MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.36478/makrjms.2024.8.251.256

OPEN ACCESS

Key Words
Oral clonidine, oral pregabalin, haemodynamic responses, heart rate

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Received: 28 May 2024
Accepted: 5 July 2024
Published: 15 July 2024

Citation: H. Prathibha and Sunil Kumar Mooknoor, 2024. Compare the Efficacy of Oral Clonidine and Oral Pregabalin Premedication 90 Min Prior to Surgery in Attenuating the Adverse Haemodynamic Responses to Laryngoscopy and Tracheal Intubation with Respect to Heart Rate. Res. J. Med. Sci., 18: 251-256, doi: 10.36478/makrjms.2024.8.251.256

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Compare the Efficacy of Oral Clonidine and Oral Pregabalin Premedication 90 Min Prior to Surgery in Attenuating the Adverse Haemodynamic Responses to Laryngoscopy and Tracheal Intubation with Respect to Heart Rate

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Abstract
Laryngoscopy and tracheal intubation are the most essential tools of an anaesthesiologist in the airway management. To compare the efficacy of oral clonidine and oral pregabalin premedication 90 min prior to surgery in attenuating the adverse haemodynamic responses to laryngoscopy and tracheal intubation with respect to heart rate. 100 adult patients of ASA grade I and II in the age group of 18-50 years of both sex were included in the study and were randomly divided into two groups of 50 each. Group A received oral tablet clonidine 0.3 mg 90 minutes before surgery while group B received oral tablet pragabalin 150 mg 90 minutes before surgery. Both groups were uniform in their distribution of age, weight, and sex. They had similar physical status with no coexisting disease. Both groups were managed with the same anaesthetic protocol. Haemodynamic variable like Heart Rate, was recorded pre-induction, post-induction, immediately after intubation and post-laryngoscopy (1,3,5,10 minutes) vitals were noted. In oral clonidine group there was significant attenuation of heart rate in all time period. In oral pregabalin group there was no significant attenuation of haemodynamic response in heart Rate. Clonidine is better compared to pregabalin in attenuating adverse hemodynamic response to direct laryngoscopy and tracheal intubation with respect to heart rate.

INTRODUCTION

The technique of laryngoscopy and tracheal intubation are not confined only to the operating room but also employed for non anaesthetic purposes. Few instances are diagnostic laryngoscopy, fiberoptic bronchoscopy, intubation may be required for prevention of aspiration and protection of airway and mechanical ventilation. All these procedures can also produce sympathetic responses and one should keep in mind that many of these critically ill patients are at increased risk.

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 opioids with variable results[1].

Pregabalin a gabapentinoid compound is structurally related to the inhibitory neurotransmitter Gamma Amino Butric Acid (GABA) but not functionally related to it. It acts by decreasing the synthesis of neurotransmitter glutamate to act on the central nervous system and possesses analgesic, anticonvulsant, anxiolytic activity[2].

Clonidine, an imidazole compound act mainly by central a2 adrenoreceptor stimulation resulting in diminished sympathetic flow. Clonidine suppresses induced central noradrenergic hyperactivity to attenuate reflex cardiovascular response to tracheal intubation and to improve stability during surgery[3].

Hence the present study is undertaken to compare oral pregabalin with oral clonidine on blunting haemodynamic stress response to laryngoscopy and endotracheal intubation during general anaesthesia.

MATERIALS AND METHODS

This prospective randomized double blind controlled study was conducted on 100 ASA physical status grade I and II patients of either sex between 18-50 years of age, undergoing elective orthopaedic, spine, otorhinolaryngeal, gynecological and general surgical procedures from October 2012-May 2014 at SSIMS and RC, Davangere. Hospital ethics committee clearance was obtained for this study. Informed consent was taken from all the patients

Inclusion Criteria:

- Patients aged between 18-50 years of age of both genders.
- American Society of Anaesthesiologists grade I and II patients.
- Patients with Mallampati airway grade I and II.
- Patients undergoing elective major or minor surgical procedures under general anaesthesia.

Exclusion Criteria:

- Patients refusal.
- Age less than 18yrs and more than 45yrs.
- Patients with medical co morbidities like Hypertension, Ischemic Heart Diseases, Arrhythmias, Renal, Respiratory, Cerebral Diseases, Asthmatics and Epileptics.
- Expected difficult intubation.
- If patient is allergic to any of drugs used in the study.
- Patients taking sedatives, hypnotics.
- Pregnancy.
- Emergency procedures.

100 similar looking thick opaque envelopes were randomly divided into 2 equal groups of 50 each (group A or B) and the code name A/B was mentioned on top of the envelope. The pharmacist separated the tablets of Pregabalin(150mg), tablets of Clonidine(0.3 mg) into 2 equal groups of 50 each. He took the tablets out of their sachets and loaded them separately into the envelopes and sealed them in such a way that an envelope was containing either,

Tablets of Pregabalin (150 mg=2 tablets of 75mg each) OR

Tablets of Clonidine (0.3 mg=3 tablets of 100 micrograms each)

Thus, 50 envelopes were containing tablets of Pregabalin and had the same code

(A/B) mentioned on them.

50 envelopes were containing tablets of Clonidine with the same code (A/B) mentioned on them. Only the pharmacist was aware of the code identity which was revealed at the end of the study. The patients were randomized by a computer generated table into 2 equal groups

A/B so that

Group “A” patient received all the tablets from one envelope labelled group “A”.

- Group “B” patient received all the tablets from one envelope labelled group “B’.

All patients were assessed the day before surgery. The drug from the closed envelope was drawn and given to the patient by ward nurse with sips of water 90 min prior to surgery. The identity of the tablet was not revealed to the patient and anaesthetist. No other premedication was given other than the study drugs. Preanaesthesia checkup was done a day prior to surgery. Patients were evaluated for systemic diseases and routine laboratory investigations recorded. On the day of surgery, systolic and diastolic blood pressures and heart rate were measured before premedication.

Anaesthetic Technique:

- Heart rate was recorded at following stages-preoperative
- On arrival in the operating room (baseline)
- Post induction (1 minute)
- Immediately after intubation
- At 1 minute, 3 minutes, 5 minutes and 10 minutes after intubation.
- At the end of surgery reversal was given with Glycopyrrolate 10mcg/kg iv and Neostigmine 0.05mg/kg.
- Extubation done when the patient was completely awake and shifted to the recovery.
- Heart Rate was recorded post extubation. Any on toward effects related to the drug and anaesthesia were noted and attended to appropriately.
- A fall in mean blood pressure by 30% from the baseline was treated with Mephentermine 6mg boluses. A fall in the Heart rate less than 40 beats/min was treated with inj Atropine 0.3mg. Analgesia if deemed necessary was supplemented with inj Fentanyl 1µg/kg IV. Patients were followed up postoperatively at hourly basis till 8 h from drug administration . Any on toward effects were observed for and noted.
- lactate was started.
- All patients were pre-oxygenated with 100% oxygen for 3 minutes before induction with a tight fitting face mask.
- All the patients were premedicated with Metoclopramide 10mg, Glycopyrrolate 0.2mg iv, and fentanyl 2mcg/kg.
- After preoxygenation, Patients in each group was induced with Thiopentone sodium 5mg/kg iv slowly till the loss of eyelash reflex. This was followed by vecuronium bromide 0.1mg/kg IV
- Patient's lungs were manually ventilated with 100% oxygen before orotracheal intubation.
- Direct laryngoscopy performed after 3 minutes by using appropriate sized Macintosh blade and tracheal intubation performed within 15 seconds using appropriate sized cuffed endotracheal tube.
- Cases where more than one attempt at laryngoscopy was made were excluded from the study.
- The patients lungs was mechanically ventilated with Tidal volume 10ml/kg and respiratory rate of 12/minute to maintain end tidal PaCo2 at around 36 mmHg.
- Anaesthesia was maintained with Oxygen 33%, Nitrous Oxide 66% and Isoflurane 1% on controlled ventilation.
- Muscle relaxant was given in intermittent doses of Vecuronium Bromide and supplemental analgesia intravenous fentanyl 1mcg/kg was given.

Statistical Analysis: Results obtained in the study are presented in a tabular manner. Statistical analysis by descriptive data presented as Mean±SD in percentage. Pair wise comparison between the groups was done by T test. For all tests a $P<0.05$ was considered significant.

RESULTS AND DISCUSSIONS

In the present study 100 patients belonging to ASA physical status I and II undergoing elective surgery under general anaesthesia were grouped into two of fifty each. Group A received oral Clonidine (0.3 mg) and Group B received oral Pregabalin (150mg) 90minutes prior to surgery. Haemodynamic parameters were noted. Demographic data were similar in all groups. No patients were excluded from the study. Baseline haemodynamic data were not different.

The age range was 18-50years for both oral Clonidine and oral Pregabalin groups. The mean values of the age with standard deviations are 32.4±7.97 and 31.6±7.40 for oral Clonidine and oral Pregabalin groups respectively. There was no significant difference between the two groups ($p>0.05$). Table 1

In oral Clonidine group , 68% patients were males and 32% were females. In oral Pregabalin group, 66% were males and 34% females. No significant difference was observed in sex wise distribution of the cases between the two groups($p>0.05$) (Table 2)

In the oral Clonidine group, the range of weights of the patients were between 48-65kgs with a mean and standard deviation of 54.64±3.78 and for oral Pregabalin group the range of weights of the patients were between 32-71kgs with mean and standard deviation of 52.60±6.50. No significant difference was observed in the weight distribution in the two groups ($p>0.05$).

Statistical analysis of changes in the heart rate(beats/min) at pre induction, post induction and at different time intervals from the onset of laryngoscopy and intubation in the oral Clonidine and oral Pregabalin groups are presented. Table 4

Analysis Of Heart Rate: Standard Analysis of changes in heart rate during premedication, during induction i.e. 90 minutes after premedication and at different time intervals from the onset of laryngoscopy and intubation in Clonidine (Group A) and Pregabalin (Group B) groups are presented.

Oral Clonidine (Group A): The Pre-operative (90 minutes before induction) heart rate in this group was 85.34±6.86. During induction (90 minutes after premedication) of anaesthesia, there was 23.2% decrease in the mean value. The mean heart rate during preinduction was 65.54±7.96. After induction the mean heart rate was 72.16±8.34. Immediately after intubation there was an increase in the HR with a mean

Table 1: Age distribution in years

Age (Years)	Oral Clonidine	Oral Pregabalin
Range	18-50	18-50
Mean	32.4	31.6
SD	7.97	7.40

Table 2: Sex distribution in percentage

Sex	Oral Clonidine	Oral Pregabalin
Male	34(68%)	33 (66%)
Female	16(32%)	17 (34%)

Table : 3 Showing the weight distribution in kilograms

Weight(kg)	Oral Clonidine	Oral Pregabalin
Range	48-65	32-71
Mean	54.64	52.60
SD	3.78	6.50

Table 4: Showing heart rate variations (Beats/min)

Time	Group	No.	Mean	SD	% change WRT Baseline	t value	p-value
Baseline	Oral Clonidine	50	85.34	6.86	0	-0.817	0.41
	Oral Pregabalin	50	86.46	6.84	0		
Pre induction	Oral Clonidine	50	65.54	7.96	23.2	-7.95	<0.001
	Oral Pregabalin	50	81.26	11.47	6.01		
Post induction	Oral Clonidine	50	72.16	8.34	20.11	-7.46	<0.001
	Oral Pregabalin	50	86.44	10.64	0.02		
Immediate after intubation	Oral Clonidine	50	84.06	10.18	1.77	-8.58	<0.001
	Oral Pregabalin	50	103.46	12.31	-19.67		
1 minute	Oral Clonidine	50	79.82	8.21	6.57	-8.31	<0.001
	Oral Pregabalin	50	97.60	12.69	-10.77		
3 Minute	Oral Clonidine	50	76.56	7.93	11	-8.48	<0.001
	Oral Pregabalin	50	93.28	11.45	-6.99		
5 Minute	Oral Clonidine	50	74.06	8.17	14.73	-8.10	<0.001
	Oral Pregabalin	50	89.14	10.30	-2.87		
10 Minute	Oral Clonidine	50	71.60	7.78	18.55	-7.72	<0.001
	Oral Pregabalin	50	86.00	10.62	0.52		

of 84.06±10.18. At one minute from the onset of laryngoscopy, a 6.57% decrease in the mean heart rate was observed with values of 79.82±8.21 and further decreased with a mean heart rate of 76.56±7.39 at 3 minute subsequently., a decreasing trend in the heart rate was noted starting from 1 minute to 10 minutes after laryngoscopy. Mean heart rate at 5 minutes was 74.06±8.17 which was 14.73% lower than the pre-medication value. The mean heart rate at 10 minutes was 71.60±7.78. The heart rate was significantly lower than the pre-medication values at all time intervals.

Oral Pregabalin (Group B): The Pre-operative (90 minutes before induction) heart rate in this group were 86.46±6.84. During induction (90 minutes after premedication) of anaesthesia, there was 6.01% decrease in the mean value. The mean HR during preinduction was 81.26±11.47. After induction there was an increase in a mean HR of 86.44±10.64. Immediately after intubation there was an increase in HR by 103.46±12.31. At one minute from the onset of laryngoscopy, a 10.77% increase in the mean heart rate was observed with values of 97.60±12.69 and further decreased with a mean heart rate of 93.28±11.45 at 3 minute subsequently., a decreasing trend in the heart rate was noted starting from 1 minutes to 10 minutes after laryngoscopy. Mean heart rate at 5 minutes was 89.14±10.30 which was 2.87% more than the pre-operative values. The mean heart rate at 10 minutes was 86.00±10.62. The heart rate was not significant lower than the pre-medication values in all time intervals.

The difference in the heart rate between clonidine (Group A) and Pregabalin (Group B) group remain highly significant at all times of assessment (p<0.001).

Maximum increase in heart rate in clonidine group was at immediate post laryngoscopy which was far less than the pregabalin group.

There was no significant difference in heart rates before premedication but during pre induction (90 minutes after premedication between clonidine and pregabalin group) there was significant difference in heart rates.

The heart rate response between clonidine and pregabalin was very significant at all times starting from pre-op to 10 minutes (p<0.001) where it is significant with clonidine showing a favourable response towards attenuation of heart rate.

Induction of general anaesthesia, direct laryngoscopy and endotracheal intubation induce marked cardiovascular changes as well as autonomic reflex activity[4]. The response may be particularly hazardous for patients with cerebral diseases and cardiovascular diseases[5]. Attenuation of these haemodynamic responses is of great importance in prevention of peri-operative morbidity and mortality. Typically blood pressure and heart rate elevations occur after about 15 seconds of laryngoscopy and become maximal after 30-45 seconds of direct

laryngoscopy[6]. A rise in mean heart rate of 29.9 beats/minute has also been noted.

Strategies to circumvent these changes have included minimizing the duration of laryngoscopy, IV Narcotics, IV and topical Lidocaine, Vasodilators, Beta-blockers, Calcium channel blockers, inhaled anaesthetics and epidural analgesia[7]. Although these drugs did obtund the cardiovascular response, they failed to fulfill the desired criteria of complete attenuation.

Variation of heart rate changes decrease with increasing age. Young patients show more extreme changes[9]. Marked fluctuations in haemodynamic response are often seen in geriatric patients[10]. In our study, we selected an optimal age range of 18-50 years.

Patients on antihypertensive drugs may exhibit a decrease in pressor response. We excluded the patients on antihypertensive medications from our study.

A variable combination of drugs used for premedication, induction, relaxation and maintenance of anaesthesia can influence the sympathetic response to laryngoscopy and intubation.

Premedication with benzodiazepines has no effect on sympathetic response to laryngoscopy and intubation. Glycopyrrolate premedication can moderately increase the heart rate. IV Metaclopramide used as premedication as anti-emetic for prevention of post operative nausea and vomiting.

Thiopentone was selected for induction since it still continues to be the most popular agent for induction. In normovolemic patients' thiopentone 5mg/kg i.v can transiently decrease 10-20mm Hg of blood pressure and increase the heart rate by 15 20 beats/min. There is an increase in catecholamine levels, both nor adrenaline and adrenaline[11]. Vecuronium a non-depolarizing neuromuscular blocking agent devoid of cardiovascular side-effects at the generally usual doses[12].

Within the last decade, several studies have reported the successful use of oral Clonidine premedication to prevent hyper adrenergic and hyperdynamic cardiovascular responses to endotracheal intubation[13].

Pregabalin had been shown to be effective in neuropathic pain, diabetic neuropathy, acute post operative pain and reducing the postoperative opioid requirements. Till now many studies have not been done on pregabalin premedication to attenuate the pressor response to tracheal intubation[14].

However, there are not many studies comparing oral Clonidine and oral Pregabalin premedication prior to induction of anaesthesia. The present study was aimed to investigate the effect of clonidine and pregabalin on the changes in blood pressure and heart rate observed during laryngoscopy and tracheal intubation.

The present study was done in 100 patients under ASA Grade I and II. The purpose of conducting this study in healthy patients was to generate data to be used in a future study in those with a history or risks of coronary artery disease with ST-T monitoring in whom beneficial effects of clonidine and pregabalin are likely to outweigh adverse effects.

There were no differences between the two groups regarding age, sex and weight.

In our study the difference in heart rate between oral Clonidine and oral Pregabalin groups was statistically significant at all times preoperative to 10 min. Attenuation of maximum rise in the heart rate by clonidine is evident and statistically highly significant when compared with pregabalin group ($p<0.001$).

CONCLUSION

Clonidine is better compared to pregabalin in attenuating adverse hemodynamic response to direct laryngoscopy and tracheal intubation with respect to heart rate.

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