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Oral clonidine vs pregabalin premedication on preoperative sedation and attenuation of pressor response to direct laryngoscopy and endotracheal intubation: a randomized double blind study

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Abstract

Background: Hemodynamic stress response resulting from direct laryngoscopy and tracheal intubation may produce adverse effects like tachycardia, hypertension which can lead to intraoperative myocardial ischemia and intracerebral haemorrhage.

Aims and Objectives: Our aim was to compare the potency of oral clonidine and oral pregabalin in attenuating the stress response due to laryngoscopy and tracheal intubation.

Materials and Methods: 100 patients of ASA (I/II), posted for elective surgeries under general anaesthesia were included in the study. All the patients were devided into two groups. Group A received oral clonidine 0.3mg and group B received oral pregabalin 150mg, 90 minutes before surgery with a sip of water. Standard anaesthesia was administered. Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), mean arterial pressure (MAP) and heart rate were recorded preoperatively, after premedication, immediately after intubation, then at 1 min, 3 min, 5 min, 10 min and 15 min after intubation. Level of sedation, postoperative pain scores and any adverse effects were also noted and compared.

Results: Both drugs were effective in attenuating haemodynamic stress response due to laryngoscopy and tracheal intubation. Post-operative analgesia was better in pregabalin group and clonidine group produced lesser sedation.

Conclusion: Both the drugs can be used to attenuate the hemodynamic stress response to laryngoscopy and endo tracheal intubation without any adverse effects. Pregabalin produced better analgesia and clonidine produced lesser sedation.

Keywords: Blood pressure, GABA receptor, Stress response, Tracheal intubation

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

INTRODUCTION

Laryngoscopy and endo tracheal intubation may cause profound alteration of the haemodynamic state of the patient. Increase in blood pressure and heart rate occurs most commonly from reflex sympathetic discharge in response to laryngotracheal stimulation.[1] These changes may be associated with morbidity and mortality which are more pronounced in patients with heart diseases provoking complications like cardiac arrhythmias,myocardial infarction and cerebral stroke.[2] Several techniques have been proposed to attenuate the haemodynamic responses to airway instrumentation such as deepening of anaesthesia, omitting cholinergic premedication, use of beta blockers, nitroglycerine, calcium channel blockers and opioid with variable results.[3] Clonidine, an imidazole compound act mainly by central α2 adrenoreceptor stimulation, resulting in diminished sympathetic flow. The efficacy of clonidine in attenuating haemodynamic stress response has been studied previously in many studies and proved its effectiveness. Orally administered clonidine in preanaesthetic period provides haemodynamic stability and attenuates the stress response to laryngoscopy and tracheal intubation.[4] Clonidine blunts the stress response of airway instrumentation are activation of central α_2 adrenoreceptors. This decreases peripheral sympathetic tone and cause stimulation of peripheral presynaptic α_2 adrenoreceptors which leads to decreased norepinephrine release from nerve endings.Pregabalin a gabapentinoid compound is structurally related to the inhibitory neurotransmitter Gamma Amino Butric Acid (GABA) but not functionally related to it.[5]Pregabalin, appears to produce an inhibitory modulation of neuronal excitability particularly in neocortex, amygdala and hippocampus of CNS. It produces analgesic, anticonvulsant and anxiolytic activity by reducing release of neurotransmitter like glutamate, nor-adrenaline, serotonin, dopamine and substance P.[6] It was effective in controlling neuropathic pain. Effect of pregabalin on attenuating stress response to laryngoscopy and tracheal intubation was evaluated previously in few studies. It was found to be very useful and effective premedicant to blunt haemodynamic stress response to tracheal intubation in all those studies.[7] As there was few studies in literature comparing clonidine and pregabalin for blunting stress response,we have done this study to compare oral pregabalin with oral clonidine for blunting haemodynamic stress response to laryngoscopy and endotracheal intubation during general anaesthesia. Our aim was to compare the hemodynamic parameters like blood pressure BP(SBP,DBP,MAP),heart rate (HR) during induction, laryngoscopy and intubation and subsequently 1, 3, 5, 10 and 15 mins after intubation and thereafter as well as to evaluate the pre and post operative sedation status between 2 study groups.

MATERIALS AND METHODS

Source of data - The present study was conducted on 100 patients between 18-60years of age of both genders, scheduled to undergo elective surgery under general anaesthesia in the Department of Anaesthesiology, SCB Medical College, Cuttack. Prior to commencement of the study ethical clearance was obtained from institutional ethical committee.

Study period-Sept 2019 to Sept2021

Study Design: This was a prospective randomized double-blind study**.**

Selection criteria

Inclusion criteria

a) Patients aged between 18 to 60 years of age of both genders posted for elective surgeries under general anaesthesia.

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

b) American Society of Anaesthesiologists grade I and II patients.
c) Patients with Mallampati airway grade I and II.

Exclusion criteria

a) Patients refusal.
b) Patients with medical co morbidities like Hypertension, Ischemic Heart Diseases, Arrhythmias, Renal, Respiratory, Cerebral Diseases, Asthmatics and Epileptics.
c) Expected difficult intubation.
d) If patient is allergic to any of drugs used in the study.
e) Patients taking sedatives and hypnotics.
f) Pregnancy.

All the patients were explained about the procedure and informed/written consent was obtained. All patients had preanesthetic evaluation, which included history, general physical examination, systemic examination, airway examination and review of biochemical investigations before enrolment. The observer was totally blind about the groups or medication received by the patients. A specially designed proforma was used to collect the pre, intra and postoperative data. All the patients were kept NPO 8 hrs prior to surgery. Tab alprazolam0.25mg given to all patients night before surgery.

Randomization and blinding

All the patients were randomly divided into two groups of 50 each using a computer generated random number table software (www.sealedenvelope.com) as described below (group A and group B) . Once a patient gave consent to enter a trial, an envelope was opened, and the patient was offered the allocated group.

Group A –received oral clonidine 0.3 mg 90 minutes prior to surgery with sips of water.

Group B –received oral pregabalin 150 mg 90 minutes prior to surgery with sips of water.

These doses were considered to provide adequate and comparable preoperative sedation, anxiolysis, and perioperative hemodynamic stability. After opening the envelop, the study drugs assigned like clonidine and pregabalin was given to the patients in double blind fashion by a investigator not involved in data recording.

Anaesthetic procedure :

- On arrival in the operating room, patient's basal parameters- Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), and Electrocardiography were monitored using, pulse oximetry, Non Invasive Blood Pressure (NIBP), and ECG monitor.
  - Level of sedation was assessed as follows-
  1: Wide awake
  2: Sleeping comfortably but responding to verbal commands
  3: Deep sleep but arousable
  4: Deep sleep but not arousable.
- Intravenous access using 18G cannula was established and an IV infusion of Ringer lactate was started.
- All the patients was premedicated with Metoclopramide 10mg, Glycopyrrolate 0.2mg iv, and fentanyl 2mcg/kg.
- After preoxygenation, patients in each group was induced by Propofol 2mg/kg iv and vecuronium bromide 0.1mg/kg iv.

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

- Patient's lungs was manually ventilated for 3minutes with 100% oxygen before orotracheal intubation.
- Direct laryngoscopy performed using appropriate sized Macintosh blade and tracheal intubation performed within 15 seconds using appropriate sized cuffed endotracheal tube.
- The patients lungs was mechanically ventilated with tidal volume 10ml/kg and respiratory rate of 12/minute to maintain end tidal Co2 at around 35 mmHg.
- Anaesthesia was maintained with Oxygen 33%, Nitrous Oxide 66% and Isoflurane 1% on controlled ventilation.
- All the hemodynamic parameters(HR,SBP,DBP and MAP) were recorded at following stages
  - –Baseline
  - Pre induction
  - -Immediately after intubation
  - At 1 minute, 3 minutes, 5 minutes ,10 minutes and 15 minutes after intubation.

  -Levels of sedation was assessed both pre and postoperatively. The incidences of blood pressure and heart rate percent changes more than 30% of baseline values during observation were recorded.

  -Postoperative visual analogue score(VAS) was recorded for pain at different time interval in postoperative period.
- Hypertension,hypotension, tachycardia and bradycardia was treated as per institutional protocol.
- At the end of surgery reversal was done with Glycopyrrolate 10mcg/kg iv and Neostigmine 0.05mg/kg and patients were extubated and were shifted to post anesthesia care unit.

STATISTICAL ANALYSIS

Taking our primary outcome as attenuation of hemodynamic stress response to laryngoscopy and intubation and assuming the minimum difference in MAP as 15% between any two groups (Group A, Group B), with 90% power of study and 5% level of significance, the minimum sample size was calculated to be 45 patients in each group. We have included 50 patients in each group anticipating dropouts. Data have been presented as mean for quantitative variables (age, weight, MAP, and HR) and percentage for categorical variables.

Statistical analysis

The sample size was calculated using the formula:

($n = [z_{(1-\alpha/2)}]^2 \times SD^2/d^2$)

Where

$z_{(1-\alpha/2)}$= standard normal deviate for 95% confidence = 1.96

SD = Standard deviation of MAP = 14 mmHg

d = precision = 5%

$n = 1.96^2 \times 14^2/5^2$

$n = 45$

Statistical significance for quantitative variables has been carried out by ANOVA test/nonparametric Kruskal–Wallis test and for categorical variables by Chi-square/Fisher's exact test. A *P* value of <0.05 was considered statistically significant. Data were analyzed using SPSS Statistical Software version 18.0 (IBM, New Delhi, India)

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

RESULTS:

The current study was a randomized control trial where we tried to find out the effectiveness of pregabalin and clonidine as pre-medication on sedation and attenuation of stress response to laryngoscopy and endo-tracheal intubation.105 patients were included in our study out of which 5 patients were excluded for not meeting inclusion criteria. Total 100 patients were divided into two groups(A and B) of 50 each.(figure 7)

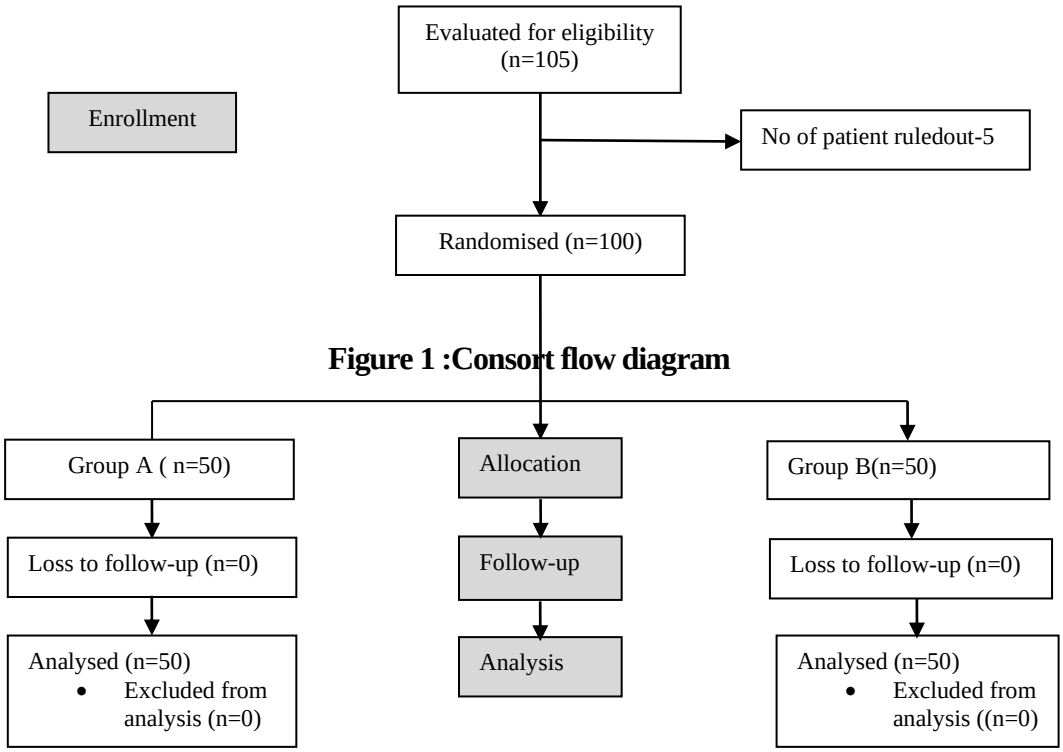

Figure 1 :Consort flow diagram

The age distribution revealed that the mean age of the study participants was 45.12 ± 8.21 years with a minimum age of 18 and maximum age of 60 years. The age distribution between the two groups was not statistically significant (P = 0.159) (Table 2).

Table 1: Demographic variables

Demographic profile	Group A (Mean±SD)	Group B (Mean±SD)	P value
Age in years	46.12±6.32	45.71±6.23	0.159
Sex(M:F)	34:16	32:18	0.215

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

ASA(I/II)	42:8	40:10	0.217
BMI(kg/m^2)	23.4±6.51	22.88± 6.2	0.521
Baseline HR (per min)	69. 15±8.65	72.42±7.93	0.142
Baseline SBP(mm of Hg)	122.54±15.23	121.42±16.64	0.127
Baseline DBP(mm of Hg)	75.4±7.8	75.5±8.1	0.149
Baseline MAP(mm of Hg)	92.57±7.38	90.33±8.13	0.163
Duration of laryngoscopy (secs)	15.56±5.14	16.11±6.17	0.182
Duration of surgery(min)	65.17 ±8.64	63.81± 9.12	0.131
Pre op sedation score	1.45±0.64	2.76± 0.77	<0.001

Gender wise distribution revealed that higher proportion of males were in Group A compared to females in Group B but this difference was not statistically significant ($P = 0.215$) (Table 1).Mean Body mass index of the participants in the Group A was 23.4±6 5.1kg/m^2 whereas the mean BMI was 22.88± 6.2kg/m^2. This difference in mean was not statistically significant. ($p = 0.521$) Distribution of participants according to ASA grade between the two groups was not statistically significant.($p = 0.217$)

There was no statistical difference regarding baseline SBP,DBP MAP and HR in both group A and B. Mean Duration of laryngoscopy was 15.56±5.14 sec in group A compared to group B (16.11 ± 6.17). This difference in mean was not statistically significant (P=0.182). There was no statistically significant difference regarding duration of surgery in both groups.(p=0.131)Pre op sedation score in group A was lower compared to group B which was statistically significant.(p<0.001) (Table 1)

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

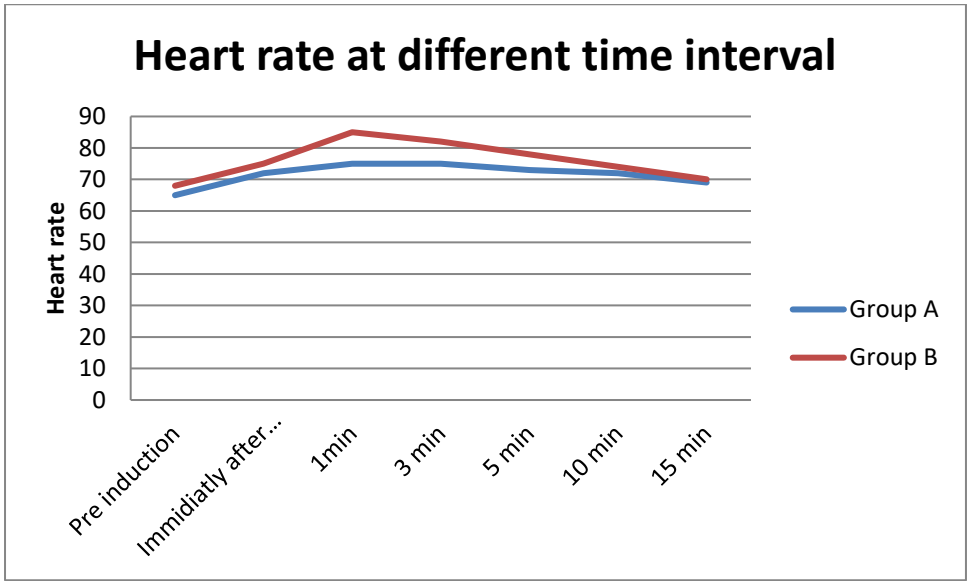

Figure 2: Comparison of heart rate(HR) at different time interval

Figure 2 shows the mean heart rate at different time interval. It was seen that at different time interval(before and after intubation) there was no significant change heart rate among group A compared to group B except at 1min which was statistically significant.

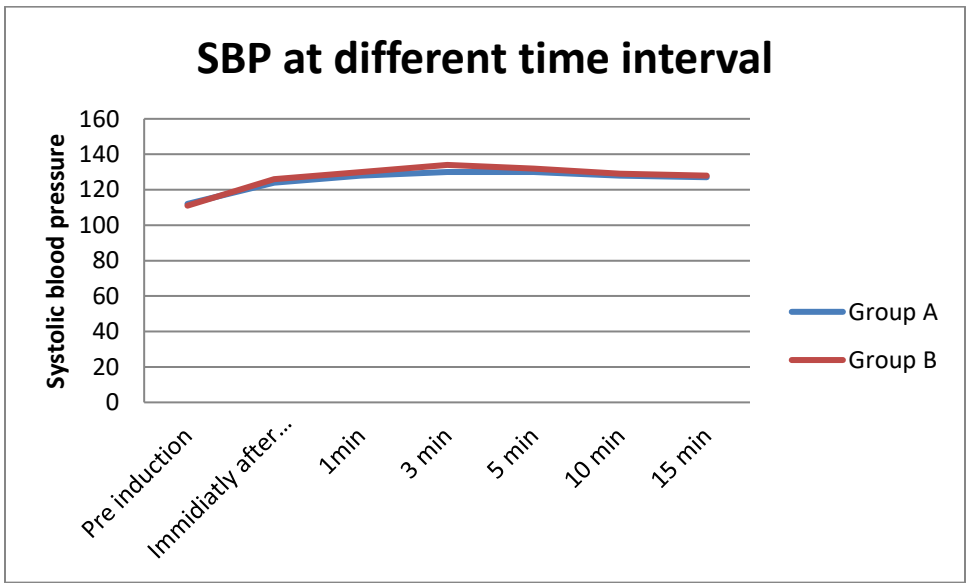

Figure 3: Comparison of systolic blood pressure(SBP) at different time interval

Figure 3 shows the systolic blood pressure at different time interval. It was seen that at different time interval (before and after intubation) there was no significant variation in systolic blood pressure among group A compared to group B.

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

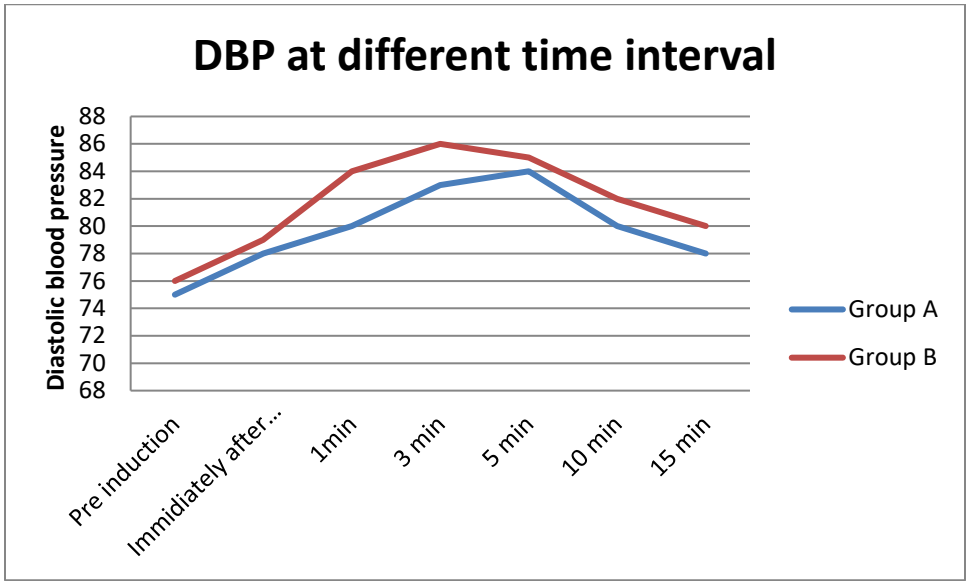

Figure 4: Comparison of diastolic blood pressure(DBP) at different time interval

Figure 4 shows the diastolic blood pressure at different time interval. It was seen that at different time interval (before and after intubation) there was no significant variation in diastolic blood pressure among group A compared to group B.

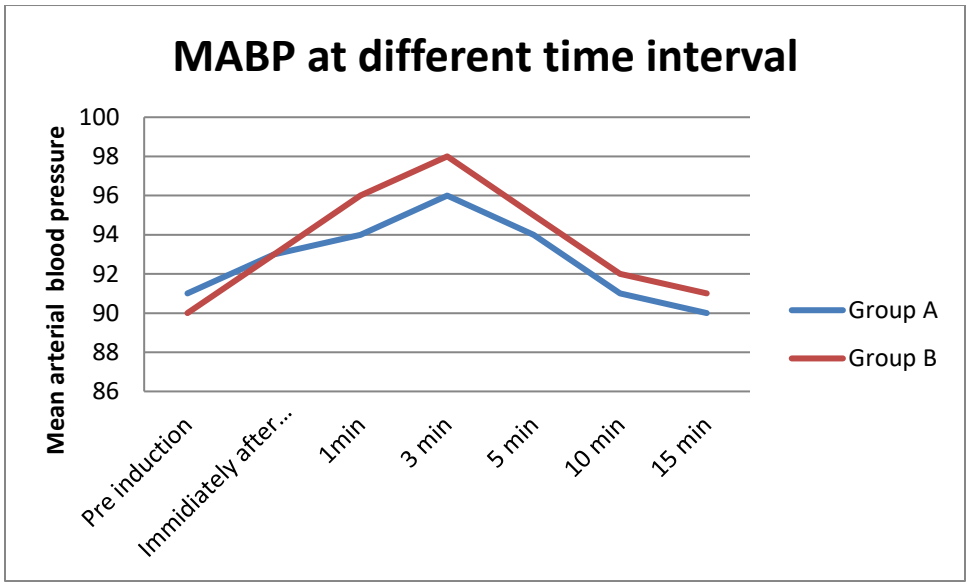

Figure 5: Comparison of mean arterial blood pressure at different time interval

Figure 5 shows the mean arterial blood pressure at different time interval. It was seen that at different time interval (before and after intubation) there was no significant variation in mean arterial blood pressure among group A compared to group B.

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

Table 2:Pre and postoperative sedation score

Time of observation of sedation	Group A		Group B		P Value
	Mean	SD	Mean	SD	
Preoperative	1.45	0.64	2.76	0.77	<0.001
Postoperative	2.16	0.73	3.11	0.26	<0.001

Table 2 shows that there was statistically significant difference in sedation score both pre and postoperatively between the two groups.Lower sedation score was found in clonidine group compared to pregabalin group.

Table 3:Postoperative VAS score

Time	Group A		Group B		P Value
	Mean	SD	Mean	SD	
5-15min	2.45	0.64	2.14	0.77	<0.001
2 hrs	2.91	0.73	2.45	0.26	<0.001
2-4hrs	3.64	0.12	3.18	0.11	0.149
4-12hrs	3.75	0.99	3.56	0.97	0.125
12-24hrs	4.16	0.15	3.95	0.92	0.184

VAS scores of clonidine group at all the observational time periods were found to be higher than that of pregabalin group. It was also found that the difference in mean VAS score of both the groups was statistically significant upto time period 2-4 hours, thereafter (4-12 hours and 12-24 hours) difference was not found to be statistically significant. (Table 3) None of the patient from either of the groups required analgesia within 0-2 hours of surgery. Within 2-24 hours of surgery, requirement of analgesia was found in higher proportion of patients from clonidine group as compared to pregabalin group. This difference was not found to be statistically significant.

DISCUSSION

This prospective randomized trial was conducted to compare the effects of oral clonidine (0.3mg) versus oral pregabalin (150mg) premedication on stress response to direct laryngoscopy and tracheal intubation in patients undergoingsurgery under general anesthesia. Hemodynamic responses of laryngoscopy and laparoscopy were attenuated by oral premedication with pregabalin and clonidine. We observed the anxiolytic and sedative effects of oral premedicants without any significant respiratory depression. Laryngoscopy and tracheal intubation are associated with haemodynamic stress responses due to sympathetic stimulation, which results in marked increase in heart rate, blood pressure, circulating catecholamines and arrhythmias.These effects are transient but can be detrimental to the patients, especially in presence of coronary artery disease and cerebrovascular disease.

Reid and Brace et al [8] first described the hemodynamic response to laryngoscopy and intubation, probably due to intense sympathetic discharges caused by stimulation of epipharynx and laryngopharynx. Shribman et al,[9] reported that laryngoscopy and tracheal intubation increases arterial blood pressure, heart rate, and catecholamine levels, whereas Hassan et al.[10] reported

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

high incidences of cardiac arrhythmias, myocardial ischemia, acute left ventricular failure, and cerebrovascular accidents following intubation in hypertensive patients. Hypertension may affect perioperative morbidity through the extent of end organ damage.Hemodynamic responses to laryngoscopy and laparoscopy should be attenuated due to associated risk of myocardial ischemia or cerebral hemorrhage. If no specific measures are taken to prevent hemodynamic response, the heart rate can increase from 26 to 66%, depending on the method of intubation, and systemic blood pressure can increased from 36 to 45% which may be due to variation in balance sympathetic and parasympathetic outflow or receptor hypersensitivity. Anxiety, an unpleasant emotion, is another factor to adversely influence the anesthetic induction and patient recovery. More recently, Aronson and Fontes et al,[11] found that among the various component of blood pressure, preoperative pulse pressure was independently and significantly associated with postoperative stroke, renal failure, and mortality in patients undergoing coronary artery bypass. Rise in pulse pressure as few as 10 mm Hg in both normotensive and hypertensive individual is associated with 20% or more increase risk of renal, coronary, and cerebral events. Numerous techniques have been used to reduce the incidence and severity of these hemodynamic responses. In order to reduce the incidence and severity of the hemodynamic responses of laryngoscopy, many pharmacological methods were evaluated either in the premedication or during induction, to attenuate these adverse hemodynamic responses with controversial results. Tachycardia and rhythm disturbances can be attenuated by omitting atropine as premedicant. Many studies have reviewed the impact of different drugs on hypertension following laryngoscopy. The most important were lidocaine, osmolol, sodium nitroprusside, and fentanyl.Among opioids, remifentanil (1.0 μg kg^{-1}), alfentanil (10-20 μg kg^{-1}), or fentanyl (0.5-1.0 μg kg^{-1}) were reported to have the most stable effect on hemodynamic response to laryngoscopy and tracheal intubation, but they prolonged the recovery time.The pregabalin and clonidine possesses several properties to make them valuable premedicants to attenuate the hemodynamic response of laryngoscopy. Pregabalin, an antiepileptic drug, is effective in controlling neuropathic component of acute nociceptive pain of surgery by inhibiting membrane voltage-gated calcium channels. It does not interact with GABA receptors. However, only few data are available in the literature regarding the effect of prebagalin on the cardiovascular system. Its analgesic, anticonvulsant, and anxiolytic activities make it useful oral premedicant. It is well absorbed after oral administration, with peak plasma concentrations occurring within 60 minutes. Pregabalin is congener of gabapentine, which, acts by inhibiting membrane voltage-gated calcium channels in central nervous system. Effect of pregabalin on attenuating stress response to laryngoscopy and tracheal intubation was evaluated previously in few studies. It was found to be very useful and effective premedicant to blunt haemodynamic stress response to tracheal intubation in all those studies. Gupta K et al [12] showed that oral pregabalin premedication effectively leads to sedation and analgesia with successful attenuation of the adverse and deleterious haemodynamic pressor response. Eren G et al,[13] evaluated the effectiveness of pregabalin in suppressing the haemodynamic response to intubation in lumber spinal surgeries. Clonidine activates the α_2 -adrenergic receptors in the brain and spinal cord to decrease sympathetic outflow, causing sedation, analgesia, hypotension, and bradycardia without significant respiratory depression. It is well absorbed after oral administration (3-5 μg.kg^{-1}) with peak plasma concentration in 75 to 90 minute and does not require transformation into another substance prior to its action. The preoperative use decreases the intraoperative stress response by reducing the nociceptive transmission and decrease norepinephrine concentration in serum, provided hemodynamic stability. Hayashi et al[14] and Sung et al.[15] reported that clonidine increases perioperative

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

circulatory stability in patients undergoing laparoscopic cholecystectomy and potentiates parasympathetic nervous system. Laisalmi et al,[16] concluded that premedication with clonidine blunts the stress response to surgical stimuli and reduces the requirement of narcotic and anesthetic doses. The study by Matot I et al[17] showed that, in patients undergoing larnygoscopic or bronchoscopic procedures under general anaesthesia, pre medication with oral clonidine (4-4.5 mcg/kg) attenuates haemodynamic response. Chaurasia SK et al,[18] showed that oral clonidine premedication is seen to significantly lower the resting haemodynamic attenuate effectively the sympatho adrenergic response to laryngoscopy and endotracheal intubation in comparison to a premedicant combination of oral diazepam and intramuscular atropine. Nishikawa T et al,[19] showed that clonidine 5mcg, a direct acting alpha 2 agonist could attenuate catecholamine release and the pressor response following laryngoscopy and endotracheal intubation.Only few studies are available in literature regarding the comparison of efficacy of both these drugs in attenuating stress response to laryngoscopy and tracheal intubation. Gupta K et al,[20] in 2011 analyzed "oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy comparative evaluation methods laparoscopic patients randomised to receive placebo Group I, pregabalin (150mg) Group II and clonidine (200microgram) Group III given 75 to 90 mins before surgery as oral premedication.They concluded that oral premedication with pregabalin or clonidine causes sedation and anxiolysis with hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy", without prolongation of recovery time and side effects. The results of our study support the observations of Gupta K et al.Raichurkar et al K et al[21] in march 2015 analysis done on comparative study of oral pregabalin 150 mg and clonidine 200 microgram for attenuation of haemodynamic responses to laryngoscopy and tracheal intubation.They concluded that both pregabalin and clonidine successfully attenuated the hemodynamic response to laryngoscopy and tracheal intubation. Pregabalin better attenuates pressor response and clonidine better attenuates tachycardia response. Bhagat et al,[22] compared the efficacy of oral premedication with pregabalin versus clonidine on stress response and hemodynamic stability during laryngoscopy in adult patients undergoing elective laparoscopic cholecystectomies and concluded that that oral premedication with pregabalin 300 mg or clonidine 200 μg produces sedation and hemodynamic stability during laparoscopic cholecystectomy and a decrease in postoperative pain and analgesic consumption.Parveen S et al,[23] compared efficacy and safety of oral clonidine and oral pregabalin premedication to attenuate stress response in patients undergoing laparoscopic cholecystectomy and concluded that both the drugs can be used as an effective premedicant to attenuate the sympathetic response to laryngoscopy and tracheal intubation without much side effects and the added advantage of intraoperative and postoperative analgesia.Jain et al,[24] compared the efficacy of preoperative single oral dose of pregabalin and clonidine in maintaining the hemodynamic parameters in the laparoscopic cholecystectomy and concluded that both pregabalin (150 mg) and clonidine (200 ug) were effective in controlling the hemodynamic parameters during LC, with clonidine providing better hemodynamic stability than pregabalin. Metoclopramide has also been shown to be an effective and safe antiemetic for both prevention and treatment of postoperative nausea and vomiting. In the present study, the metoclopramide was used as it acts both centrally and peripherally, speeds gastric emptying time, and increases the tone of the lower esophageal sphincter. Postoperative nausea and vomiting were not found in any group of our study.Pregabalin produced more sedation and anxiolysis both pre and postoperatively compared to clonidine.

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

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