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EFFECT OF ORAL CLONIDINE PREMEDICATION ON PRESSOR RESPONSE FOR PATIENTS UNDERGOING ABDOMINAL SURGERIES UNDER GENERAL ANAESTHESIA.

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ABSTRACT **Introduction:** Preanesthetic medication forms an integral part of anaesthesia management. The premedicant should be easy to administer and should have analgesic and anti-emetic properties, should not impair cardiovascular stability or depress respiration, should have antisialagogue effect and should effectively alleviate apprehension of the patient[1]. Alpha-2 adrenoceptor agonists have been used as premedicant from 1999 onwards. Clonidine hydrochloride when used as premedicant, it facilitates conduct of anaesthesia and attenuates hemodynamic responses to laryngoscopy and intubation, reduction in stress response to surgery, dose of inhalational anaesthetic, narcotic requirements and provides perioperative hemodynamic stability[2][3]. Proposed study was designed to evaluate the effects of oral clonidine premedication on pressor response 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. **Results:** The study conducted clearly indicated that the oral clonidine premedication attenuates the sympathoadrenal response during critical phases of anaesthesia like laryngoscopy and endotracheal intubation, intraoperatively, during extubation and in immediate postoperative period. **Conclusion:** The study provides clear evidence in support of premedicating the patients with clonidine under varieties of surgical circumstances. Clonidine whether administered by oral or by intravenous route provides statistically significant and clinically meaningful beneficial effects. Preoperative medication with clonidine reduces preoperative anxiety and provides sedation with mild analgesia & hemodynamic stability in stressful times of anaesthesia and surgery and postoperatively. It does cause minor side effects like bradycardia and hypotension that are easily manageable.

KEYWORDS : Clonidine, haemodynamic, premedication, α2-adrenergic receptor agonist, laryngoscopy, intubation, pressor response, analgesic.

BACKGROUND

Autonomic Nervous System (ANS) is the portion of the nervous system that controls most visceral functions of the body. ANS is divided into two major and one minor system namely sympathetic, parasympathetic and enteric nervous system. Sympathetic and Parasympathetic nervous system is usually physiological antagonist[4]. Two classes of receptors for parasympathetic system (acetyl choline) are identified – muscarinic and nicotinic receptors. Similarly, two classes of sympathetic receptors are recognized on the basis affinity to adrenergic agonists namely - alpha and beta-adrenergic receptors. Alpha receptors based on the pharmacological criteria have been classified as α1 and α2 and not on the anatomical location. Molecular cloning has further identified 3 subtypes of α1 and α2 receptors namely α1A, α1B and α1D; α2A, α2B and α2C[5].

Clonidine hydrochloride is a centrally acting selective partial α2 adrenergic agonist (220:1 α2 to α1 activity) that acts as an antihypertensive drug by virtue of its ability to decrease sympathetic output from the central nervous system (CNS). Clonidine produces clinical effects by binding to α2 receptors of which there are three subtypes (α2A, α2B, α2C) that are distributed ubiquitously. α2A receptors mediate sedation, analgesia, and sympatholytic, whereas α2B receptors mediate vasoconstriction and possibly antishivering effects[6]. The startle response may reflect activation of α2C receptors. Clonidine also has the ability to modify the function of potassium channels in the CNS which may be the mechanism for profound decrease in anaesthetic requirements[1].

Thus, the major clinical effects observed and useful in anaesthesia are sedation, analgesia, moderate hypotension and bradycardia and decreased requirement of anaesthetic drugs. Prolonged administration of clonidine as an antihypertensive drug may result in xerostomia, orthostatic hypotension and rebound hypertension on sudden withdrawal[6].

Our study is based on null hypothesis stating that there is no difference in premedicating the patient with oral clonidine in attenuating the pressor response while undergoing abdominal surgeries under general anaesthesia. Due to the dearth of medical literature about the effect on perioperative hemodynamics of oral clonidine as premedication, this study was conducted.

OBJECTIVES

Primary objective was to study effects offered by single per oral dose of clonidine on pressor response to laryngoscopy & intubation. Other objective was to evaluate whether per oral administration of single dose of clonidine affects the dose requirement of volatile anaesthetics to keep optimal control pulse & blood pressure within ± 20 % of the preoperative values.

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[7].

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 hemodynamic fluctuations medical intervention was done other than adjusting the dose of isoflurane.

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[8].

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 as the number of patients exhibiting these and managed accordingly.

Statistical Analysis

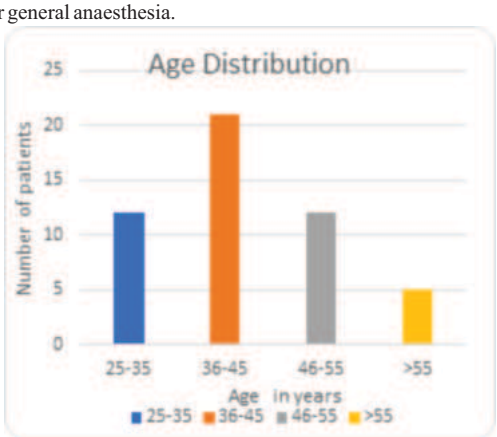
The data was analysed by calculating mean and standard deviation and standard error of mean; comparison was made between two study groups by student's t test and with standard institutional method.

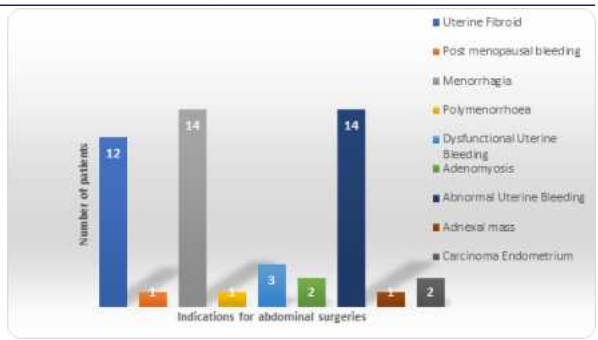
Continuous numeric data were analysed by Mean and standard deviation and give its significant values by two sample t-test. P value of <0.05 was considered significant.

RESULTS

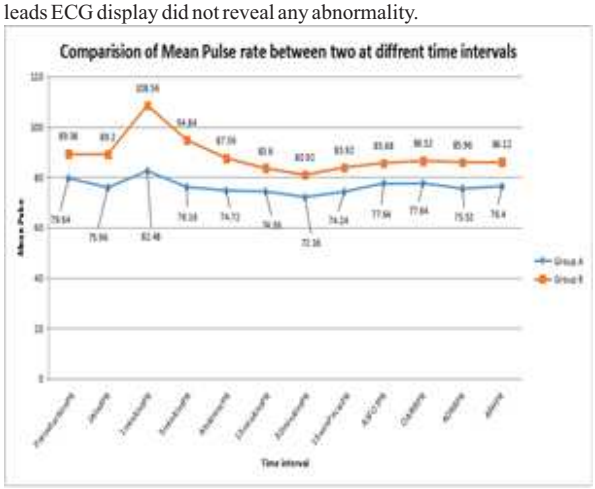
After the collection, tabulation, and analysis of the data, the following inferences were drawn;

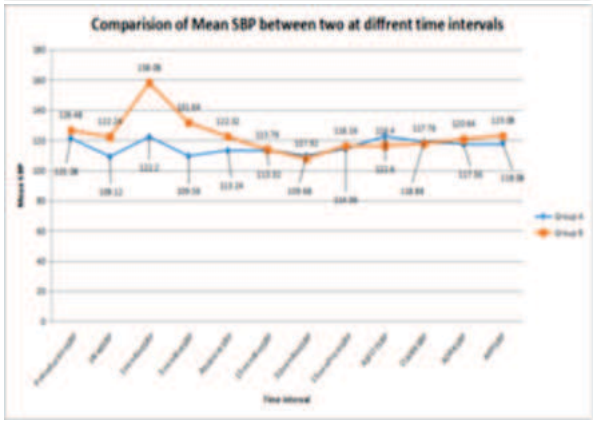
The mean age of the patients included in the study was 44.0 years. Majority of patients included were in their late thirties or early forties. 33 patients were between the age group of 36 – 55 years as depicted by the bar diagram along with the indications for abdominal surgeries under general anaesthesia.



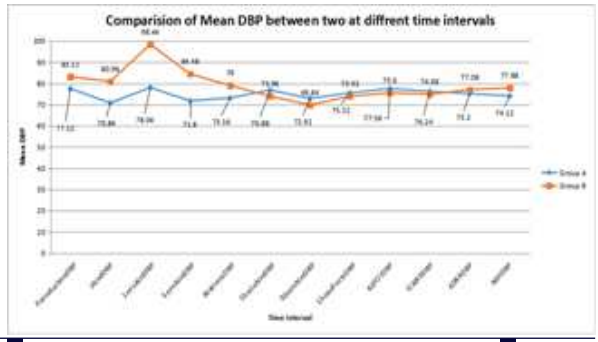


The bar diagram below shows the mean preoperative baseline hemodynamic parameters. All the parameters observed in both group A & B were comparable and difference observed was statistically not significant. Mean pulse rate in group A patients was 83.6±6.6 bpm and 86.1±6.4 bpm in group B patients. Mean systolic, diastolic and mean arterial pressure in group A patients was 129.4± 17.6, 81.0 ± 6.2 and 96.7 ± 9.7 mm of Hg respectively. In group B patients SBP, DBP and MAP observed was 126.4 ± 8.9, 83.1 ± 5.6 and 97.4 ± 6.3 mm of Hg. 12 leads ECG display did not reveal any abnormality.



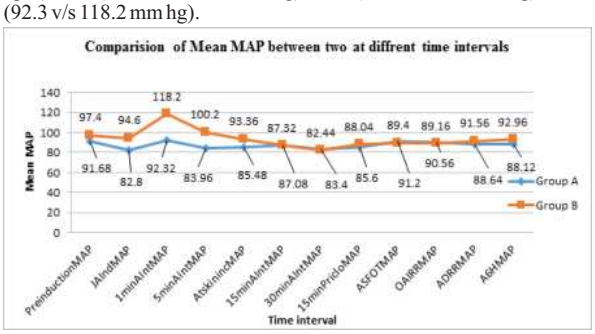


The change in mean pulse rate observed in group A & B patients was 79.6±10.7 bpm and 89.8±9.8 bpm respectively. The statistical difference observed between the two groups was highly significant.



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 whereas highly significant change in DBP (77.5 v/s 83.1) and significant change in MAP (91.6 v/s 97.4) was observed.

In both groups we observed hemodynamic response to laryngoscopy and endotracheal intubation. Placebo treated patients showed a greater response to laryngoscopy and endotracheal intubation while in oral clonidine treated patients the response was of lesser magnitude. 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), DBP (78.0 v/s 98.4 mm hg), MAP (92.3 v/s 118.2 mm hg).



The statistical analysis of all observed cardiovascular parameters was highly significant.

For clonidine treated patients mean value of pulse rate was lower than in control group patients and the change observed was highly significant at all time of observations.

Complication	Group A	Group B	Z value	P value
Bradycardia	14	3	3.28	0.001
Hypotension	6	2	1.54	0.123
Vomiting	1	8	2.57	0.009
Shivering	2	10	2.64	0.008

Above table shows the incidences of adverse effects observed in study and control group patients. Sinus bradycardia and hypotension was a common observation in clonidine treated patients. 14 out of 25 patients showed sinus bradycardia that responded to injection atropine 0.6 mg intravenously and 6 out of 25 patients had hypotension that responded to fluid loading and injection mephentramine 6 mg intravenously. In 3 patients out of 25 of group B showed bradycardia that responded to injection atropine. 2 patients of group B had shown hypotension that responded to fluid loading.

The incidence of postoperative nausea and vomiting and shivering was higher in group B than in group A patients. 8 out of 25 patients in group B showed post-operative nausea and vomiting and 10 out of 25 patients had shivering.

The statistical analysis was done by applying Z test for comparing proportions of two different groups. The proportion of patients showing bradycardia was highly significant. The incidence of vomiting and shivering was in high proportion in control group patients and change was highly significant.

DISCUSSION

During the operative period there are occasions like laryngoscopy & endotracheal intubation, skin incision, handling of organs and viscera that result in surgical stress and subsequent rise in pulse rate and blood pressure. These changes are usually short lasting and are handled well in patients who are normotensive or not having any other cardiovascular dysfunction. In patients with uncontrolled hypertension, coronary artery disease, valvular disease, cerebrovascular accidents; these changes may prove deleterious and precipitate cardiac event in such population.

Clonidine and other alpha 2 agonist (dexmedetomidine) are under intense clinical investigation as an adjuvant to anaesthesia. Sedation, analgesia and anti-shivering properties are their desirable pharmacological actions in perioperative period[6]. Use of clonidine improves perioperative cardiovascular stability as this drug is expected to prevent patient from surgical and anaesthetic stress.

In the present study a fixed dose of 150 mcg was administered to average built patients approximating to 2.5-3 mcg/kg for a patient of 50-60kg body weight. The drug was administered orally with a sip of water 90 minutes before induction of anesthesia. Pharmacokinetic studies have established that peak plasma concentration of clonidine is achieved within 60-90 minutes after oral administration[9]. In most of the studies reviewed Dr Dipak L Rawal[10] and Dr Malini K Mehta; B. Brinda, S. Chakravarthy, S. Majunatha; Rashmi Rani, S S Nesargi employed oral clonidine in similar dose. Shuichi Yokota, Toru Komatsu, Kayo Yano, Kazumi Taki and Yasuhiro Shimada; Abhishek Chatterjee, D.P. Samaddar, Srividhya, Deb Sanjay Nag, Nishant Sahay; Rashmi Rani, S S Nesargi observed dose dependent sedation and cardiovascular effects of orally administered clonidine.

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. During the remaining intraoperative and in immediate postoperative period pulse rate was more or less to close preoperative mean value.

Savitha K.S, Sampa Anupurba, Smita L. Almeida (2014), compared the effects of intravenous lidocaine, intravenous esmolol and intravenous clonidine on haemodynamic responses to laryngoscopy and oro-tracheal intubation in normotensive patients. Results showed that there was significant rise in Heart Rate one minute following intubation in all three groups ($p<0.001$). HR reached near to baseline at 4 minutes in patients who received esmolol which was statistically significant ($p<0.01$) whereas with lignocaine and clonidine the raised heart rate settled after 8 – 10 minutes and reported clonidine and lignocaine are not better choice for reducing heart rate in stressful situation [11].

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[2].

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[3].

We observed a significant difference in SBP, DBP and MAP between both groups at the time of induction of anaesthesia, laryngoscopy and intubation and at skin incision; 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); Dr Dipak L Rawal and Dr Malini K Mehta (2002); Joan W. Flacke et al (1987); Anjan Das et al. (2013) . Some authors reported dose dependent reduction in blood pressure (Abhishek Chatterjee, D.P. Samaddar, Srividhya, Deb Sanjay Nag, Nishant Sahay, (2015); Rashmi Rani, S S Nesargi, (2015); and some reported clonidine to be more effective than gabapentin (Saikat Majumdar et al, 2015 and Jay Brijesh S.Yadav, Usha Shukla, S.P. Singh, 2015) but Seyed Mojtaba.Marashi, Mohammad Hossein.Ghafari and Alireza Saliminia 2009 found clonidine less effective than gabapentin and also lesser effective than pregabalin (Archana Raichurkar, Dinesh K, Ravi M, Anand T Talikoti, Somasekharam P, 2015) in controlling the pressure response.

We observed a frequent occurrence of bradycardia and hypotension in clonidine treated patient that responded well to the treatment with atropine, fluid load and or vasopressor. Shivering and vomiting was observed more commonly in control group patients. Antishivering effect of clonidine could be the cause of less incidence than in control group. Similar findings were reported by Joan W. Flacke et al (1987); Dr. Rita Singh, Dr Punam Raghove, Dr Manju Chawla, Dr Karampal

Singh, Dr Susheela Taxak (2015); Kalpana Kulkarni, Rupesh Goel and Shirish Kumar Talakanti 2016.

CONCLUSION

Thus, the above discussion provides clear evidence in support of premedicating the patients with clonidine under varieties of surgical circumstances for attenuation of pressor response to laryngoscopy & endotracheal intubation. The drug also provides hemodynamic stability in stressful times of anaesthesia, surgery and postoperatively. It does cause minor side effects like bradycardia and hypotension that are easily manageable.

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