required for maintenance of clinical anesthesia reported by a multicenter study.[33] Clonidine is known to produce a frequency shift and a pattern of synchronization of the EEG similar to that of morphine.[34] This may explain the apparent lack of specific effects of the narcotic supplementation on the EEG pattern observed.

The reduction of isoflurane dose agrees with the reduction of halothane MAC observed in dogs after clonidine administration,[3] and may be explained by its inhibitory effect on both spontaneous and evoked activity of the locus coeruleus, a noradrenergic pontine structure involved in control of sleep/wake cycle and cortical arousal, and in modulation and integration of inputs from other systems.[35] Support for the locus coeruleus as a possible primary site of interaction between isoflurane and clonidine to reduce anesthetic requirement stems from the observation that the norepinephrine content increased in this pontine structure during halothane anesthesia.[36] Furthermore, restricted electrolytic lesion of the locus coeruleus or generalized lesion of central noradrenergic systems with a neurotoxin, such as 6-hydroxydopamine,[37] led to a reduction in halogenated agent requirements similar to that seen in the present study.

Moreover, the selective inhibition of nociceptive inputs mediated by an alpha$_2$-adrenoceptor mechanism[38] produced by clonidine at the spinal cord level,[39] may also have contributed to the reduction of the anesthetic dose.

We conclude that preoperative administration of clonidine, in addition to careful anesthetic management, results in improved perioperative hemodynamic stability in patients with mild to moderate arterial hypertension and in a reduction of the anesthetic requirement. Further studies are necessary to investigate whether this approach may be safely extended to include uncontrolled, severely hypertensive patients presenting for emergent surgery.

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