ORIGINAL RESEARCH PAPER

Anaesthesiology

KEY WORDS: Clonidine, rate pressure product, 2-adrenergic receptor agonist, anxiolysis, sedation.

EFFECT OF ORAL CLONIDINE PREMEDICATION ON PERIOPERATIVE CARDIAC WORKLOAD FOR PATIENTS UNDERGOING SURGERIES UNDER GENERAL ANAESTHESIA

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ABSTRACT

Introduction: Term premedication refers to the drugs that are administered to patients before conduct of anesthesia with specific objectives for intended anesthesia technique. During conduct of general anesthesia there are occasions that leads to increase in cardiac workload that may be harmful in patients having prior chronic cardiac and respiratory diseases[1]. To control the deleterious effects of enhanced sympathetic activity which results from increased catecholamine release, alpha2 agonist Clonidine hydrochloride has also been tried as oral premedication drug to control perioperative hemodynamic changes affecting the cardiac workload (RPP) in patients undergoing surgery. Proposed study was designed to evaluate the effects of oral clonidine premedication on cardiac workload, pain relief & sedation in patients undergoing abdominal surgeries. **Methodology:** On the approval of the Institutional Ethical Committee 50 adult patients belonging to ASA grade I and II scheduled for elective surgery were divided in two groups of 25 each. Group I: Patients were given Tablet clonidine 150 mcg orally 90 mins before induction of anaesthesia. Group II: Patients were given Vitamin C tablets 100 mg (placebo) orally 90 mins before induction of anaesthesia. After 90 minutes, the patients were shifted to operating room and the preoperative hemodynamic parameters – Heart rate, ECG, SBP, DBP, MAP recorded along with Ramsay sedation score. **Results:** The clonidine-induced reduction in blood pressure and heart rate decreases the cardiac workload. The drug is also beneficial in patients with coronary artery disease, and appears to have a coronary vasodilating effect thus enhancing the effect as premedication. The reduction in Rate pressure product was significantly higher in clonidine treated patients. **Conclusion:** The magnitude of increase in mean rate pressure product was higher in control group than study group patients during all periods of observation indicating its use as premedication is effective to control cardiac workload because of sympathoadrenal activation. Postoperatively study group of patients were cooperative, oriented and responding to verbal commands according to Ramsay sedation score.

INTRODUCTION

In the earlier days before 1840, all patients used to receive decoction of herbs like hyoscyamus, poppy, marijuana and other plant to render patients stuporous for surgery. Many times, alcoholic drinks were offered to the patients for the similar purposes and the patients were operated speedily under stuporous condition.

It was observed that during the conduct of light general anesthesia there are occasions when sympathetic stimulation occurs like laryngoscopy and endotracheal intubation, skin incision, handling the viscera, extubation that results in uncontrolled rise in pulse rate and blood pressure in patients and causes hemodynamic instability effecting cardiac workload that may be harmful in patients having prior cardiac & respiratory diseases.

As an established measure of myocardial load, rate pressure product (RPP) may provide a more reliable assessment of cardiac workload. The RPP is a derived cardiovascular index that defines the work done by the heart and the energy requirement. It is obtained by multiplying systolic blood pressure and heart rate. A value above 30,000 indicates risk of developing adverse cardiac event. RPP indirectly reflects myocardial blood supply and oxygen consumption. RPP was a stronger predictor of Cardiac mortality than SBP or heart rate alone[1].

Clonidine hydrochloride is a centrally acting selective partial 2 adrenergic agonist (220:1 2 to 1 activity) that acts as an antihypertensive drug by virtue of its ability to decrease sympathetic output from the central nervous system (CNS).

Thus, the major clinical effects observed and useful in anesthesia are sedation, analgesia, moderate hypotension and bradycardia and decreased requirement of anesthetic drugs.[3]

Objectives

Primary objective of the study was to evaluate the effect of oral clonidine as premedication on cardiac workload. Other objective of this study was to study the sedation score of oral clonidine perioperatively.

Inclusion &exclusion Criteria

Patients belonging physical status classification 1 and 2 As per American Society of Anaesthesiologists age group 20 – 60 years & patients scheduled for elective surgery under general anaesthesia were included in this study.

Following patients were excluded from the study: Unwilling patient or patients not fulfilling inclusion criteria; Patients with cardiovascular diseases like Hypertension, CAD, LVH and LVF, CVA, Diabetes; Patients on MAO inhibitor drugs & known case of COPD/asthma.

Methodology

Study type: Prospective, randomized, controlled, observational clinical investigation.
Sample size: Two groups of 25 each was made, Group A received clonidine 150 mcg orally and Group B patients received placebo tablet of Vitamin C.

All patients underwent thorough preoperative evaluation, history of present illness, past medical illness and previous exposure to anaesthesia was obtained and recorded in predesigned proforma. Examination included general and systemic examination and baseline biochemical investigations were performed as per institutional protocol to rule out presence of occult systemic diseases. A written informed consent was obtained from patients for inclusion in the present clinical study[4].

Method Of Randomisation

Case number 1,3, 5, 7.... till 50 received tablet Vitamin C. Case

number 2, 4, 6, 8..... till 50 received tablet clonidine hydrochloride 150mcg. Patients were given either a tablet of clonidine (150 mcg) or a similar looking vitamin C tablet 90 minutes before the scheduled time surgery on arrival in reception area of operation theatres. Two groups of 25 each was made, Group A received clonidine 150 mcg orally and Group B patients received placebo tablet of Vitamin C.

Details Of Anesthesia Procedure & Data Procuring

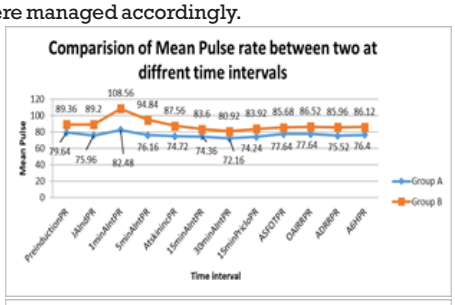
Intravenous line with intracath was secured and infusion with ringer lactate solution was started. Multiparameter monitor was applied to continuously record ECG, NIBP, SpO2, heart rate.

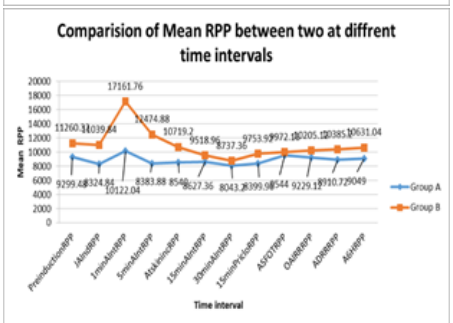
In all patients general anaesthesia was induced with injection propofol, succinyl choline and endotracheal intubation was rapidly carried out. Anaesthesia was maintained with Gas, Oxygen, relaxant (atracurium / vecuronium), narcotic analgesic (pentazocine 30 mg) and traces of isoflurane 0.6 to 1.2 %. Controlled ventilation using Bain circuit was carried out.

The arterial pressure was maintained by adjusting the dose of isoflurane within ±20% of baseline value. For bradycardia heart rate less than 60 bpm, injection atropine 0.6mg intravenously was administered. For hypotension, a fluid bolus of 500 ml was given and if hypotension not controlled with fluid bolus, then injection mephentramine 6 mg was given[5].

Although hemodynamic parameters and ECG were monitored continuously and these were recorded at prior to induction, 1minute, 5 and 10 minutes after endotracheal intubation, at skin incision and 15 minutes prior to closure. In postoperative period vital parameters were recorded at 30, 60 minutes after 4 and 6 hours. Residual effect of neuromuscular blockade was reversed with injection neostigmine and injection glycopyrrolate. After which the patient was shifted to recovery room.

Occurrence of adverse events like nausea, vomiting, hypotension, hypertension, and bradycardia were recorded and were managed accordingly.





Statistical Analysis

The data was analysed by calculating mean and standard deviation and standard error of mean;

The mean age of the patients included in the study was 47.0 years. Majority of patients included were in their late thirties or forties.

Accompanying bar diagram shows Mean pulse rate in group A patients was 83.6±6.6 bpm and 86.1±6.4 bpm in group B patients. Mean systolic pressure in group A patients was 129.4± 17.6mmHg. In group B patients SBP observed was 126.4 ± 8.9mmHg.

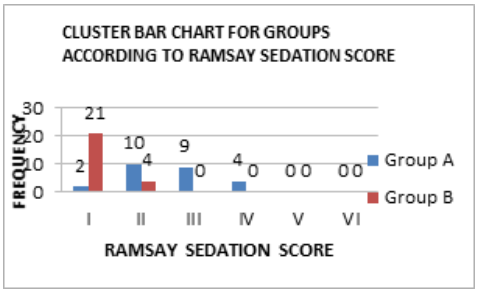
The change in mean pulse rate observed in group A & B patients was 79.6±10.7 bpm and 89.8±9.8 bpm respectively. The statistical difference observed between the two groups was highly significant. Mean SBP in group A patients was 121.2±18.7 and 126.4±8.9 mm hg in group B patients. The change observed in SBP between the two groups was not significant. The rate pressure product (RPP) an index of myocardial oxygen supply/demand was lower in study group patients -9299.4±2809.6 in comparison to 11260.3±1476.6 for control group patients and the difference between the study and control group was highly significant.

We observed highly significant changes in all the monitored parameters. Patients belonging to clonidine group had a lower mean pulse rate (75.9 v/s 89.2 bpm), SBP (109.1 v/s 122.2 mmhg), RPP (8324.8 v/s 11039.8). Rate pressure product in both groups remained below critical value that indicates increasing myocardial oxygen demand. The reduction in RPP was of higher magnitude in clonidine treated patients than the patients who received vitamin C.

The changes observed in mean values of different cardiovascular parameters in group A and B patients were: pulse rate (82.4 v/s 108.5 bpm), SBP (122.2 v/s 158.0 mm hg. Rate pressure product during this period rose in both groups; it was slightly above critical value of 15,000 in control group patients while it was below the critical value in patients who received clonidine. The observed values were 10122.0± 2237.8 and 17161.7 ± 1757.8 for clonidine and placebo group respectively. The statistical analysis of all observed cardiovascular parameters was highly significant.

The above data clearly indicates that the oral clonidine premedication reduces the cardiovascular stress during the perioperative period more so at critical phases of anesthesia like laryngoscopy and endotracheal intubation, intraoperatively, during extubation and in immediate postoperative period.

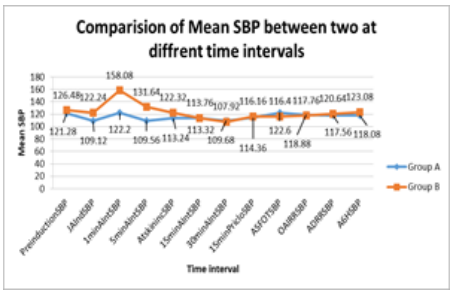
Accompanying cluster bar diagram shows the level of pre-operative sedation as assessed using Ramsay Sedation Score. In group A patients majority of patients (19/25) had sedation score of II or III meaning that patients were cooperative, oriented and responding to commands. Only 2 / 25 patients in group A and 21/25 patients in group B had Ramsay Sedation Score of 1 indicating that these patients were anxious and awake. 4 patients in group A were asleep but responded to light glabellar tap and responded to loud auditory stimulus.



DISCUSSION

Apprehension, fear, anxiety, pain and psychological stress are not uncommon in surgical patients. All together activates hypothalamus hypophyseal adrenal axis (HPE) and results in increased level of stress hormones & high catecholamine levels in the entire operative period causes cardiovascular stress manifests as hypertension, tachycardia, perspiration, etc.

Use of clonidine improves perioperative cardiovascular stability as this drug is expected to prevent patient from surgical and anesthetic stress.



The present study is carried out on 50 adult female patients undergoing total abdominal hysterectomy and other gynecological surgical procedures under general anesthesia causing moderate to severe grade of surgical stress. The study was aimed to find out the extent of cardiovascular protection provided by the single oral dose of clonidine and its other pharmacological benefits.

Change In Pulse Rate:

The observations revealed clearly that before premedication pulse rate was similar in both groups. 90 minutes after pre medication with clonidine mean pulse rate was decreased by 4.0 bpm and did not change much before induction of general anesthesia. 1 minute after induction of anesthesia, laryngoscopy and intubation the pulse rate increased in both groups that settled after 5 minutes but the change observed was highly significant between both the groups. The values observed for clonidine group were lower than placebo group. At 6 hours after surgery pulse rate was close to its preoperative mean value.

In a prospective, randomized, double blinded study Idit Matot, J.Y. Sichel, Valeri Yofe and Yaacov Gozal (2000), studied the effect of clonidine premedication on hemodynamic responses to microlaryngoscopy & rigid bronchoscopy. The authors found that during the procedure the patients receiving placebo exhibited a significant increase in and heart rate (79±15 to 97±12 bpm) when compared with the clonidine group. Authors concluded that premedication with oral clonidine attenuates rate responses and suggested routine use of clonidine during microlaryngoscopy and bronchosocpy[6].

In a prospective, randomized controlled, double blind study, Rashmi Rani, S S Nesargi, 2015, evaluated the efficacy of oral clonidine as a premedicant in attenuating hemodynamic stress response to laryngoscopy and intubation. Authors found that there was a statistically significant difference in heart rate in both groups. The increase in heart rate persisted for a longer time in control group than in clonidine group[7].

Jay Brijesh S.Yadav, Usha Shukla, S.P. Singh, 2015, compared the effects of oral gabapentin and clonidine on preoperative anxiolysis and attenuation of stress response to endotracheal intubation and reported lesser increase in heart rate during laryngoscopy and intubation as compared to gabapentin and placebo. Clonidine group had 12 % increase in heart rate compared to 33 % and 37 % in gabapentin and placebo groups; and found the difference observed to be statistically significant[43].

Changes In Blood Pressure

Similar to our observations in almost all studies reviewed showed a statistically significant reduction in systemic blood pressure following clonidine administration either by oral or intravenous route(B. Brinda , S. Chakravarthy , S. Majunatha (2014)[40]; Dr Dipak L Rawal and Dr Malini K Mehta (2002)[26]; Joan W. Flacke et al (1987)[2]; Anjan Das et al. (2013)[38] .

Changes In Rate Pressure Product:

It can be observed that magnitude of increase in RPP was higher in control group than in study group patients during all periods of observation and a lower mean value were obtained for clonidine.

Rashmi Rani, S S Nesargi, 2015, reported that RPP was well within control in clonidine treated patients with a peak during endotracheal tube placement slightly more than baseline value but within safe range. In control group patients RPP was higher than clonidine treated patients at all interval of time and above the safe limit during laryngoscopy and tracheal intubation[7].

Sheikh Sadat, Tasaduq Javed, Fezoz Ahmad Dar and A.Q. Lone (2015) reported that RPP remained highly significantly elevated in placebo group when compared to clonidine group. The elevated RPP in clonidine group fell to baseline after 5 minutes. During carboperitoneum RPP slightly raised but subsequently decreased.

Abhishek Chatterjee, D.P. Samaddar, Srividhya, Deb Sanjay Nag, Nishant Sahay, (2015), found clonidine to be better than lignocaine in controlling RPP. Only 10/35 patients had 25 % increase in RPP while lignocaine treated patients had higher RPP in 88.58 % of the patients.

Level Of Sedation:

Assessment of preoperative sedation was done using Ramsay Sedation Score. (RSS) In the study group patients 19/25 patients had sedation score of 2 or 3 as opposed to score of 1 in 21/25 patients of control group. The clonidine premedication rendered majority of patients as co-operative, oriented and responding to commands.

Braz L.G. et al (2002) using Bi-Spectral (BIS) index and Ramsay Sedation Score found a significant difference in level of sedation with oral clonidine premedication and found superior to placebo but similar to midazolam. Further authors stated that although Ramsay sedation Score being 25 years old is still the best subjective method to evaluate sedation level. Authors also commented that the level of sedation increased when patients were in proximity of operating room due to increased stress level.

Shuichi Yokota, Toru Komatsu, Kayo Yano, Kazumi Taki and Yasuhiro Shimada (1998), has reported that clonidine has sedative and an analgesic effect. The authors did not found significant effect difference with hydroxizine. They reported no sleepy patient with clonidine premedication and suggested that oral dose up to 5 mcg / Kg dose not affect sedation level[8].

Dr. Rita Singh, Dr Punam Raghove, Dr Manju Chawla, Dr Karampal Singh, Dr Susheela Taxak (2015) studied the effects of oral clonidine premedication ob-served that the anxiety level was significantly lower in patients who received oral clonidine in comparison to placebo and found a higher sedation level[9].

Hidalgo et al (2005) in patients undergoing abdominal hysterectomy under lumbar epidural anesthesia observed a statistically significant decrease in anxiety level in clonidine group as compared to placebo.

Dr Dipak L Rawal and Dr Malini K Mehta (2002) using subjective method found that clonidine produced marked sedation and better anxiolysis as compared to placebo but lesser sedation and similar anxiolysis than with diazepam.

Archana Raichurkar, Dinesh K, Ravi M, Anand T Talikoti, Somasekharam P (2015), compared the effects of oral Pregabalin and Clonidine and that sedation scores were more pronounced among the patients who received pregablin and was statistically significant.

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