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ROLE OF ORAL GABAPENTIN VERSUS CLONIDINE AS PREMEDICATION IN PATIENTS WITH CORONARY ARTERY DISEASES POSTED FOR NONCARDIAC SURGERIES .-A RANDOMIZED CONTROLLED TRIAL

Anaesthesiology

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ABSTRACT

Background: Laryngoscopy and endotracheal intubation (L and I) is associated with rise in blood pressure (BP), heart rate (HR), leading to adverse cardiological outcome especially in coronary artery diseases . To compare haemodynamic responces during L and I as well as to evaluate the preoperative status between oral clonidine (Group C) and oral gabapentine (Group G) as premedication for the patients undergoing noncardiac surgeries having coronary artery diseases.

Materials and Methods: In this prospective, double-blinded, and randomized controlled study; 100 adult patients of either sex, aged 20-70, of American Society of Anesthesiologists status II and III scheduled to undergo noncardiac surgeries, randomly allocated into groups C and G were pre treated with oral clonidine (200 µg) and gabapentin (800 mg) respectively prior to induction. Hemodynamic parameters were noted just before induction, during L and I 1,3,5,7, and10 min after intubation. The results obtained were then analyzed with statistical unpaired "t" test and Chi-square test and compared.

Results and Analysis: Group C attenuated HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) more significantly before induction, during L and I, 1, 3, and 5 min, following L and I, while comparing with group G. Again gabapentin-reduced HR, BP, (SBP, DBP, MBP) significantly more at 7 and 10 min after L and I on comparison clonidine.

Conclusion: Oral clonidine is more efficacious in reducing laryngoscopic stress response than oral gabapentin in patients with coronary artery disease posted for noncardiac surgeries.

KEYWORDS

Clonidine, gabapentin, laryngoscopy and endotracheal intubation, , coronary artery bypass grafting surgery.

INTRODUCTION

The aim of anaesthesiologist is not only to ensure a smooth induction and intubation but also to ensure an uneventful postoperative period. The challenge in anesthesia is to maintain a balance between the stress of the laryngoscopy, tracheal intubation, and surgical procedure with the cardiorespiratory depressant effects of deeper levels of anesthesia. Laryngoscopy and tracheal intubation (L and I) is a strong stimulus for cardiovascular system under light anesthesia.[1] The magnitude of response is great with increasing force and duration of laryngoscopy.[2] The elevation in arterial pressure typically starts within 5 s of laryngoscopy, peaks in 1-2 min and returns to control level within 5 min.[1] Such hemodynamic changes can result in myocardial ischemia, especially in patients with cardiovascular disease.[2]

To attenuate the hemodynamic response, many techniques have been tried but none is ideal. It can be prevented by increasing the depth of anaesthesia but concentration changes of anesthetic agents in blood and effector sites occur slowly in relation to the onset and offset of airway stimuli and hemodynamic response. Volatile anesthetic agents with N2O may be beneficial. Large doses of fentanyl, (5-10 µg/kg) may attenuate the hemodynamic response but cause prolonged respiratory depression. Aerosol or other application of topical anesthetics may be beneficial.[3] Combination of topical anesthetics and parenteral opioids may be useful.[4] Labetalol and esmolol may be used in combination with narcotics.

Gabapentin, 1–(aminomethyl) cyclohexane acetic acid, is a structural analogue of the neurotransmitter, γ–amino butyric acid (GABA) was introduced in 1993 as an adjuvant antiepileptic drug for the treatment of refractory partial seizure.[5] It was shown to be effective in treating postherpetic neuralgia,[6] other neuropathic pain,[7] postpoliomyelitis neuropathy[8] reflex sympathetic dystrophy.[9] Diabetic neuropathy[10] and it has antinociceptive, antihyperalgesic, and antiallodynic properties.[11] More recently, it has been used to attenuate the stress response to direct L and I. The mechanism by which gabapentin attenuates the pressor response to laryngoscopy and intubation is unknown. The drug inhibits membrane bound voltage gated calcium channels, thus acting in a manner similar to calcium channel blockers.[12,13] Memis et al.,[12] concluded that gabapentin 800 mg before induction of anaesthesia is a simple and practical method for attenuating pressor response to L and I.

Clonidine, the α2 agonist has shown properties that are potentially beneficial for premedication to reduce sympathetic activity, to diminish incidence of shivering and oxygen consumption during recovery from anaesthesia, to decrease anesthetic and analgesic requirement and to minimize post operative pain, nausea, and vomiting.[14] Carabine et al.,[15] concluded that 200 µg oral clonidine-reduced anxiety and laryngoscopy associated hemodynamic surge well in eighty female patients.

In view of these observations, the present study was designed to evaluate the efficacy of oral gabapentin (600 mg) versus oral clonidine (100 µg) premedication for, blunting the haemodynamic variability as well as pressor response to direct L and I in patients with coronary artery diseases posted for noncoronary surgeries.

Aims and Objectives

1. To compare the attenuation of haemodynamic responses during direct laryngoscopy and tracheal intubation of clonidine(100µg) and gabapentin(600mg) premedication.
2. To compare the post operative analgesic requirement.

Materials and Methods -

After in detailed procedure explained and written consent was obtained from all the patients' .ASA Physical status II & III, age between 20 – 70 years and patients put for elective CSBG were included in the study. Study Period – From February 2015 to January 2016. Refusal to give consent ,patients with known allergy to study drug, history of seizure, previous treatment with gabapentin & clonidine ,chronic pain syndrome,psychiatric disorder,history of concomitant medical diseases like –heart block, arrhythmia ,ejection

fruction<45%,respiratory diseases, heart failure, renal diseases, and pregnanant patients were excluded from this study .

Sample Size Total 100 patients ,Group C (n = 50) received 100 µg clonidine,Group G (n = 50) received 600 mg gabapentin Pre-Operative Assessment- Before surgery preoperative assessment, patient counseling and written consent taken from all the patients.

Study technique - After 8 hours fasting, on the day of surgery the patients were brought to the observation room, baseline parameters such as heart rate (HR), systolic BP (SBP), distolic BP (DBP), mean arterial BP (MBP) and oxygen saturation (SpO2) , were measured. Premedication of gabapentin 600 mg (two capsules of 300 mg) or clonidine 100 µg (tab) given by an independent anaesthesiologist. After one hour patient was shifted to the operation table and multi channel monitor was attached Following parameters were recorded before insertion of a 18G IV canula. Radial artery cannulation done . Heart rate (HR),systolic blood pressure (SBP),diastolic blood pressure (DBP),mean blood pressure (MBP) respiratory rate ,electrocardiography ,temperature recorded.

Induction of Anaesthesia Patients were kept on fasting for 8 hours before operation, i.v infusion was started with ringer's injection. Pre oxygenation with 100% O2 was done through Magill's circuit for 5 minutes. Premedication was given with Inj.midazolam 1 mg, Inj. fentanyl citrate 5-8 µg/kg. Induction was done with Inj. etomidate sleeping dose and intubation was done with Inj. vecuronium bromide 0.1mg/kg and cuffed endotracheal tube of appropriate size. Anaesthesia was maintained with 70% N2O in O2, inj. vecuronium bromide (0.02mg/kg) supplemental and sevoflurane inhelation to maintain BIS between 40-60. After completion of surgery all patients were shifted to ITU .

Monitoring during Anaesthesia Following parameters were recorded during laryngoscopy and tracheal Intubation, 1 min, 3 mins, 5 mins, 7 mins and 10 mins following laryngoscopy & tracheal intubation. Continuous ECG (lead-II) & Heart rate, SpO2, invasive arterial blood pressure (SBP, DBP, MBP), EtCO2, temperature.

Statistical analysis - The result obtained in the study were presented in a tabulated -manner and expressed as mean + SD in the following sections. Raw data were entered into a MS Excel spreadsheet and analyzed using standard statistical software SPSS®statistical package version 18.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using the Pearson's Chi-square test. Normally distributed continuous variables were analyzed using the independent sample t test and P < 0.05 was considered statistically significant.

Results and Analysis

Table – 2.Comparison of heart rate in (beats per minute) between the groups at various time points of L & I.(n=100)

P <0.05 denotes significant difference between the groups. There is statistically significant difference found at most of the time in mean HR between the two groups during L & I.

Variables		GROUP-C	GROUP-G
Age (in year) (MEANSD)		53.01±8.2544	51.42±9.3056
Sex	Male	26(52%)	25(50%)
	Female	24(48%)	25(50%)
Body weight(MEANSD)		58.42±4.88	56.52±3.80
Height(Cm) (MEANSD)		157.20 5.48	159.22 6.37
ASA	II	26	27
	III	24	23
Duration of surgery(MEANSD)		226.7329.41	234.4425.93
Sedation Score(>3)		2/19	2/21
PONV(NAUSIA,)		3/50(6%)	0/21(0%)

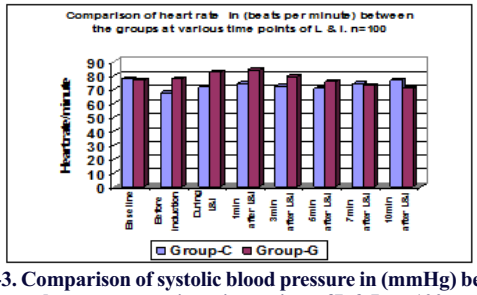

Table-3. Comparison of systolic blood pressure in (mmHg) between the two study groups at various time points of L & I..n=100

P <0.05 denotes sig. dif. between the groups there is statistically significant difference found at all the time in mean systolic blood pressure between the two groups during L & I.

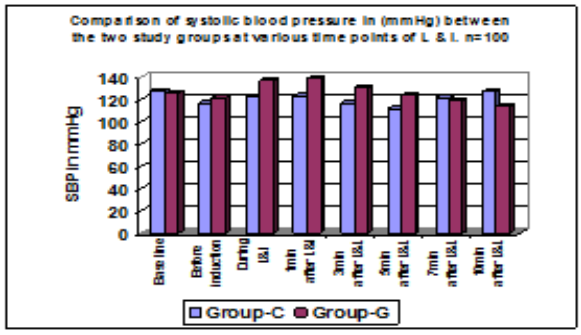

Table – 4.Comparison of diastolic blood pressure in (mmHg) between the groups at various time points of L & I. n=100

P <0.05 denotes sig. dif. between the groups .there is statistically significant difference found at most of the time in mean diastolic blood pressure between the two groups during L & I.

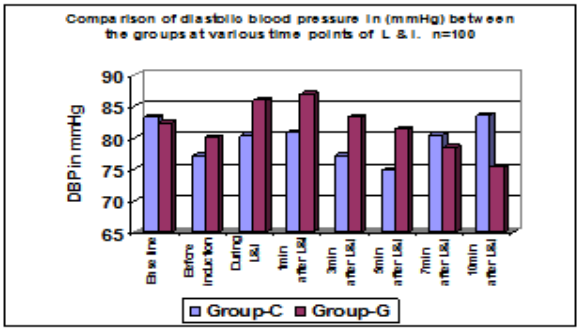

Table – 5. Comparison of mean blood pressure in (mmHg) between the groups at various time points of L & I n=100

P <0.05 denotes sig. dif. between the groups. There is statistically significant difference found at all the time in mean blood pressure between the two groups during L & I.

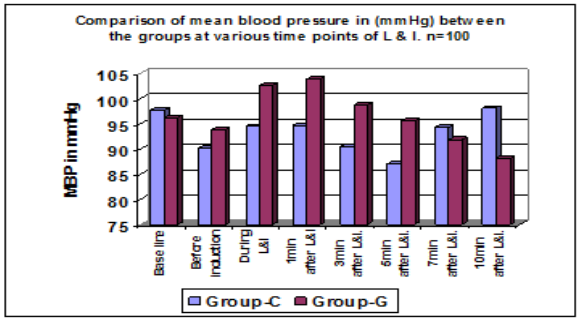

Table – 6 Comparison of 24 hours injection Fentanyl consumption between the groups.n=100

Variables	100-300mcg	300-500mcg	Total
Clonidine	14 (no.of pt.) (28%)	36 (no. of pt.) (72%)	50
Gabapentin	42 (no.of pt.) (84%)	8 (no. of pt.) (16%)	50

Discussion- Endotracheal intubation has become the mainstay of modern anesthesia as it secures the airway, prevents aspiration of gastric contents, delivered predictable Fio2 and eliminates CO2 from the body. It has been observed that laryngoscopy and tracheal intubation leads to reflex cardiovascular response, producing tachycardia and systemic arterial hypertension. These circulatory changes may produce detrimental effect in patients with cardiovascular and cerebrovascular disease & various operation. In order to reduce the incidence and severity of this deleterious effects on haemodynamics , numerous technique have been used with varying degrees of success. These techniques include deepening[16] of the plane of anaesthesia (King et al.; 1951). A variety of drugs[17] have been used to control this hemodynamic response (Kovac; 1996).

The present study was carried out with oral premedication with clonidine(100µg) & gabapentin (600mg) 1 hour before surgery to compare the attenuated haemodynamic response following L&I and post operative analgesic requirement .

Clonidine, an imidazoline derivative, is a selective α2A adrenergic receptor agonist. It is a potent antihypertensive drug. It produces a fall in heart rate and blood pressure associated with decreased cardiac output but unchanged peripheral resistance. Activation of central nervous system α2A receptors, resulting in a decreased central outflow of impulses in the sympathetic nervous system and recently proved to have some beneficial premedicating effects like sedation,[18] reduction of dose of induction agent,[19,20] attenuation of laryngoscopic stress response.[18,21]

Gabapentin, 1-(aminomethyl) cyclohexane acetic acid, is a structural analogue of the neurotransmitter γ–aminobutyric acid. The mechanism of gabapentin in controlling this haemodynamic response remains unknown. Since, gabapentin inhibits membrane voltage gated calcium channels (VGCCs), it is possible that it may have a similar action to calcium channel blockers. There is, as yet, no data, on the possible role of gabapentin in the attenuation of other aspects of the stress response to surgery.[4] Some studies demonstrated that the descending noradrenergic system, spinal α2 adrenergic receptors and an intact spino-bulbo-spinal circuit are crucial elements influencing the analgesic effects of gabapentin in addition to α2Ainteraction of VGCCs.[22,23]

The demographic profile (age, sex, body weight, ASA status) between two groups which was statistically insignificant (P > 0.05) of our patients was quite similar with other research investigations and provided us the uniform platform to evenly compare the results obtained. A study conducted by Marashi et al.,[24] in a total of 75 patients yielded similar results. The mean duration of anesthesia and surgery were almost comparable in both the groups with no significant statistical difference [Table 1].

In our study base line heart rate comparable between the groups (p > 0.05). In group G there was significant rise of heart rate during, 1 min and 3 mins following (L & I),those are statistically highly significant between the groups (p=<0.0001). Thereafter decrease below the base line at 7mins (p>0.05) & 10 mins after L & I. In group C – there was no significant rise of heart rate throughout the observation period.

In group G there was a significant rise of systolic blood pressure during , 1 min and 3 mins following L & I, thereafter it decreases below base line during 7 mins & 10 mins after L & I. In group C – there was mild increase in systolic blood pressure during, and 1 min after L&I those are statistically insignificant, but there are significant difference between the two groups (P < 0.05) throughout the observation period following L & I. Regarding diastolic pressure, group G showed significant increase in diastolic pressure during, 1 min and 3 mins following L & I (ref. table- 4) thereafter it decreases at 5 mins, 7 mins and 10 mins after L& I. In group C there was mild increase in diastolic blood pressure during 7 mins after L & I which is statistically insignificant (P = 0.07), otherwise statistically highly significant difference found between the groups(p<0.0001).

In comparison of mean arterial blood pressure, group G showed a significant increase in mean arterial blood pressure during, 1 min and 3 mins following L & I (ref. table-5). Thereafter decreases towards base line following 5 mins, 7 mins and 10 mins after L & I. In group C – mild increase during L & I & 1 min after L&I then decrease at 3 mins & 5 mins but again increase at 7 mins & 10 mins after L & I. There was statistically significant difference found between the group throughout the observational period (P < 0.05).

Howie MB25 conducted a study among 54 patients undergoing elective coronary artery bypass graft (CABG) surgery. Patients received approximately 5 micrograms/kg of oral clonidine or a placebo together with 40 micrograms/kg lorazepam 90 minutes prior to titrated sufentanil induction of anesthesia. Thirty minutes prior to cardiopulmonary bypass, a second dose of either approximately 5 micrograms/kg clonidine or placebo was given as a slurry via a nasogastric tube. Patients receiving clonidine required significantly (p < 0.04) less sufentanil for induction (clonidine: 2.19 +/- 0.95 micrograms/kg vs. placebo: 2.93 +/- 1.07 micrograms/kg) and total amount of sufentanil (clonidine: 9.1 +/- 3.9 micrograms/kg vs. placebo: 11.7 +/- 4.6 micrograms/kg). Patients receiving clonidine required significantly (p < 0.01) less isoflurane (9.7 +/- 6.8 MAC min vs. 19.7 +/- 9.9 MAC min) to maintain heart rate (HR) and mean arterial pressure (MAP) to within 15% of baseline without significant differences in other vasoactive drugs. Catecholamine concentrations were significantly (p < 0.02) lower in patients receiving clonidine without any difference in beta-endorphin concentrations. Patients receiving clonidine had significantly (p < 0.02) lower HR, systolic arterial pressure, MAP, and systemic vascular resistance prior to induction than patients receiving placebo without differences in other hemodynamic variables. He concluded Clonidine decreases opioid use and lowers hormonal response while maintaining stable hemodynamics in patients undergoing CABG with sufentanil anesthesia. We compared clonidine and gabapentine in CABG but we deliberately avoided glypopyrrolate and used midazolam, fentanyl based induction. Clonidine proved as better, than gabapentine in maintaining haemodynamics during L&I.

Marashi S M, and coworkers 24 conducted a double blind, placebo-controlled randomized study for elective orthopaedic surgery. The author used 900 mg gabapentin and 200 µg clonidine, 2 hours before surgery and concluded that both gabapentin and clonidine have effective role in blunting the hyperdynamic responses following L&I more so with gabapentin.In our study,blunting the haemodynamic,reflex response following L & I,clonidine have better response than gabapentin.

Dipak K Raval and coworkers (2002)26 studied the effect of oral clonidine premedication for attenuation of haemodynamic responses to L & I. They studied 100 ASA Gr – I, II ,age between 18-65 years compare the effectiveness of oral clonidine as a premedicant and for attenuation of haemodynamic responses to L&I with oral diazepam and placebo. The patients were divided into 3 groups, group C [n = 40] received tablet clonidine 4 µg/kg ,group D [n =40] received tablet diazepam 0.2mg/kg and group-P [n = 20] received tablet placebo (antacid), about 90 minutes before induction of anaesthesia. Clonidine provided advantage over diazepam and placebo by blunting haemodynamic responses duringL&I. This study results corroborated with our study though we have given 600 mg gabapentin and 100µg clonidine 1 hour before surgery.

Indira Kumari and coworkers (2009)27 conducted a randomized double – blind placebo controlled study of oral gabapentin (900 mg) given 2 hours before induction and concluded that attenuation of blood pressure response to L&I was effectively seen only after 10 minutes of intubation. In our study we have seen gabapentin induced haemodynamic response was attenuated after 7 mins following L & I.So, this study results nearer to with our study though we have given less dose (600 mg gabapentin).

In our study, when we compared the two groups postoperative mean heart rate was significantly higher in gr.C compared to gr.G at 1 hour,6 hour & 12 hour of postoperative period (p < 0.0001) .But no significant difference at 24 hour period (p>0.05). In comparison of post operative mean arterial blood pressure, highly significant decrease in MBP was found at 1 hour, 6 hour, 12 hour & 24 hour post-operative period in group G(p<0.0001).

Summary and Conclusion

In this prospective clinical comparative study,an attempt was made to compare efficacy of oral clonidine & gabapentine premedication on haemodyneamic response to laryngoscopy and endotracheal intubation in patient undergoing coronary revascularization surgery.

Hundred healthy ASA physical status I & II patients for either sex belonging to age group of 20-60 yrs, scheduled to undergo surgery of > 1 hour duration ,were selected for the study.The patients were divided into two groups (50 patients in each group), Group C and Group G were pre treated with oral clonidine (100 µg) and gabapentin (600 mg) respectively. After inducing the patients with thiopental and succinylcholine following pre oxygenation, the act of laryngoscopy and intubation were performed in a smoothest possible manner and as quickly as possible. The anaesthesia was maintained with nitrous oxide, oxygen and vecuronium. Hemodynamic parameters were noted before study drug administration, just before induction, during laryngoscopy and intubation 1,3,5,7 and 10 minutes after intubation, in the post operative period VAS score, HR, MBP and analgesic requirements were measured at 1,6,12 and 24 hour after operation. Untoward side-effects like PONV, dizziness, pruritus, headache and sedation were also noted postoperatively. The results obtained were

then analysed with statistical unpaired 't'test and chi-squre test and compared. Analyzing the different data obtained from this study it was found that group C(clonidine) attenuated HR,SBP,DBP and MBP more significantly before induction, and during 1,3 and 5 minutes following L&I compare to group G. But gabapentin reduced HR, SBP,DBP and MBP significantly more at 7 and 10 minutes after L&I compare to clonidine.

Highly significant decrease in VAS score & analgesic consumption (fentanyl) was found in group G in post operative first 24 hours.

So, clonidine and gabapentin were effective in attenuating the cardiovascular stress response associated with laryngoscopy and intubation but clonidine is more effective during laryngoscopy and intubation, 1 min, 3 mins and 5 mins after L&I. Gabapentin is effective after 7 mins following L&I .

CONCLUSION- Oral clonidine (100 µg) is the better attenuator amongst the two drugs studied over here to attenuate the cardiovascular responses to L&I .Oral gabapentine (600 mg) is the better preemptive analgesic amongst the two drugs studied here. Further studies are required to find out the optimal dose of the drugs which will effectively prevent the pressor response to laryngoscopy and tracheal intubation and post operative analgesic requirement without increase in side effects of the drugs.

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