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ORIGINAL RESEARCH ANESTHESIA FOR ENT SURGERY

Effect of oral clonidine premedication on PR interval in patients undergoing rhinoplasty and functional endoscopic sinus surgery (FESS)

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ABSTRACT

Background & Objective: Clonidine, an alpha-2-agonist, plays a pivotal role in mitigating the sympathetic response during general anesthesia, thereby enhancing intraoperative hemodynamic stability. Despite its recognized benefits, reports of adverse cardiopulmonary effects have surfaced. This study investigates the impact of oral clonidine administered as premedication on patients undergoing rhinoplasty or Functional Endoscopic Sinus Surgery (FESS), with a focus on assessing alterations in the PR interval observed in postoperative electrocardiograms (ECG).

Methodology: A Randomized Clinical Trial (RCT) comprised fifty patients scheduled for rhinoplasty or FESS under general anesthesia. Each participant underwent a standard 12-lead ECG, followed by the administration of 300 µg oral clonidine 30 min prior to entering the operating room. Anesthesia induction adhered to a uniform protocol for all subjects. Comprehensive ECG monitoring throughout the surgical procedure and recovery period facilitated the recording of any observed changes. Six hours post-clonidine administration, a second standard 12-lead ECG was obtained and juxtaposed with the initial recording.

Results: Analysis revealed a lengthening of the PR interval in 23 (46%) of the cases. Within this cohort, 21 instances exhibited a prolongation falling within the normal range (0.12-0.2 sec), while the remaining two cases displayed abnormal prolongation (> 0.2 sec) ($P < 0.001$).

Conclusion: This investigation suggests that premedication with oral clonidine, in the patients undergoing rhinoplasty or functional endoscopic sinus surgery, has the potential to extend the PR interval.

Key words: Clonidine; PR interval; Rhinoplasty; Functional Endoscopic Sinus Surgery

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1. INTRODUCTION

In the realm of ear, nose, and throat (ENT) surgeries, the crucial role of general anesthesia (GA) in influencing surgical efficacy and postoperative results cannot be overstated. Postoperative cardiovascular events need to be foreseen due to their association with complications, substantial escalation in healthcare expenditures and increased mortality rates.[1-2] Post-surgical cardiac

incidents and the occurrence of hypertension and tachycardia during the emergence from anesthesia necessitate vigilant measures to maintain cardiovascular stability.[3-4] Various pharmacological interventions, including β-blockers, α2-agonists, calcium channel blockers and nitroglycerin, have been used to attenuate the cardiovascular effects stemming from heightened sympathetic system activation.[1]

Excessive bleeding encountered during ENT surgeries interferes with the surgical field, leading to complications and suboptimal outcomes. Various measures undertaken to mitigate intraoperative bleeding, include adjustments in patient positioning, premedication, and the use of intraoperative drugs to induce controlled hypotension during procedures.[2] Various pharmacological agents, such as magnesium sulfate, vasodilators, nitroglycerin, volatile anesthetics, β-blockers, and α2-agonists, including clonidine, are employed to induce controlled hypotension and minimize intraoperative bleeding.[3]

Clonidine help in modulating arterial blood pressure and heart rate, thereby reducing intraoperative bleeding.[3] Acting selectively on α2-receptors with 200 times greater affinity than α-receptors, clonidine primarily functions as an antihypertensive agent, inhibiting norepinephrine release and consequently curbing sympathetic activity and peripheral vasodilatation.[5-7] Apart from its hemodynamic effects, clonidine induces negative chronotropy, hypotension,[5,8-12] and exhibits sedative properties through stimulation of α2-receptors in the central nervous system.[13-14]

Administered orally, clonidine boasts rapid and nearly complete absorption from the gastrointestinal tract, exhibiting 100% bioavailability. Its effects manifest within 30-60 min, reaching peak plasma concentration within 1-3 hours.[15] As a preoperative premedication, clonidine demonstrates a spectrum of beneficial effects, including sedation, anxiolysis, reduced analgesic and anesthetic requirements, and favorable cardiovascular outcomes owing to decreased catecholamine levels.[6,16-19] Additionally, clonidine reduces postoperative oxygen consumption, and exhibits anti-emetic properties.[20-21] Notably, it contributes to a decline in the prevalence of delirium and muscle stiffness following opioid use.[22]

Despite its merits, it has its side effects including fever, headache, muscle weakness and pallor.[19-24] Cardiovascular complications, including bradycardia, congestive heart failure, sinus node arrest, junctional bradycardia, high degree AV block, and arrhythmia, necessitate careful monitoring and, at times, medical intervention.[13-25]

While extant literature predominantly highlights clonidine's desired effects, a comprehensive exploration of its side effects is warranted. This study addresses this gap, focusing on the prevalence and severity of clonidine's side effects. Vigilant monitoring during intra and postoperative phases, coupled with early identification of significant ECG changes, holds the promise of enhancing prognoses. The objective of this study was to scrutinize the early alterations in ECG parameters induced by oral clonidine premedication in patients undergoing rhinoplasty and Functional Endoscopic Sinus Surgery (FESS). Parameters such as PR interval, QRS complex, and QT intervals were meticulously documented and analyzed before and 6 h after the administration of oral clonidine.

2. METHODOLOGY

This randomized clinical trial spanned over four months, comprising 50 patients classified as ASA class I and II, aged between 20 and 60 years, and scheduled for rhinoplasty or FESS under GA at Shaikh Zayed Hospital, Lahore. The ethical underpinning of this research adhered to the principles outlined in the 1964 Helsinki Declaration and its subsequent amendments, as well as other standards of comparable ethical significance. The approval of the University of Medical Sciences' Ethics Committee, vide registration number IR.SBMU.RETECH.REC.1395.444, was obtained.

2.1. Patient selection

Inclusion criteria were patients from both genders, ASA class I and II, ages 20-60 y, normal serum creatinine, scheduled for rhinoplasty or FESS under GA. The patients with history of alcohol abuse, use of specific psychotropic and β-blocker drugs, gastrointestinal disorders affecting drug absorption, left bundle branch block, baseline heart rate below 50 bpm before premedication, were excluded. Patients were excluded with a history indicating possible bleeding exceeding 10%, a need for vasoactive drugs during surgery, or surgical durations surpassing 240 min.

A preliminary investigation was conducted, involving a cohort of ten patients, with the primary aim of ascertaining an appropriate sample size. PR intervals were meticulously recorded on two occasions for each participant, subsequently enabling the computation of both mean and standard deviation for the entire sample. The essential determination emerged that, at an 80% confidence level, a minimum of 24 patients would be required, whereas at a 95% confidence level, the sample size escalated to 39 patients.

2.2. Procedure

In the pursuit of enhancing patient safety and optimizing perioperative care, this study delves into the meticulous pre-surgical assessments and interventions undertaken in

a cohort of subjects. Prior to surgery, the researcher conducted thorough consultations with each patient, elucidating the nuances of the study protocol, culminating in the procurement of written informed consent. A universal 12-lead ECG was meticulously obtained from all participants, setting the stage for a comprehensive investigation.

Pre-operatively 300 µg of clonidine was administered orally precisely 30 min preceding surgery. Ringer's solution infusion was initiated upon the patient's arrival in the operation room. GA was induced with fentanyl at 3 µg/kg, propofol 2.5 mg/kg, and atracurium 0.5 mg/kg. Post-intubation, lung ventilation commenced with 100% oxygen. Maintenance of anesthesia involved propofol infusion at 100 µg/kg/min and remifentanil 0.2 µg/kg/min. Atracurium 0.15 mg/kg was judiciously administered to sustain muscle relaxation.

Intraoperative monitoring included Lead II electrocardiogram, automated blood pressure monitoring, pulse oximetry, and end-expiratory CO_2 analysis, facilitated real-time monitoring of hemodynamic and ECG dynamics. Post-surgery, prior to tracheal tube removal, residual muscle relaxation was reversed using neostigmine 4-8 µg/kg and atropine 2 µg/kg. Subsequently the patient was transferred to the recovery room and, subsequently, to the ward.

Six hours post-clonidine administration, a standard 12-lead ECG was obtained, enabling a comparative analysis with the baseline ECG. Correcting QT intervals based on heart rate (QTc) was paramount, prompting the application of various correction formulas, including Bazett, Fridericia, and Framingham. Notably, the study highlights the pitfalls of over-correction at high heart rates and under-correction at low heart rates associated with the Bazett formula, advocating for the superior accuracy of the Fridericia and Framingham formulas in calculating QTc. The Framingham formula, in particular, elucidates normative lower and upper limits for QTc in both women and men, contributing valuable insights to perioperative cardiac monitoring practices.

2.3. Data analysis

The quantitative variables are documented as mean values plus standard deviations, while qualitative variables are presented numbers and percentages. To ascertain the variance between two distinct measurements captured six hours prior and six hours subsequent to the electrocardiogram (ECG), both the paired t-test and the Wilcoxon non-parametric tests were used. All statistical evaluations were made at a significance threshold of 5%, employing a two-tailed testing approach. The data analysis was conducted with SPSS version 29 software.

3. RESULTS

In this investigation, we enrolled a cohort comprising fifty individuals, characterized by a mean age of 38.34 ± 12.02 y. The frequencies of the gender distribution, types of surgery, ASA classification and concurrent diseases are presented in Table 1.

Table 1: Baseline and demographic data

Parameter	Result
Age (y)	38.34 ± 12.02
Gender	
• Male	26 (52)
• Female	24 (48)
ASA class	
• I	42 (84)
• II	8 (18)
No underlying disease	42 (84)
Surgical procedure	
• FESS	29 (58)
• Rhinoplasty	21 (42)

Data presented as mean ± SD or n (%)

Examining the electrocardiographic parameters, it was observed that, prior to clonidine administration, all patients manifested normal PR intervals within the range of 0.12 to 0.2 sec. The mean PR interval before clonidine administration was 0.17 ± 0.03 sec. Following clonidine administration, six hours later, the mean PR interval increased to 0.19 ± 0.02 sec. Within this context, 23 patients exhibited an increase in their PR interval in the electrocardiogram, with 21 demonstrating an elevation within the normal range (0.12-0.2 sec), while in two patients, the increase surpassed the normal threshold (PR > 0.200 sec). The disparity between the mean PR intervals at the two measurement points was 0.02 ± 0.02 sec, proving to be statistically significant with a $P < 0.001$ (Table 2).

Preceding the administration of clonidine, the QRS duration in all patients was within the normal range, denoted by a mean of 0.09 ± 0.02 sec. Interestingly, six hours post-clonidine prescription, this value remained constant, with no significant variance observed between the mean of QRS durations at the two distinct measurements ($P > 0.999$).

Prior to clonidine administration, all patients exhibited normal QT durations, with a mean of 0.38 ± 0.03 sec. Following the administration of clonidine, the mean duration increased to 0.40 ± 0.03 sec after six hours. The statistical analysis disclosed a significant difference between the mean of QT intervals at the two temporal points, indicating a noteworthy increase ($P < 0.001$).

Table 2: Comparison of ECG variables before and six hours after clonidine administration

	Before clonidine	After clonidine	P-value
PR interval	0.17 ± 0.03	0.19 ± 0.02	**< 0.001**
QRS duration	0.09 ± 0.02	0.09 ± 0.02	> 0.1
QT duration	0.38 ± 0.03	0.40 ± 0.03	**< 0.001**
QTc	423.08 ± 42.87	432.34 ± 41.03	> 0.1

Data presented as mean ± SD; P < 0.05 was considered significant

At the commencement of the study, the corrected QT (QTc) intervals were within normal limits for all patients, marked by a mean of 423.08 ± 42.87. Following clonidine administration, 62% of patients (31 individuals) maintained normal QTc values, with the mean QTc recorded as 432.34 ± 41.03. However, the difference between the mean QTc at the two measurements, amounting to 47.21 ± 9.26, did not reach statistical significance (P = 0.172) (Table 2).

4. DISCUSSION

The primary objective of this investigation was to study the impact of oral clonidine as a pre-anesthetic premedication on the prolongation of the PR interval in the postoperative electrocardiograms (ECG) of patients undergoing rhinoplasty and endoscopic sinus surgery (FESS). Notably, the PR interval exhibited increase in 23 cases (46%), with 21 cases falling within the normal range (0.12-0.2 sec) and 2 cases surpassing the abnormal threshold (> 0.2 sec) (P < 0.001). Subsequent monitoring by the cardiovascular service revealed a return to the normal PR interval range for the two patients after 12 h of clonidine administration. The observed increase in PR interval reached statistical significance (P < 0.001), implying that administering oral clonidine as a pre-anesthetic measure before GA holds the potential to protract the PR interval.

Comparatively scant research has been undertaken to discern the prevalence of cardiovascular complications associated with clonidine, especially when weighed against its beneficial effects.[12] Certain studies have researched the chronic and long-lasting complications of clonidine among users, such as those employing the medication for Attention Deficit Hyperactivity Disorder (ADHD). A noteworthy study in 2011, conducted at a North Carolina hospital, enrolled 198 ADHD patients, segregating them into two groups: the first received clonidine + stimulant, while the second received stimulant + placebo.[11] After weeks 3, 4, and 5, the first group exhibited a 14-millisecond increase in the QT interval, in stark contrast to the mere one-millisecond increase in the second group. A case report from 1987 detailed a 65-year-old patient with multiple comorbidities who manifested vertigo, syncope, sinus bradycardia, and multiple episodes of sinus arrest in the ECG one week after initiating clonidine (0.45 mg/d). Ceasing clonidine administration resulted in a decline in the frequency of sinus arrest, and within three days, the ECG normalized.[26] Furthermore, a study in 1977 chronicled a 22-year-old woman with lupus, hypertension, and mild renal failure who developed cardiac abnormalities, including atrial-ventricular block 2 to 1, and eventually progressed to complete heart block following clonidine administration. Upon discontinuation of the drug, the ECG returned to a normal state.[27] A 2014 study on 40 patients undergoing cataract surgeries revealed that intravenous clonidine (4 µg/kg) administered 30 min before surgery resulted in a lower prevalence of arrhythmias and a reduced myocardial attack rate compared to the placebo group.[28]

A separate investigation encompassed five hypertensive cases assessed four weeks after clonidine therapy (0.2 mg/day), revealing insignificant changes in electrocardiography or echocardiography.[5] Similarly, a 2008 study at Isfahan University of Medical Sciences involving 88 patients aged over 50, scheduled for surgery, demonstrated that administering 0.1 mg clonidine to the first group, as opposed to a placebo to the second group, resulted in a higher frequency of electrocardiographic changes in the second group. This suggests that low doses of clonidine as premedication in elderly patients could mitigate cardiovascular issues stemming from heightened sympathetic activity.[8] Additionally, a study focusing on patients aged ten years without a history of heart disease displayed no alterations in electrophysiological parameters, specifically atrioventricular conduction, following intravenous administration of 150 µg clonidine at varying times post-administration.[12]

In tandem with the primary emphasis of this study, the investigation also explored QTc, QT, and QRS intervals. The QRS duration remained unaltered before and after clonidine administration, indicating that the pre-anesthetic use of oral clonidine before general anesthesia does not extend the duration of QRS. However, it is imperative to acknowledge that this deduction is grounded in a limited number of case studies, warranting further exploration for validation.

5. CONCLUSION

In summary, our investigation indicates that the administration of oral clonidine appears to extend the PR interval. While the use of oral clonidine may impart

certain beneficial hemodynamic effects, such as the reduction of blood pressure and heart rate during and post-surgery, it is noteworthy that a singular dose of clonidine is associated with a significant prolongation of ECG intervals. Nevertheless, it is imperative to interpret the findings of this study in the context of acknowledged limitations.

6. Data availability

The numerical data generated during this research is available with the authors.

7. Acknowledgement

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8. Conflict of interest

The study did not utilize any grant. No external or industry funding was involved.

9. Authors' contribution

All authors took equal part in the conduct of the study, literature search, data collection and analysis, manuscript preparation and final approval.

10. REFERENCES

1. Wijeysundera DN, Naik JS, Scott Beattie W. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: A meta-analysis. Am J Med. 2003;114(9):742-752. [PubMed] DOI: 10.1016/s0002-9343(03)00165-7
2. Musini VM, Pasha P, Wright JM. Blood pressure lowering efficacy of clonidine for primary hypertension. Cochrane Database Syst Rev. 2015;2015(5):CD003825. [PubMed] DOI: 10.1002/14651858.CD003825.pub4
3. Jan M, Reshi FA, Gupta S, Aara S, Wani IH, Saleem B. Evaluation of Oral Clonidine Premedication on Intraoperative Blood Loss and Bleeding Severity Score in Functional Endoscopic Sinus Surgery – A Prospective Placebo Controlled Study. J Adv Med Med Res. 2014;4(10):1970–1979. DOI: 10.9734/BJMMR/2014/4168
4. Enlow WM, Greenfield S, Roberson C, eds. Pharmacology for Nurses. In: Autonomic Nervous System Drugs. Jones & Bartlett Learning, LLC; 2016. p. 131-156.
5. Boyar RM, Fixler DF, Kaplan NM, Graham RM, Price KP, Chipman JJ, et al. Effects of clonidine on 24-hour hormonal secretory patterns, cardiovascular hemodynamics, and central nervous function in hypertensive adolescents. Hypertension. 1980;2(1):83-89. [PubMed] DOI: 10.1161/01.hyp.2.1.83
6. Basker S, Singh G, Jacob R. Clonidine in pediatrics - a review. Indian J Anaesth. 2009;53(3):270-280. [PubMed]
7. Zhao J, Zhao J. Dexmedetomidine versus Midazolam as Premedication in Anesthesia: A Meta-Analysis from Randomized Controlled Clinical Trials. J Anesth Clin Res. 2014;5(10). DOI: 10.4172/2155-6148.1000457
8. Ataran D, Towhidi M, Asnaashari AH, Mansouri F, Khajeh Dalouei M. Effects of Clonidine Premedication on Hemodynamic Responses during Fiberoptic Bronchoscopy. Tanaffos. 2005;4(13):21-25. [FreeFullText]
9. Daviss WB, Patel NC, Robb AS, McDermott MP, Bukstein OG, Pelham WE Jr, et al. Clonidine for attention-deficit/hyperactivity disorder: II. ECG changes and adverse events analysis. J Am Acad Child Adolesc Psychiatry. 2008;47(2):189-198. [PubMed] DOI: 10.1097/chi.0b013e31815d9ae4
10. Mohseni M, Ebneshahidi A. The effect of oral clonidine premedication on blood loss and the quality of the surgical field during endoscopic sinus surgery: a placebo-controlled clinical trial. J Anesth. 2011;25(4):614. [PubMed] DOI: 10.1007/s00540-011-1157-9
11. Kollins SH, Jain R, Brams M, Segal S, Findling RL, Wigal SB, et al. Clonidine extended-release tablets as add-on therapy to psychostimulants in children and adolescents with ADHD. Pediatrics. 2011;127(6):e1406-13. [PubMed] DOI: 10.1542/peds.2010-1260
12. Toussaint C, Cave D, Saoudi N, Moore N, Letac B. Electrophysiological effects of intravenous clonidine on sinus node function and conduction in man. J Cardiovasc Pharmacol. 1984;6(1):56-60. [PubMed]
13. De Vos H, Bricca G, De Keyser J, De Backer JP, Bousquet P, Vauquelin G. Imidazoline receptors, non-adrenergic idazoxan binding sites and alpha 2-adrenoceptors in the human central nervous system. Neuroscience. 1994;59(3):589-598. [PubMed] DOI: 10.1016/0306-4522(94)90179-1
14. Huber D, Kretz FJ. Efficacy of clonidine in pediatric anesthesia. Anasthesiol Intensivmed Notfallmed Schmerzther. 2005;40(10):567-575. [PubMed] DOI: 10.1055/s-2005-870158
15. Giovannitti Jr JA, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. Anesth Prog. 2015;62(1):31-39. [PubMed] DOI: 10.2344/0003-3006-62.1.31
16. Bangera A. Anesthesia for adenotonsillectomy: An update. Indian J Anaesth. 2017;61(2):103-109. [PubMed] DOI: 10.4103/0019-5049.199855
17. Guyenet PG, Cabot JB. Inhibition of sympathetic preganglionic neurons by catecholamines and clonidine: mediation by an alpha-adrenergic receptor. J Neurosci. 1981;1(8):908-917. [PubMed] DOI: 10.1523/JNEUROSCI.01-08-00908.1981
18. Hackmann T, Friesen M, Allen S, Precious DS. Clonidine facilitates controlled hypotension in adolescent children. Anesth Analg. 2003;96(4):976-981. [PubMed] DOI: 10.1213/01.ANE.0000052713.72875.13
19. Wallace AW, Galindez D, Salahieh A, Layug EL, Lazo EA, Haratonik KA, et al. Effect of clonidine on cardiovascular morbidity and mortality after noncardiac surgery. Anesthesiology. 2004;101(2):284-293. [PubMed] DOI: 10.1097/00000542-200408000-00007
20. Nguyen M, White KA, Bussing R. Clonidine extended release in the treatment of attention-deficit/hyperactivity disorder. Curr Psychiatry Rep. 2011;13(5):313-315. [PubMed] DOI: 10.1007/s11920-011-0209-z
21. Grottke O, Muller J, Dietrich PJ, Krause TH, Wappler F. Comparison of premedication with clonidine and midazolam

combined with TCI for orthopedic shoulder surgery. Anasthesiol Intensivmed Notfallmed Schmerzther. 2003;38(12):772-780. [PubMed] DOI: 10.1055/s-2003-45396

22. Gowing L, Farrell MF, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane database Syst Rev. 2014;(3):CD002024. [PubMed] DOI: 10.1002/14651858.CD002024.pub4
23. Williams PL, Krafcik JM, Potter BB, Hooper JH, Hearne MJ. Cardiac toxicity of clonidine. Chest. 1977;72(6):784-785. [PubMed] DOI: 10.1378/chest.72.6.784
24. Santiago AEQ, Issy AM, Sakata RK. Effects of preoperative intravenous clonidine in patients undergoing cataract surgery: a double-blind, randomized trial. J Ophthalmol. 2014;2014:346549. [PubMed] DOI: 10.1155/2014/346549
25. Ambrose C, Sale S, Howells R, Bevan C, Jenkins I, Weir P, et al. Intravenous clonidine infusion in critically ill children: dose-dependent sedative effects and cardiovascular stability. Br J Anaesth. 2000;84(6):794-796. [PubMed] DOI: 10.1093/oxfordjournals.bja.a013594
26. Kumari I, Naithani U, Harsha, Singhal Y, Meena K, Mohan CM. Clonidine as an adjuvant in monitored anesthesia care for ENT surgeries: A prospective, randomized, double blind placebo controlled study. Anaesth Pain Intensive Care. 2015;19(3):260-268. [Free full text]
27. Schwartz E, Friedman E, Mouallem M, Farfel Z. Sinus arrest associated with clonidine therapy. Clin Cardiol. 1988;11(1):53-54. [PubMed] DOI: 10.1002/clc.4960110118
28. Hadjem M, Naït-Abdesselam F. An ECG T-wave Anomalies Detection Using a Lightweight Classification Model for Wireless Body Sensors. In: IEEE ICC 2015 - Workshop on ICT-Enabled Services and Technologies for EHealth and Ambient Assisted Living. London: IEEE; 2015:278-283. DOI: 10.1109/ICCW.2015.7247191

