Journal of Medicine in the Tropics (2016) 18:1:12-17

Journal of Medicine in the Tropics

Original Article

Preinduction oral clonidine: Effects on ketamine cardiostimulation at induction of anesthesia

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Abstract

Background and Purpose: Most of the available intravenous (IV) induction agents produce hypotension except ketamine. However, its use is limited due to cardiovascular stimulation. We therefore investigated the effects of oral clonidine premedication on ketamine-induced cardiostimulation.

Methodology: This was a prospective, double-blind, randomized controlled study of 156 patients scheduled for general anesthesia. The patients were randomized into three Groups A, B, and C of 52 patients each and all the patients received 10mg diazepam the night before the surgery and 90 minutes before induction of anaesthesia. In addition, patients in Groups A and B received 0.1 mg and 0.3 mg oral clonidine, respectively, at the time of premedication while no clonidine was administered to patients in Group C. Anesthesia was induced with IV ketamine 2 mg/kg and 100% oxygen 8 L/min via the Bain's circuit. The pulse rate (PR), systolic blood pressure, diastolic blood pressure, and mean arterial pressure were measured noninvasively and recorded every minute for 10 min before induction of anesthesia.

Results: The peak values of PR in the 0.1 mg and 0.3 mg clonidine groups were significantly lower than the corresponding value in the control (C) group (86 ± 5 bpm and 83 ± 7 bpm vs. 118 ± 14 bpm, $P < 0.05$). However, the peak mean blood pressure in the Group B was significantly reduced when compared with the corresponding values in the Groups A and C (97 ± 9 mmHg vs. 117 ± 7 mmHg and 115 ± 14 mmHg, respectively $P < 0.05$).

Conclusion: Preanesthetic oral clonidine reduced cardiostimulation following ketamine-induction in spontaneously breathing patients.

Key words: Attenuation, cardiovascular stimulations, ketamine-induction, preanesthetic clonidine, spontaneous breathing

Introduction

Ketamine has some of the characteristics of an ideal induction agent except for the associated significant cardiovascular stimulation with resultant hypertension and tachycardia due to its sympathomimetic effects. As an N-Methyl-D-Aspartate receptor antagonist, studies have demonstrated that perioperative administration of a small dose of ketamine causes a lower incidence of postoperative nausea and vomiting and 40% to 60% reduction in perioperative opioids requirements.[1] In contrast, few ketamine-based studies on normovolemic patients have demonstrated a deleterious increase in the hemodynamic parameters.[2-4] However, these hyperstimulatory effects can be explored to achieve hemodynamic stability in critically-ill hypovolemic or septic shock patients.[5] Similarly, interests in the use of ketamine for regional anesthesia and analgesia have surged in advanced countries. Addition of preservative-free ketamine to caudal bupivacaine has been shown to improve the duration of

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Access this article online	
Quick Response Code:	Website: www.jmedtropics.org
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How to cite this article: ***

analgesia without affecting the analgesic intensity,[6] and a recent questionnaire-based study conducted in the UK revealed that 32% of the pediatric anesthetists reported their use of epidural ketamine.[7]

Clonidine, a selective α-2 adrenergic agonist, has been shown to reduce mean arterial blood pressure and cardiac output with no alterations in norepinephrine and epinephrine plasma concentrations following endotracheal intubation.[8] Several studies have exploited the sympathoadrenal inhibition of clonidine to show its minimizing effects on the hemodynamic changes during laparoscopic surgery.[9-11] Moreover, some researchers have demonstrated good attenuations of the cardiostimulatory effects when patients were premedicated with clonidine 90 min before induction of anesthesia.[11,12] The bioavailability of clonidine after oral administration is between 75% and 95%, its onset of action is about 30 min with its peak effects occurring 2–4 h necessitating its ingestion at least 90 min prior to induction to have clinically desirable actions. As intravenous (IV) clonidine has an onset of action within 15 min (with a peak at 30 min), its administration half an hour before induction of anesthesia is a better option. The oral clonidine is available in our environment has a long shelf half-life, and it is less expensive when compared with IV form. The use of oral clonidine premedication will be beneficial in most Nigerian secondary health care centers where the majority of the surgical procedures are done under ketamine anesthesia administered by nonanesthetists[3,4] whose consideration is to attain surgical anesthesia with little or no attention to the stable cardiovascular system.

In order to demonstrate this beneficially-proven effect of clonidine, this prospective, double-blind, controlled study was designed to assess the effects of two different doses of clonidine premedication on hemodynamic changes following induction of anesthesia with ketamine.

Methodology

The protocol for the study was approved by the Ethical Review Committee of the University of Ilorin Teaching Hospital, Ilorin. The study was a prospective experimental study conducted on 156 American Society of Anesthesiologists (ASA) Physical Status I or II patients, aged 18–60 years scheduled for elective general, plastic, orthopedic, and gynecologic surgical procedures under general anesthesia over a year period, April 2009 to March 2010.

The sample size was determined using the formula $n = z^2 \times p\ (1 - p)/d^2$ (n is sample size, z is standard normal deviate (set at 1.96 usually corresponds to 95%) and d is degree of accuracy (confidence interval)) with P being the proportion of surgery done under ketamine in our hospital a year earlier. The minimum sample size calculated was 52 per group with 20% as attrition rate.

One hundred and fifty-six patients were randomized to Group A, B, or C by paper balloting. Patients with hypertension, raised intraocular and intracranial pressures, psychiatric, neurological, myocardial ischemia and/or infarction, endocrine, or seizure disorders were excluded. Others excluded from the study were patients in whom face mask ventilation was anticipated to be difficult, those receiving medications that could affect the cardiovascular system, patients with ASA classification physical status greater than Class II and patients who refused to participate in the study.

Patients were visited and assessed the night before the operation and their resting pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) values were recorded. The patients' sociodemographic characteristics including age, sex, height, and weight were documented. Following preanesthetic assessment, all patients were given 10 mg oral diazepam the night before the surgery. The patients were fasted according to the recommended fasting guidelines and were randomly assigned to three groups; no drug at all (C), 0.1 mg clonidine (A), or 0.3 mg clonidine (B) 90 min before the induction of anesthesia. All medications were served by a trained assistant who did not take further part in the administration of anesthesia.

In the operating room, basic checks of the anesthetic machine and equipment were done and each patient was connected to the multi-parameter patient monitor, Nellcor Puritan Bennett Model 4000, (Pleasanton, CA 94588, USA) and standard lead II electrocardiography was monitored. Baseline PR, SBP, DBP, MAP, and arterial oxygen saturation (SPO_2) were measured noninvasively and recorded. IV access was secured with an 18-gauge cannula on a forearm vein for drug and fluid administration. Normal saline solution was infused at 1.5 ml/kg/h for the first 10 min.

Anesthetic technique was standardized, and anesthetic care was performed by three dedicated anesthetists who were blinded to the treatment groups of the patients. The patient was preoxygenated with 100% oxygen, delivered via a tight-fitting face mask and a Bain circuit, for 5 min. Anesthesia was induced with IV ketamine 2 mg/kg which was given over 5 s, and the patient was allowed to breathe spontaneously 100% oxygen at a flow rate of 8 L/min via the face mask connected through a Bain breathing system to the anesthetic machine. The HR, SBP, DBP, MAP, and SPO_2 values were measured and recorded every minute for 10 min, and this constituted the study duration. No airway adjunct was required to maintain the patency of the airway.

At the end of the 10 min study duration, the patient was managed in accordance with the standard anesthetic technique, employing suxamethonium for intubation, and pancuronium and halothane for maintenance of anesthesia. The patient was subsequently extubated at the end of surgery after adequate reversal of residual neuromuscular block with neostigmine and atropine.

Data generated from this study were expressed as percentages, means, and standard deviations (SDs). The patients' characteristics were compared using unpaired Student's *t*-test and Chi-square test. Comparison of hemodynamic parameters among groups was done by using two-way repeated-measures analysis of variance (ANOVA) followed by unpaired Student's *t*-test. Changes in the parameters over time were analyzed by repeated-measures ANOVA (one-way ANOVA) followed by Student's *t*-test for paired data in each group, using the computer software package epi-info version 2002 (Centre for Disease Control, Atlanta, Georgia, USA). A $P < 0.05$ was considered statistically significant and was adjusted to $P < 0.01$ in the case of multiple comparisons.

Results

The study groups, each consisting of 52 patients, were not different with respect to demographic variables [Table 1].

However, there were significant differences in the hemodynamic parameters among patients in two of the three Groups, A versus C and B versus C, before premedication [Table 2] and these were used as reference values and compared with data obtained at T0, T5, and T10.

The PR and MAP arterial pressure changes for the measurement intervals are represented in Tables 3-6 (all results mean ± SD).

Table 1: Demographic characteristics of surgical patients given oral 0.1 mg clonidine, 0.3 mg clonidine, and no clonidine

	Group A	Group B	Group C	*P*
Age (years)	35.6±11.1	38.4±11.1	40.6±12.1	0.09
Weight (kg)	68.5±8.6	66.9±6.9	65.1±11.3	0.18
Height (m)	1.62±0.03	1.62±0.03	1.61±0.05	0.9
Male: female ratio	27:25	27:25	22:30	0.5265

P value analyzed by ANOVA. ANOVA - Analysis of variance

Table 2: Hemodynamic parameters (mean±standard deviation) before clonidine premedication

	Group A	Group B	Group C	*P*
PR (bpm)	81±7	83±6	86±8	A versus B - 0.12 A versus C - 0.001 B versus C - 0.033
MAP (mm Hg)	89±7	90±7	93±7	A versus B - 0.463 A versus C - 0.004 B versus C - 0.0311

n=52 patients in each group, *P* value analyzed by Student's *t*-test. MAP - Mean arterial pressure, PR - Pulse rate

After premedication, the PR in the clonidine-treated patients was significantly lower than in those patients who received no clonidine. Only patients who had 0.3 mg - clonidine had a significant reduction in MAP when compared with the corresponding preanesthetic values [Table 3].

At all the measurement intervals after induction with IV ketamine, PR and MAP obtained in the clonidine-treated patients were significantly lower than values obtained in the control; Group C [Tables 4-6].

Table 3: Hemodynamic parameters (mean±standard deviation) after clonidine premedication

	Group A	Group B	Group C	*P*
PR (bpm)	76±7	75±6	93±13	A versus B - 0.436 A versus C - 0.0001 B versus C - 0.0001
MAP (mm Hg)	93±7	82±7	98±8	A versus B - 0.0001 A versus C - 0.001 B versus C - 0.0001

n=52 patients in each group, *P* value analyzed by Student's *t*-test. MAP - Mean arterial pressure, PR - Pulse rate

Table 4: Hemodynamic parameters (mean±standard deviation) 1 min postinduction with ketamine

	Group A	Group B	Group C	*P*
PR (bpm)	80±6	80±6	105±17	A versus B - Nil A versus C - 0.0001 B versus C - 0.0001
MAP (mm Hg)	101±6	89±8	111±13	A versus B - 0.0001 A versus C - 0.0001 B versus C - 0.0001

n=52 patients in each group, *P* value analyzed by Student's *t*-test. MAP - Mean arterial pressure, PR - Pulse rate

Table 5: Hemodynamic parameters (mean±standard deviation) 5 min postinduction with ketamine

	Group A	Group B	Group C	*P*
PR (bpm)	92±6	89±7	125±17	A versus B - 0.021 A versus C - 0.0001 B versus C - 0.0001
MAP (mm Hg)	117±7	97±9	115±14	A versus B - 0.0001 A versus C - 0.359 B versus C - 0.0001

n=52 patients in each group, *P* value analyzed by Student's *t*-test. MAP - Mean arterial pressure, PR - Pulse rate

Table 6: Hemodynamic parameters (mean±standard deviation) 10 min postinduction with ketamine

	Group A	Group B	Group C	*P*
PR (bpm)	86±5	83±7	108±14	A versus B - 0.013 A versus C - 0.0001 B versus C - 0.0001
MAP (mm Hg)	105±6	90±8	104±14	A versus B - 0.0001 A versus C - 0.637 B versus C - 0.0001

n=52 patients in each group, *P* value analyzed by Student's *t*-test. MAP - Mean arterial pressure, PR - Pulse rate

At the 5th and 10th min after induction, the differences in the measured mean blood pressure between 0.1 mg clonidine and control groups were insignificant, $P = 0.359$ and 0.637, respectively [Tables 5 and 6].

The use of 0.3 mg oral clonidine was more effective than 0.1 mg clonidine in attenuating the increase in MAP when separately compared with the control group at the baseline and at the various intervals the data were collected, $P = 0.0001$ [Tables 3-6].

The calculated rate pressure product, RPP (heart rate × SBP) in the 0.1 mg, and 0.3 mg clonidine-treated groups, when compared with the control group, were significantly lower (12,773 ± 1204 beats/min mmHg, 10,532 ± 1465 beats/min mmHg and 17259 ± 3201 beats/min mmHg, respectively, $P = 0.001$), representing 74% and 61% of the control value for 0.1 mg and 0.3 mg clonidine groups, respectively.

Overall, the average peaks MAP in the 0.3 mg and 0.1 mg clonidine-treated groups were 97 ± 9 mmHg and 117 ± 7 mmHg, respectively, 5 min postinduction, increases of 15 mmHg and 24 mmHg (+18% and + 20%, respectively, above their respective baseline values). Corresponding heart rates increased to an average peak of 89 ± 7 bpm and 91 ± 6 bpm, respectively, 5 min postinduction (16% and 17% above their respective baseline values). The average peak MAP and PR in the control group were 120 ± 13 mmHg and 125 ± 17 bpm 4th and 5th min postinduction, respectively, increases of 22 mmHg (23%) and 32 bpm (34%) above baseline, respectively.

Discussion

Our results showed that 0.1 mg oral clonidine premedication attenuated the PR increase following ketamine-induction while both the PR and MAP were significantly less in patients who received 0.3 mg dose. These findings show that there is a dose-dependent suppression of the cardiovascular variables by clonidine after induction of anesthesia with ketamine.

The observed reductions in the PR and MAP among the 0.3 mg clonidine-treated patients in this study are similar to the findings of significant attenuation in the arterial pressure by Tanaka and Nishikawa[13] and Gupta and associates.[14] We observed that the values of PR among the 0.1 mg clonidine-treated patients were significantly attenuated following ketamine-induction. This is in contrast to the findings in the work of Tanaka and Nishikawa where no observable changes in the values of PR were recorded among the 5 μg/kg treated patients, equivalent to 0.35 mg in a standard adult. They induced anesthesia with IV ketamine 1 mg/kg and patients were manually ventilated with N_2O in oxygen during the data collections. From the pharmacokinetic point, the lower induction dose of ketamine should produce lower cardiovascular stimulation which might need no intervention to attenuate. However, the values of arterial pressure among the control group in their study were significantly higher due to the probable unevenness in the respiratory variables from the instituted manual ventilation and the likely stimulatory cardiovascular effects of N_2O thereby justifying oral clonidine premedication. The manual ventilation did achieve normocapnia, as revealed by the value of end-tidal carbon dioxide ranged between 4–4.7 kPa. This indicated that hypercapnia did not contribute to cardiostimulatory effects of ketamine in their study.

Similar to our findings, Doak and Duke[15] also demonstrated profound reductions in PR and MAP among patients who received preanesthetic administration of oral clonidine 5 μg/kg compared with those premedicated with 0.15 mg/kg diazepam or placebo following ketamine-induction (1 mg/kg). Despite similarity in the results, there are differences in the designs of the two studies. Whereas, they administered clonidine in mg/kg body weight we administered fixed doses of clonidine, 0.1 mg and 0.3 mg, due to the inability to get the exact dose of the drug compounded in our environment. Moreover, the method of induction of anesthesia with ketamine also distinguished the two studies; in this study, bolus IV ketamine 2 mg/kg was used whereas infusion of ketamine at the rate of 1 mg/kg/min was used by the other researchers. The infusion of ketamine would have allowed cessation of its further administration once amnesia was achieved with a resultant reduction in total induction dose of ketamine, and this can be explained, in part, by the anesthetic-sparing effects of clonidine.

The findings in the current study are also consistent with the published results of previous studies where ketamine-induced cardiovascular stimulations were significantly attenuated by orally-administered clonidine premedication.[16-20]

Munro *et al.*[16] demonstrated, as we did, that preanesthetic 0.3 mg oral clonidine significantly reduced the increase in PR and MAP after IV ketamine 2 mg/kg. It would have been more appropriate and precautionary to measure arterial blood gas tensions and $EtCO_2$ throughout the 10 min study period with the aim of keeping the $PaCO_2$ within the acceptable range. This would have ensured that the observed high hemodynamic variables were solely due to hyperdynamic effects of ketamine alone with no contribution from carbon dioxide retention possibly caused by mild respiratory depressant property[18] of ketamine, diazepam, and/or clonidine.

The preanesthetic oral clonidine administration has proven to have the blunting effect to the hypertensive response after laryngoscopy and tracheal intubation in addition to its ability to reduce ketamine-induced cardiovascular stimulation.[19] However, we did not determine the pattern of hemodynamic variables in our patients after tracheal intubation in this study.

Apart from attenuation of MAP, pre- and post-induction estimations of plasma catecholamines and oxygen consumptions in clonidine-treated patients were also found to be lowered when compared with midazolam treated group.[20] Our center lacks the facility to measure serum epinephrine and norepinephrine when this study was conducted.

Our study as were the conclusions from the studies earlier cited showed that clonidine was able to reduce the ketamine-induced hypertension but could not abolish it completely. The reason for this partial attenuation has been explained by a concept of functional antagonism of ketamine-induced centrally mediated sympathetic discharge. Thus, activation of presynaptic α-2 adrenergic receptors inhibits norepinephrine release, and activation of postsynaptic α-2 adrenergic receptors in the vasomotor centers in the brain abolishes hyperdynamic effects of ketamine.[21] It is a contrasting fact that there are robust evidence to indicate that preanesthetic oral clonidine 5 μg/kg boosts peripheral vascular responsiveness to various pressor agents.[21,22] Therefore, the predominance of the central inhibitory effects of clonidine over the peripheral vessels reactivity accounts for its ability to reduce the cardiovascular stimulations produced by ketamine. Apart from its hypotensive property that was exploited as an adjunct to ketamine anesthesia, some of the side effects of clonidine include dry mouth, dizziness, and drowsiness. Though some of the clonidine-treated patients in our study were observed to be less anxious before induction, we did not collect further information on it or look out for other side effects of the drug because they are not captured in the study objectives.

Conclusion

Oral clonidine premedication with 0.3 mg clonidine in patients without cardiovascular disorders was able to attenuate the ketamine-induced tachycardia and hypertension, while 0.1 mg clonidine was only effective in reducing the PR increase following IV ketamine-induction in spontaneously breathing patients. These findings suggest that using oral clonidine premedication, especially in a dose of 0.3 mg is beneficial during ketamine anesthesia.

Acknowledgments

We wish to sincerely thank all the residents of the Department of Anaesthesia, University of Ilorin Teaching Hospital, Ilorin for helping in the randomization of patients to the study groups, administration of anesthetic drugs to the patients, and collection of data. We also express our appreciation to Dr. Sunday Aderibigbe of the Department of Epidemiology and Community Medicine, University of Ilorin, Ilorin for the data analysis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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