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Evaluation of the Effect of Oral Clonidine Premedication on PR- interval, in Rhinoplasty and Functional Endoscopic Sinus Surgery

Masoud Nashibi[1,2,4], Sara Nashibi[3], Shahrokh Khoshsirat[1], Fatemeh Nazari[5], Sogol Asgari[5]*

1. Hearing Disorders Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Dental Research Center, Research Institute for Dental Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
4. Department of Anesthesiology, School of Medicine, Anesthesiology Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5. Department of Anesthesiology, Loqhman Hakim Educational Hospital, Faculty of Medicine, Shahid Beheshti University of Medical Science, Tehran, Iran

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Corresponding Authors:

Dr. Sogol Asgari

Email:
drasgari98429@gmail.com

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Abstract

Background: Clonidine, an alpha-2-agonist, attenuates the sympathetic response during general anesthesia and improves intra-operative hemodynamic stability. Clonidine has been associated with certain adverse cardiopulmonary effects.

Aim: This study aimed to investigate the impact of oral clonidine, administered as premedication, on the post-operative PR interval of the electrocardiogram (ECG) in patients who underwent rhinoplasty or Functional Endoscopic Sinus Surgery (FESS).

Methods: This study enrolled 50 patients scheduled for rhinoplasty or FESS under general anesthesia. Before arriving at the operation room, each patient received 300µg of oral clonidine 30 minutes before the standard 12-lead ECG was obtained. Induction of anesthesia was performed using the same standard protocol in all patients. Any changes in ECG monitoring during operation and in the recovery, room were registered. Six hours after clonidine administration, the standard 12-lead ECG was obtained and compared with the first ECG.

Results: The PR interval was prolonged in 23 cases (46%). In 21 cases, the prolongations were in the normal range (0.12-0.2 Sec.), and in two cases were in abnormal ranges (> 0.2 Sec.). (P value < 0.001).

Conclusion: It seems that premedication with oral clonidine can prolong the PR interval.

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Introduction

The majority of ear, nose, and throat (ENT) surgeries are performed under general anesthesia the quality of which is effective on surgical procedures and post-operative outcomes. One of the problems that surgeons and anesthesiologists commonly face is post-operative cardiovascular events that increase complications, reduced physical abilities, increased mortality, and a significant increase in medical expenses. The rate of cardiac attacks increases with each surgery, and after anesthesia, hypertension and tachycardia are more likely due to the increase in sympathetic system activity; thus, maintaining

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cardiovascular stability decreases these risks. There are several ways to reduce the cardiovascular effects due to increased sympathetic system activity, including using β-blockers, α2-agonists, calcium channel blockers, Nitroglycerin, and Aspirin (1). Another challenge during ENT surgeries is significant bleeding that obscures the surgical field, making the procedure more difficult and resulting in poor prognoses. To minimize intra-operative bleeding, various techniques are employed to position the patient, and preoperative medications are prescribed as premedication, along with intraoperative drugs to induce controlled hypotension during the procedures. Several drugs are used to achieve this, including magnesium sulfate, vasodilators, nitroglycerin, volatile anesthetics, β-blockers, and α2-agonists such as clonidine (2).

The α-2 agonists decrease arterial blood pressure (without orthostatic hypotension), heart rate, and consequently, intra-operative bleeding would be reduced The α2-agonists act as additive drugs in anesthetic techniques for certain surgeries. These would reduce the release of norepinephrine and are used as antihypertensive drugs. Clonidine is one of these drugs and is a selective α2-agonists primarily used to control blood pressure and its α2-agonist property is 200 times more than that of α1 (4). The α2-receptors are located in the presynaptic region of the nerve endings. Activation of α2-receptors inhibits the activity of adenylate cyclase enzyme reduces the entry of calcium to the nerve terminus and ultimately limits the release of norepinephrine. This process reduces sympathetic activity and peripheral vasodilatation (5, 6). Clonidine has a negative chronotropic effect and causes hypotension Also, the stimulation of α2-receptor in the central nervous system has sedative effects (12, 13). After oral administration, clonidine is rapidly and almost completely absorbed from the gastrointestinal duct with 100% bioavailability. The effects begin at 30-60 minutes after oral administration and its peak plasma concentration is obtained after 1-3 hours (14). Clonidine, administered as preoperative premedication, exhibits several beneficial effects. It induces sedative and anxiolytic effects(5), , thereby reducing the necessity for analgesics and anesthetics(15), , Additionally, it possesses cardiovascular benefits due to a decrease in catecholamine levels(16). This leads to a reduction in heart rate and blood pressure and a decrease in oxygen consumption during the postoperative period(17, 18), 19), Furthermore, clonidine exhibits anti-emetic and ague-reducing properties (3, 20), Ultimately, it contributes to a decreased prevalence of delirium and muscle stiffness following opioid usage. (21). Understanding the side effects is required due to its common preoperative use in ear, nose, and throat surgeries to control blood pressure, heart rate, and intraoperative bleeding. (2). The common side effects of clonidine include: fever, headache, muscle weakness, and pallor. The other known side effects of clonidine are cardiac complications such as bradycardia, congestive heart failure, electrocardiographic abnormalities such as Sinus node arrest, junctional bradycardia (19), high-degree AV block (22), arrhythmia (18, 23). Central nervous system effects are agitation, anxiety, hallucinations, and insomnia (5). The dermatologic complications are alopecia, skin rash, and urticaria. Also, there are some hematologic complications, such as thrombocytopenia, and ophthalmologic symptoms, such as blurred vision and decreased lacrimation. The cardiovascular complications are the most remarkable and sometimes require medical intervention (12). Only a few studies have been conducted on the prevalence of cardiovascular complications of clonidine compared with its desirable effects (11). In some studies, chronic and long-term complications of clonidine have been investigated in its users (for example, for the treatment of ADHD) (8, 19, 24). In a study in 2011 at a hospital in North Carolina, 198

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patients with ADHD were enrolled in the study and divided into two groups; the first group received clonidine + stimulant, and the second, received stimulant + placebo. At the end of weeks 3, 4, and 5, the QT interval in the first group increased by 14 milliseconds, but in the second group, it increased by only 1 millisecond (10). In a case report in 1987, a 65 years old patient with multiple underlying problems presented by vertigo, syncope, sinus bradycardia, and also multiple episodes of sinus arrest in the ECG one week after the use of clonidine (0.45 mg/d); by cutting off the clonidine, sinus arrest frequency was decreased and ECG was normalized after 3 days (25).

In another study in 1977, a 22-year-old woman with Lupus, hypertension, and mild renal failure was reported to develop cardiac abnormalities (including Atrial-Ventricular block 2 to 1) and ultimately complete heart block after clonidine administration. By discontinuation of the drug, the ECG returned to the normal state (22). In 2014, a study on 40 patients undergone cataract surgery showed that the prevalence of arrhythmias at the end of the surgery in the group that received intravenous clonidine (4 µg/Kg)30 min before surgery was lower compared with the placebo group; also, the myocardial attack rate was lower in the clonidine group. (23). In another study, five hypertensive cases were evaluated 4 weeks after clonidine therapy (0.2 mg/day); there were no significant changes in electrocardiography or echocardiography. (6). Another study conducted in 2008 at Isfahan University of Medical Sciences involved 88 patients over the age of 50 who were scheduled for surgery. Before anesthesia, one group received 0.1 mg of clonidine, while the other group received a placebo. Electrocardiographic (ECG) changes were recorded during the surgery, in the recovery room, and on the first postoperative day. Notably, the frequency of ECG changes was significantly higher in the placebo group compared to the clonidine group. This suggests that low doses of clonidine could be used as a premedication in elderly patients to prevent cardiovascular complications associated with increased sympathetic activity. (7). Another study on 10 old patients without a history of heart disease showed no changes in electrophysiological parameters (atrio-ventricular conduction) due to intravenous administration of 150µg clonidine at different times after administration (11). As previous studies have primarily focused on the desired effects of clonidine, it is crucial to thoroughly investigate its side effects' prevalence and severity. Close monitoring during the intra and postoperative periods and early diagnosis of significant ECG changes can significantly improve patient outcomes. The primary objective of this study is to identify early changes in ECG as a clonidine side effect and, if necessary, provide early therapeutic intervention to enhance patient outcomes.

This study aimed to evaluate oral clonidine's impact as a general anesthesia premedication on the electrocardiography of patients undergoing rhinoplasty and FESS. Specifically, the PR interval (as well as the QRS complex and QT intervals) will be documented and analyzed before and 6 hours after oral clonidine administration.

Methods

During a four-month period, 50 patients with ASA class I and II, in the age range of 20-60 years old who were scheduled for rhinoplasty or functional endoscopic sinus (FESS) surgeries under general anesthesia in Loghman Hospital, Tehran, Iran, were enrolled. The study was by the standards of the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1403.474) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The aims of this study were:

1. To investigate the effect of oral clonidine as a premedication before general anesthesia on the PR interval of the electrocardiogram of

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patients who are candidates for rhinoplasty and FESS surgery six hours after receiving the drug.
2. To investigate the effect of oral clonidine on the QRS interval of the electrocardiogram of patients who are candidates for rhinoplasty and FESS surgery six hours after receiving the drug.
3. To investigate the effect of oral clonidine on the QT interval of the electrocardiogram of patients who are candidates for rhinoplasty and FESS surgery six hours after receiving the drug.
4. The goals of this study are that early detection of ECG abnormalities and, if necessary, early therapeutic intervention can improve the outcomes of patients. During the procedure, ECG monitoring is performed using lead II electrocardiography.
5. After six hours of drug administration, a twelve-lead ECG is taken from the patients and its changes are recorded.
6. Finally, if there are any life-threatening pathological changes in the patient's ECG, the cardiovascular service will be consulted for therapeutic intervention.

Permuted Randomized Blocks

In this method, a computer generates 10 random blocks, each containing five individuals from the intervention group and five individuals from the control group. The computer randomly arranges the order of these individuals, and they are assigned to groups similarly. After each block, a new block of 10 is produced, and this process continues until the desired sample volume is achieved.

The data analyst and the nurse anesthetist will be unaware of the study group of patients. Forms with numbers 1 and 2 will be used in closed envelopes, which will be given to patients randomly.

After dividing the patients, the needle is inserted through the same area for both intervention groups to avoid accidental disclosure for participants. During surgery, the nurse anesthetist will not know about the study group. Also, after the procedure, the researcher who will evaluate the result will be unaware of the randomization.

Inclusion and exclusion criteria

Inclusion criteria were lack of previous use of clonidine, no history of alcohol abuse, no use of psychotropic drugs (tricyclic antidepressants, phenothiazines, butyrophenones), no use of β-blocker drugs, no gastrointestinal disorders that interfere with drug absorption, normal serum creatinine, no left Bundle branch block and baseline heart rate above 50 beats per minute before premedication. Exclusion criteria included patients with more than 10% bleeding during the surgery, patients requiring vasoactive drugs during the operation to maintain blood pressure, and patients with surgical duration of more than 240 minutes.

Sample Size Calculation

A pilot study was performed on a sample of 10 patients to determine the sample size. So, PR intervals for each patient at two times were obtained and then the mean and standard deviation of these intervals were calculated in the sample. The mean differences were compared with zero, and the required minimum sample size with a confidence level of 80% was 24 patients and with a confidence level of 95% was 39 patients, based on the following formula:

Mean difference (μ) = 0.007

$\mu_0 = 0$

SD (S) = 0.012

$\alpha = 0.05$

$\beta = 0.2$ (Power = 80%)

$$n \geq \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \times S^2}{(\mu - \mu_0)^2}$$

Procedure

All patients underwent a thorough pre-surgery visit with the researcher. The researcher thoroughly explained the study's different stages and obtained written informed consent from each patient. Additionally, a 12-lead ECG was performed on all cases. All patients received 300 µg oral clonidine (approximately 4-4.5 µg/Kg) administered by the nurse about 30 minutes before the surgery (as per hospital protocol). Intravenous Ringer's infusion (5

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ml/kg) was initiated upon the patient's arrival in the operating room. General anesthesia was induced with 3 µg/kg fentanyl 2.5 mg/kg propofol and also muscle relaxant (atracurium 0.5 mg/kg). After intubation, ventilation of the lungs was performed with 100% oxygen. Anesthesia was maintained using 100 µg/kg/min propofol infusion and remifentanil 0.2 µg/kg/min. Atracurium (0.15 mg/kg) was prescribed to maintain muscle relaxation, if necessary. Intraoperative monitoring was performed by Lead II electrocardiogram, automated BP monitoring, pulse oximetry and end-expiratory CO2 analysis (ETCO2). During the operation, hemodynamic and ECG changes were recorded. At the end of surgery, before the removal of the patient's tracheal tube, muscle relaxation residue was reversed by using 4-8 µg/kg neostigmine and 2 µg/kg atropine. The patients were transferred to the recovery room and then to the ward. Six hours after clonidine administration, the standard 12-lead ECG was obtained and compared with the first ECG.

Definitions and formulas

• PR interval: The time extended from the beginning of P-wave (the onset of atrial depolarization) to the beginning of QRS-complex (the onset of ventricular depolarization). The normal PR interval is 0.120 - 0.200 seconds.

• The QRS complex is related to ventricular depolarization, and its natural range is 0.080 to 0.110 seconds.

• QT interval: The time between the beginning of the ventricular depolarization and the end of the ventricular repolarization. The prolongation of this interval increases the arrhythmia risk. QT should be corrected based on the heart rate (QTc) (Figure 1).

Different formulas have been used to correct QT including the Bazett formula (QT/RR1/2); Fridericia formula (QT/RR1/3); Framingham formula (QT+ 0.154×[1-RR]).

Various studies have demonstrated that the Bazett formula leads to overcorrection in high heart rates and under-correction in low heart rates. The Fridericia and Framingham formulas are considered the most accurate for calculating QTc. The Framingham formula was employed in the study, and its results indicate that the normal lower limit of QTc for women and men is 0.351 and 0.350 seconds, respectively, while the upper limit is 0.467 and 0.449 seconds, respectively.

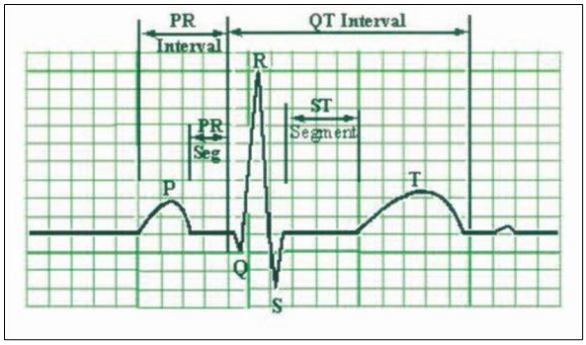

Figure 1: Electrocardiogram

Data analysis

The data was recorded in a form for statistical analysis. All quantitative variables were expressed as mean ± standard deviation and qualitative variables as the numbers (percentage). Also, the paired t-test and Wilcoxon non-parametric test were used to compare quantitative variables at two different times. All statistical tests were performed at a significant level of 5% and as a two-tailed test. SPSS21 software was used for data analysis.

Results

Fifty patients with a mean age of 38.34 ± 12.02 years were enrolled in this study. Sexual distribution in the patients was 52% (26 patients) male and 48% (24 patients) female. 58% of patients (29 patients) underwent endoscopic sinus surgery, and 42% (21 patients) the rhinoplasty surgery. Among patients, 84% (42 patients) had ASA class I, and 18% (8 patients) had ASA class II. There were five patients with controlled hypertension, one patient with controlled asthma, one patient with hypothyroidism under medical treatment and one patient with controlled epilepsy. Fourty-two patients (84%) also had no

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underlying disease. No arrhythmias were observed during anesthesia in patients. 100% of patients had normal PR interval (0.12-0.2 second) before clonidine administration. The mean ± SD of PR interval in patients before clonidine administration was 0.17 ± 0.03 second. Six hours after clonidine administration, patients' mean ± SD of PR interval was 0.19 ± 0.02 second. Among the 23 patients who had the increase in PR interval in ECG, 21 patients showed the increase in PR interval within the normal range (0.12-0.2 second), but in two patients, this increase was abnormally higher than the normal range (PR> 0.200 s). The difference between the mean ± SD of the PR interval at the two mentioned times was 0.02 ± 0.02 second with a P-value <0.001, which was statistically significant (Table 1).

Table 1. Changes in PR interval before and after administration of clonidine

mean ± SD of PR interval (second)	before administration	0.17±0.03
	after administration	0.19±0.02
mean ± SD difference (second)	0.02±0.02	
P-value	<0.001	

Before clonidine administration, 100% of patients had normal QRS duration; Mean ± SD of QRS duration was 0.09 ± 0.02 second. Six hours after the clonidine prescription, this value remained constant. There was no significant difference between the mean ± SD of QRS duration at the two times (P value> 0.999) (Table 2).

Table 2. Changes in QRS duration before and after administration of clonidine

mean ± SD of QRS interval (second)	before administration	0.09±0.02
	after administration	0.09±0.02
mean ± SD difference (second)	0	
P-value	>0.999	

Before clonidine, all patients had normal QT duration; Mean ± SD of QT interval was 0.38 ± 0.03 second.

Six hours after clonidine administration, patients' mean ± SD of QT duration was 0.40 ± 0.03 seconds. The difference between the mean ± standard deviation of QT interval at two times mentioned in patients was 0.03 ± 0.02 statistically significant second (P value <0.001) (Table 3). Corrected-QT (QTc) was normal in all patients at the beginning of the study; the mean ± SD of QTc was 423.08 ± 42.87. Six hours after clonidine administration, 62% of patients (31 patients) had normal QTc, and the mean ± SD of QTc in patients was 432.34 ± 41.03. The difference between the Mean ± SD of QTc at two times was 47.21 ± 9.26, which was not statistically significant (P-value = 0.172) (Table 4).

Table 3. Changes in the QT duration before and after administration of clonidine

mean ± SD of QT interval (second)	before administration	0.38±0.03
	after administration	0.40±0.03
mean ± SD difference (second)	0.03±0.02	
P-value	<0.001	

Table 4. Changes in QTc before and after clonidine administration.

mean ± SD of QTc interval (seconds)	before administration	423.08±42.87
	after administration	432.34+41.03
mean ± SD difference (seconds)	9.26±47.21	
P-value	=0.172	

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Discussion

This study aimed to evaluate the effect of oral clonidine as pre-anesthetic premedication on PR interval prolongation in post-operation ECG of patients in rhinoplasty and endoscopic sinus surgery (FESS). This study prolonged the PR interval in 23 cases (46%). In 21 cases, this prolongation was in the normal range (0.12-0.2 Sec.), and 2 cases were in the abnormal range (> 0.2 Sec.) (P-value < 0.001). These two patients were monitored by cardiovascular service, and then 12 hours after the clonidine prescription, the PR interval returned to normal range. The increase in PR interval in this study is significant (P value <0.001) and suggests that pre-anesthetic prescription of oral clonidine before general anesthesia can prolong the PR interval.

In addition to the main study, QTc, QT, and QRS intervals were also investigated. The duration of QRS did not change before and after the clonidine, which indicates that pre-anesthetic prescription of oral clonidine before general anesthesia cannot prolong the duration of QRS.

Clonidine has been shown to have positive effects on cardiovascular health in several studies. Numerous papers have reported the desired hemodynamic effects of a single dose of clonidine before surgical procedures.

Due to the high prevalence of pre-operative use of clonidine, it is necessary to know the side effects of this drug to control intraoperative bleeding during the surgery. Among the known side effects of clonidine, cardiovascular complications are remarkable and it requires therapeutic intervention in some cases(26).

In some studies, chronic and long-term complications of clonidine have been investigated in its users (for example, for the treatment of ADHD) (8, 19, 24). The most commonly reported side effect of high-dose clonidine usage was kidney dysfunction, as the drug is primarily excreted through the kidneys. However, only a few studies have been conducted to assess the prevalence of cardiovascular complications associated with clonidine compared to its intended benefits. (11, 26).

Conclusion

It seems that premedication with oral clonidine can prolong the PR interval. In summary, while oral clonidine might have some beneficial hemodynamic effects during and after surgeries, it would cause significant prolongation of ECG intervals even with a single dose. Further studies in a larger statistical population are suggested. Additionally, investigating other cardiac complications of clonidine is recommended.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Ethics

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Authors ORCIDs

Masoud Nashibi
https://orcid.org/0000-0003-3825-9889
Sara Nashibi
https://orcid.org/0000-0002-8556-7211
Fatemeh Nazari
https://orcid.org/0009-0007-6054-0999
Sogol Asgari
https://orcid.org/0000-0001-7837-8888
Shahrokh Khoshsirat
https://orcid.org/0000-0002-8568-627X

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