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Effects of Oral Clonidine Premedication on Haemodynamic Response to Laryngoscopy and Tracheal Intubation: A Clinical Trial

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Abstract: The objective of this study was to evaluate the efficacy of pre-anesthetic orally administration of clonidine on pulse rate and blood stress response to laryngoscopy and tracheal intubation. In a double-blinded, randomized study, 274 ASA I and II subjects with age of 18 to 45 years scheduled for elective surgery under general anesthesia were enrolled. They were randomly allocated to receive oral clonidine (0.2 mg) or placebo as premedication 90-120 min before surgery. All the patients received Succinylcholine (1.5 mg kg^{-1}) after induction of anesthesia with Fentanyl (50 μg) and Thiopentone (5 mg kg^{-1}). The anesthesia was maintained with halothane (1.5 Mac) in 50% mixture of N_2O/O_2. Heart rate and systolic blood pressure were recorded before, immediately after and then every 5 min after intubation until 20 min. The Clonidine group showed a significant superiority over placebo in the prevention of increase in systolic blood pressure as well as heart rate over the intubation. A significant difference was observed in both heart rate and systolic blood pressures were significantly higher in Control group at three subsequent measurements following intubation. The results of this study suggest that orally administered clonidine in preanesthetic period, provides more haemodynamic stability and attenuates the stress response to laryngoscopy and intubation.

Key words: Clonidine, premedication, haemodynamic response, laryngoscopy, tracheal intubation

INTRODUCTION

The hemodynamic responses due to sympathetic stimulation to laryngoscopy and tracheal intubation and their hazards have been well documented (Edwards *et al*., 1994; Fox *et al*., 1977). Pharmacological modification has been considered as one of the most common ways to attenuate the pressor response (Fassoulaki and Kaniaris, 1983; Kamra *et al*., 1986; Stoelting, 1979). Among them, there has been a considerable interest in the clonidine and other α_2-adrenergic receptor agonists which are under intense investigation for attenuation of haemodynamic responses to laryngoscopy and intubation (Ghignone *et al*., 1986). These drugs reduce anesthetic requirements, attenuate adrenergic, hormonal and hemodynamic stress responses to surgery, reduce anxiety and lead to sedation (Kulka *et al*., 1995). However, it has been revealed that in comparison with other medications, clonidine has beneficial effects on the hyperdynamic response during stressful conditions like laryngoscopy and endotracheal intubation (Aho *et al*., 1990; Carabine *et al*., 1991; Flacke *et al*., 1987; Ghignone *et al*., 1986; Mikawa *et al*., 1993; Nishikawa *et al*., 1991; Orko *et al*., 1987; Pouttu *et al*., 1987; Raval and Mehta, 2002; Zalunardo *et al*., 1997), there are only few placebo controlled studies in the literature.

The objective of this placebo-controlled, prospective study was to evaluate the effects of oral clonidine premedication on the hemodynamic response to laryngoscopy and tracheal intubation.

MATERIALS AND METHODS

Following approval of ethical committee of Arak University of Medical Sciences (AUMS) and obtaining written informed consent, 274 adult patients (18 to 45 years) with American Society of Anesthesiologists (ASA) physical status of I or II scheduled for elective surgery under general anesthesia in Valiasr hospital of AUMS between July and December 2006 were enrolled in a double-blinded, randomized study. Patients with ischemic heart diseases or myocardial infarction, history of cerebrovascular accidents, heart block and pregnancy were excluded from the study. Moreover, critically ill patients, hypertensive patients and those undergoing emergent surgeries were excluded.

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Using a table of random numbers, patients were randomly assigned to two groups of Clonidine (Clonidine tablet 0.2 mg, manufactured by Sina Drug Production Co. Iran) or Control (placebo). Both groups received their tablets orally, 90-120 min before surgery with sips of water. No anti-cholinergic drug was given either before or at the time of induction of anesthesia.

On arrival in the operation room, an intravenous line was set up and patients were given crystalloid fluid corresponding to the total fluid requirements (compensatory intravascular volume expansion, deficit replacement, maintenance fluids, restoration of losses and substitution for fluid redistribution) and they were premedicated with fentanyl 50 μg before induction of anesthesia. Under standard monitoring, comprised, ECG, pulse oximetry and non-invasive blood pressure, general anesthesia was induced with incremental doses of thiopentone up to 5 mg kg^{-1} until disappearance of the ciliary reflex after 3 min preoxygenation for with oxygen 100%. To facilitate laryngoscopy and endotracheal intubation, Succinylcholine 1.5 mg kg^{-1} was used. Later, laryngoscopy using Macintosh blade size 3 and intubation using intratracheal tube (size 7.5-8) were performed by an anesthesiologist. Minimizing the duration of laryngoscopy, all the laryngoscopies were performed by a single experienced anesthesiologist. Furthermore, all cases with duration of laryngoscopy and intubation of more than 30 sec were expelled from final analysis.

After successful intubation, anesthesia was maintained with 1-1.5 MAC (inspiratory saturation) of Halothane in O_2 and N_2O (50% mixture). Atracuronium 0.2 mg kg^{-1} was used for neuromuscular blockade, with additional doses as required. Fentanyl 3 μg kg^{-1} was given before skin incision. The patients were ventilated mechanically with tidal volume of 10-15 mg kg^{-1} and a respiratory rate of 12 min^{-1}.

Concomitantly, systolic blood pressure via conventional sphygmomanometer (Riester, Germany) and heart rate through continuous ECG monitoring (Poyandegan Rahe Saadat, Novin 1800S, Iran) were recorded by a single observer before and immediately after laryngoscopy and after intubation and then every 5 min following intubation until 15 min in both groups.

Data are expressed as Mean±SD or number of patients. A two-way repeated measures ANOVA (Time × Haemodynamic variables) was used. The two groups as the between subjects factor (group) and the five measurements (during induction, intubation and maintenance of anesthesia) as the within-subjects factor (time) were considered. This was done for heart rate and systolic blood pressure. A Greenhouse-Geisser correction was used for sphericity. In addition, to compare two groups at baseline and at each time of the trial, an independent samples t-test was used. Paired sample t-test was used for comparison of two subsequent measurements in each group. To compare the categorical data between groups, Fisher's Exact Test was performed. Statistical calculations were performed utilizing SPSS (SPSS Inc, Chicago, Illinois, USA) version 12.0. Differences were considered significant at $p<0.05$.

RESULTS

No patients were excluded. 46% of practitioners were male. No significant differences were identified between patients randomly assigned to two groups with regard to basic demographic data including age and sex.

There were no significant differences between the two groups at the baseline on the systolic blood pressure ($p = 0.34$) and heart rate ($p = 0.14$). However, both heart rate and systolic blood pressure were significantly higher in Control group at three subsequent measurements following intubation (Fig. 1, 2).

The differences in systolic blood pressures between the two groups were significant as indicated by the effect of group, (The between-subjects factor corrected by Greenhouse-Geisser: $F = 230.5$, $df = 2.32$, $p<0.001$). The behavior of the two treatment groups was not homogeneous across time (Groups × Time interaction, Greenhouse-Geisser corrected: $F = 1104$, $df = 2.32$, $p<0.001$) (Fig. 1).

The same was true for heart rate. The results revealed that there were significant differences in heart rates

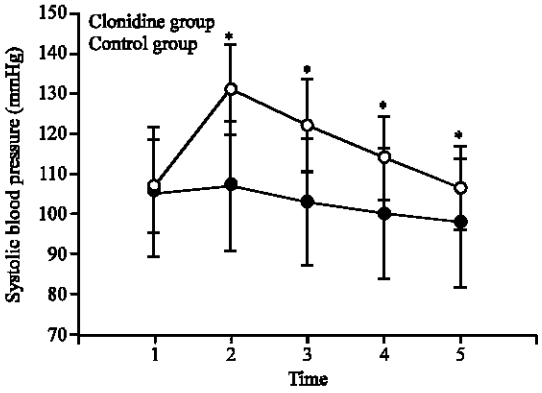

Fig. 1: Mean±SD of the two groups on the systolic blood pressure. 1: Before after laryngoscopy and intubation, 2: Immediately after laryngoscopy and intubation, 3: 5 min following intubation, 4: 10 min following intubation, 5: 15 min following intubation, *:$p<0.001$

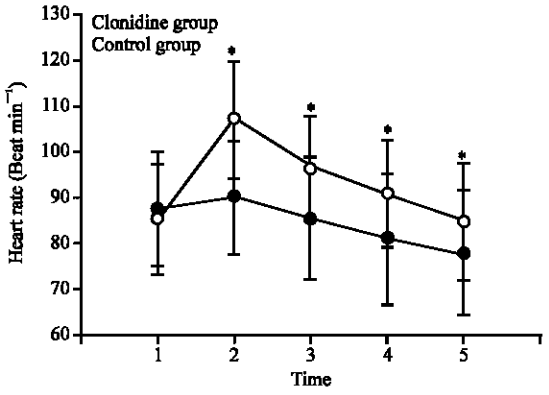

Fig. 2: Mean±SD of the two groups on the heart rate. 1: Before after laryngoscopy and intubation, 2: Immediately after laryngoscopy and intubation, 3: 5 min following intubation, 4: 10 min following intubation, 5: 15 min following intubation, *: $p<0.001$

between the two groups as indicated by the effect of group (The between-subjects factor corrected by Greenhouse-Geisser: $F = 58.1$, $df = 1.8$, $p<0.001$). The behavior of the two treatment groups was not homogeneous across time for heart rate as well (Groups × Time interaction, Greenhouse-Geisser corrected: $F = 714$, $df = 1.8$, $p<0.001$) (Fig. 2).

A significant difference was observed on the changes of systolic blood pressure ($p<0.001$) and heart rate ($p<0.001$) at the time of intubation compared to baseline in the control group, but not in the Clonidine group ($p = 0.38$ and $p = 0.08$, respectively) (Fig. 1, 2).

DISCUSSION

This study showed that while systolic blood pressure and heart rate revealed a statistically significant change at the time of intubation compared with the baseline values in the control group, no change was observed in Clonidine group. It is in concordance with other studies which showed that preoperative administration of clonidine attenuates stress-induced sympathoadrenal responses to painful stimuli and improves the intraoperative hemodynamic stability (Abi-Jaoude *et al*., 1993; Engelman *et al*., 1989; Lemes *et al*., 2008; Strebel *et al*., 2004; Wallenborn *et al*., 2008).

Sung *et al*. (2000) also shown that premedication with oral clonidine helped to provide perioperative hemodynamic stability. The same has been revealed by De Deyne *et al*. (2000) showing that there was statistically better perioperative hemodynamic stability (i.e., fewer episodes of hypertension and tachycardia) with clonidine pretreatment. Moreover, Yokota *et al*. (1998) concluded that the oral clonidine premedication might contribute to hemodynamic stability during sedated fiberoptic nasal intubation. Same results were obtained in other studies (Costello and Cormack, 1998; Ezri *et al*., 1998).

The rise in the pulse rate and blood pressure after noxious stimulus like laryngoscopy and endotracheal intubation is attributed to the sympathoadrenal activation (Raval and Mehta, 2002). Adrenergic reactions frequently occur in association with anesthesia and surgery as well (Derbyshire and Smith, 1984). Although, these changes are of little consequence in-patients with normal cardiovascular function, they may be of clinical importance in those with coronary artery diseases or in elderly patients with accompanying lung disease. The increased blood pressure and heart rate and the decrease in oxygen saturation may lead to an imbalance between myocardial oxygen demand and supply, which could result in arrhythmias, myocardial ischemia and eventual infarction (Fleisher, 1992; Gill *et al*., 1992).

Clonidine, an α_2-adrenoceptor agonist, prevents tachycardia and rise in blood pressure in response to laryngoscopy and intubation. It applies its properties through a complex underlying mechanism in which it interacts with the catecholaminergic neuronal system which modulates tonic and phasic (reflex) blood pressure control. Two different central and peripheral components have been considered for this achievement. In the central pathway, centrally activation of α_2-adrenoceptors causes both a reduction in peripheral sympathetic tone and an increase of vagally induced reflex bradycardia, which in turn resulted to the attenuation of heart rate acceleration. Peripherally acted, stimulation of presynaptic α_2-adrenoceptors diminishes release of norepinephrine from the nerve endings towards the vasculature and to a reduction in peripheral sympathetic tone towards the heart (Doxey, 1979).

Our study has several limitations. A single observer was chosen to measure the blade-tooth distance in order to eliminate inter-observer variability. Another limitation of this study, as with most studies regarding haemodynamic stability, is the fact that haemodynamic changes during laryngoscopy and intubation is affected by several other factors. For instance, although the anesthesiologists who performed laryngoscopies and intubations had extensive experience, there is a possibility for confounding effect of this variable. It is possible that the results are biased in the handling of the laryngoscopes (e.g., applying more forces in pulling or more tilting the handle). The other possible confounder is the cardiovascular reserve of patients. In patients with

limited cardiovascular reserve, diminished haemodynamic response is observed. Furthermore, our patients had no obvious coronary artery diseases and thus extrapolation of these results to all patients undergoing general anesthesia may not be applicable.

In conclusion, the results of this study showed that orally administration of 0.2 mg clonidine provides haemodynamic stability and attenuates the stress response to laryngoscopy and intubation.

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