www.jmscr.igmpublication.org
Impact Factor 5.244
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v4i12.37

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Evaluation of Oral Pregabalin Premedication for Attenuation of Pressor Response during Laryngoscopy and Endotracheal Intubation – A Randomised Clinical Study

Authors
Gagandeep Singh[1*], Pavan Dhulkhed[2], Indrajit Gupta[3], V.K.Dhulkhed[4], Bilal Mohammad[5], Tushar Munnoli[6]
[1,3,5,6] Post Graduate Residents, Dept of Anaesthesiology, Krishna Institute of Medial Sciences, Karad, Maharashtra
[2]Assistant Professor, Department of Anaesthesiology, J.N. Medical College, Belagavi, Karnataka
[4]Professor & HOD, Dept of Anaesthesiology, Krishna Institute Of Medial Sciences, Karad, Maharashtra
*Corresponding Author
Gagandeep Singh
Department of Anaesthesiology
Krishna Institute of Medial Sciences, Karad, Maharashtra

Abstract
Background & Objective: *This clinical study was designed to evaluate and compare single preoperative dose of pregabalin to placebo regarding hemodynamic responses to laryngoscopy and endotracheal intubation, to assess perioperative fentanyl requirement and any side effects.*
Methods: *60 ASA I and II patients undergoing elective surgical procedures were randomly selected and divided into 2 groups of 30 each. Group A received placebo and Group B received pregabalin 150mg orally 1hour before induction. The patients were compared for hemodynamic changes before the start of surgery, after induction, 1, 3, 5 & 10 minutes after intubation. Additionally fentanyl requirement during surgery and analgesia requirement during first 24 hrs of post operative period was also compared.*
Result: *Preoperative sedation levels were higher with pregabalin premedication. Oral pregabalin significantly attenuated the heart rate(HR), systolic blood pressure(SBP),diastolic blood pressure (DBP) and mean arterial pressure(MAP) due to laryngoscopy and endotracheal intubation.*
Conclusion: *The present study shows that single oral dose of 150mg pregabalin given 1hr before surgery attenuated the pressor response to tracheal intubation in adults, has adequately sedated the patients and was devoid of side effects in the given dose.*

INTRODUCTION

Pre-operative sedation and cardiovascular stability during induction, laryngoscopy, intubation and throughout the surgical procedure is the most essential part of anaesthesia for better patient outcome. Hemodynamic pressor response to airway instrumentation is a hazardous complication of general anaesthesia as these are associated with hypertension and tachycardia, transient and often unwanted body response[1]. This response to laryngoscopy and endotracheal intubation is due to intense sympathetic discharge caused by stimulation for the upper respiratory tract both during laryngoscopy and endotracheal

intubation, giving rise to changes in plasma catecholamine concentrations.[2]

Transitory hypertension and tachycardia are probably of no consequence in healthy individuals. They may be hazardous to those with hypertension, myocardial insufficiency or cerebrovascular diseases[2]. This hemodynamic response predisposes susceptible individuals to development of pulmonary edema, myocardial insufficiency and cerebrovascular accident.[3,4]

Reid and Brace[1] (1940) were the first to recognize that cardiovascular stability may be effected by intubation. From that time to that of King and Harris in 1950 who also came to the same conclusion as Reid that while inducing patients it is imperative to avoid this pressor response.

Many drugs like midazolam, barbiturates, alpha 2 agonist, opioids etc have been used as premedicaltions to attenuate these adverse hemodynamic responses to airway instrumentation[5,6]. Opioid related side effects contribute to delayed discharge and recovery of activities. A drug that has analgesic properties, opioid sparing effects, possibly reduces opioid tolerance, relieves anxiety, and is not associated with adverse effect would be an attractive adjuvant.[7]

Pregabalin is a gabapentinoid, described structurally as (S)-3 aminomethyl 5-methylhexanoic acid. Pregabalin is structurally related to inhibitory neurotransmitter Gamma Amino Butyric Acid but it is not functionally related to it. It selectively bind to alpha 2 subunit of voltage dependent calcium channel which result in decreased synthesis of neurotransmitter glutamate to act on CNS and possess analgesic, anticonvulsant and anxiolytic activity[8]. It is effective in preventing neuropathic component of acute nociceptive pain of surgery and is several times more potent than gabapentin.[9]

With the above pharmacological profile Pregabalin, like its pharmacological predecessor gabapentin, can be a drug to attenuate hemodynamic response associated with direct laryngoscopy and intubation.

There is a need to study the effectiveness of pregabalin in attenuating the hemodynamic response to laryngoscopy and intubation, in decreasing the level of acute state anxiety before intubation and in decreasing perioperative opioid requirement. Hence this study has been selected using 150 mg oral pregabalin as a premedicant 1 hour before surgery.

AIM AND OBJECTIVES

AIM: We aim to assess the heamodynamic stability by attenuation of pressor response during laryngoscopy and endotracheal intubation with pregabalin 150 mg premedication, including its effect of pregabalin on preoperative anxiety and sedation level.

OBJECTIVES: The study objectives were to measure :

1. The level of preoperative sedation and anxiety
2. Hemodynamic response to induction, laryngoscopy and intubation
3. Intra operative hemodynamic parameters (HR, NIBP,O_2 saturation)
4. Intra operative analgesic (Fentanyl) requirement
5. Possible side effects like dizziness, pain, nausea, vomiting.

METHODOLOGY

This was a prospective, double blind, randomized controlled study, conducted after approval of ethical committee and informed consent on 60 patients, undergoing elective surgeries under General anaesthesia at tertiary care centre over span of 2 years. The inclusion criteria were patients of ASA grade I and II, age 20 to 50 years, BMI 18-25 and undergoing elective surgeries. The exclusion criteria was patient refusal, ASA grade III and IV, patients with liver, renal and cardiovascular disorders, Epilepsy, COPD, Pregna-ncy, patients on antipsychotics like tricyclic antidepressants or serotonin reuptake inhibitor and history of any drug allergy like PABA.

PROCEDURE: Preanesthetic checkup and preparation. The patients was randomly divided into 2 equal groups using a computer generated

table of random numbers, of 60 each, in a double blinded manner. A detailed history, complete physical examination and routine investigations was done for all patients.

Anesthetic technique: Patient was premedicated on the night before surgery with Tablet Diazepam 5mg. On the day of surgery, on arrival in preoperative room, intravenous line was secured with 18 gauge cannula. Baseline heart rate, BP, MAP will be recorded before giving the placebo or study drug one hour before surgery. Inj. Ranitidine 50mg i.v. and Inj. Metclopramide 10mg i.v. was given to all patients. Preoperative sedation level was assessed by the RAMSAY SEDATION SCALE.

Group A – study group - received pregabalin 150 milligram orally with sips of water 1 hour before induction.

Group B -- control group - received multivitamin capsules orally with sips of water 1 hour before induction.

After one hour Sedation level was again assessed using Ramsay Sedation Scale.

On arrival in operating room, monitors were attached and baseline heart rate and systolic, diastolic and mean arterial blood pressure were assessed again. Patients were premedicated with Inj Fentanyl 0.5mcg/kg and Inj Midazolam 1mg IV, Induction were done with Inj Thiopentone Sodium (5mg/kg) in a dose sufficient for loss of verbal command, followed by Inj Vecuronium bromide(0.1mg/kg) to provide neuromuscular blockade. Laryngoscopy was performed and intubation will be done with cuffed endotracheal tube of appropriate size. Anaesthesia was maintained with 33:66 O_2 and N_2O respectively, Inj Vecuronium bromide plus Sevoflurane 2%. Sevoflurane concentration and fentanyl top-up dose were adjusted to maintain systolic blood pressure and heart rate within 20% of preoperative values. Hemodynamic and respiratory parameters were continuously monitored and recorded before and after induction, immediately after intubation and 1, 3, 5 and 10min, thereafter at every 15min interval till completion of surgery. Any inadequate intraoperative pain relief, suggested by >20% increase in heart rate & mean arterial pressure from the basal values was treated with i.v. fentanyl boluses. Interval time of fentanyl top up dose was recorded. At the end of surgical procedure residual neuromuscular blockade was antagonized with Inj neostigmine 0.04mg/kg and Inj glycopyrrolate 0.01mg/kg IV. Extubation was carried out as a routine procedure and stress response to extubation was recorded. Patient was shifted to recovery room and was monitored for postoperative complications and postoperative pain was assessed by visual analogue scale for an hour. Inj. Tramadol 50mg i.v. was given as rescue analgesia in postoperative period and frequency of rescue analgesic topup was noted for 1st 24 hrs in the postoperative period.

Before and after induction period, level of sedation and anxiety, hemodynamic parameters, hemodynamic response to laryngoscopy and intubation and frequency of additional fentanyl top-up and possible side effects were compared among the 2 groups.

DEFINITIONS

- **Tachycardia:** is defined as heart rate greater than 90beats/min.
- **Hypertension:** is defined as systolic blood pressure of more than 140mm of Hg or more than 20% above the mean arterial pressure baseline.
- **Hypotension:** is defined as reduction in systolic blood pressure (SBP) of more than 20% below the mean arterial pressure baseline or fall in SBP less than 90mm of Hg.
- **Bradycardia:** is defined as heart rate of less than 60 beats per minute.

Statistical Methods

- Descriptive and inferential statistical analysis has been carried out in the present study.
- The Microsoft Excel 2007 and SPSS 14.0 version software packages were used for data entry and analysis.

- The categorical factors are represented by the number and frequency (%) of cases.
- The continuous variables are represented by measures of central frequency (like mean, median, mode) and deviation (SD and range).
- Statistical Analysis done by Unpaired student's t-test, Fisher's exact test, Mann Whitney test, Univariate analysis of variance and repeated measure analysis of variance.
- P-value <0.05 was considered statistically significant.

OBSERVATION AND RESULTS

1. AGE DISTRIBUTION

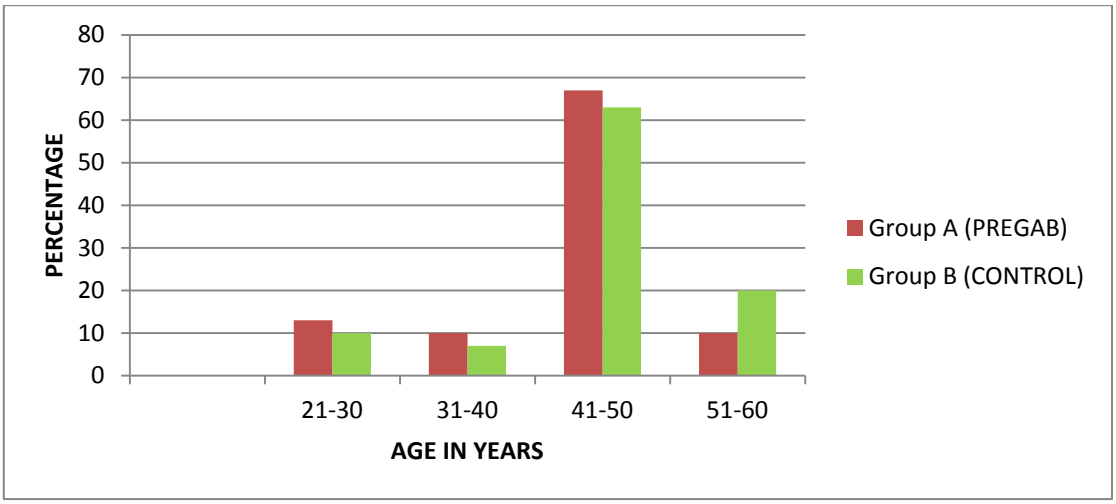
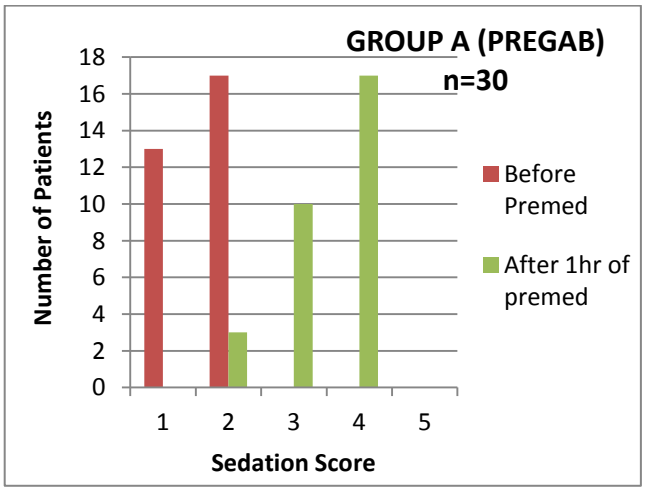


Figure 1 showing age distribution, shows that the predominant age group in both groups was between 41-50 years.

Comparision of age distribution of patients in both the groups. The mean age in group A and B were 43.66±8.31 and 44.76±7.76 respectively. The both groups are comparable. There was no significant change in the gender, with females predominating in both groups.

2. Mean Ramsay Sedation Scores



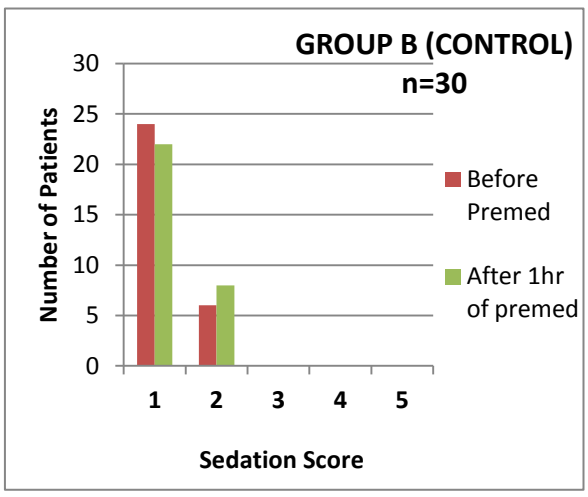


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Figure 2 shows the change in Ramsay sedation score before and 1hr after premed in Group A and Group B

The change in Ramsay sedation score after 1 hour of premed as compared to before premed is greater in the pregabalin group as compared to the control group. Before premedication, all the patients in both the groups were having sedation score of equal or less than 2.After one hour of premedication, 90% of patients (27/30) in pregabalin group were having sedation score of more than 2 (Fischer exact test, p <0.00001), while in control group, all the patients were having score less than or equal to 2.

3. Mean Heart Rate Changes after direct laryngoscopy and intubation

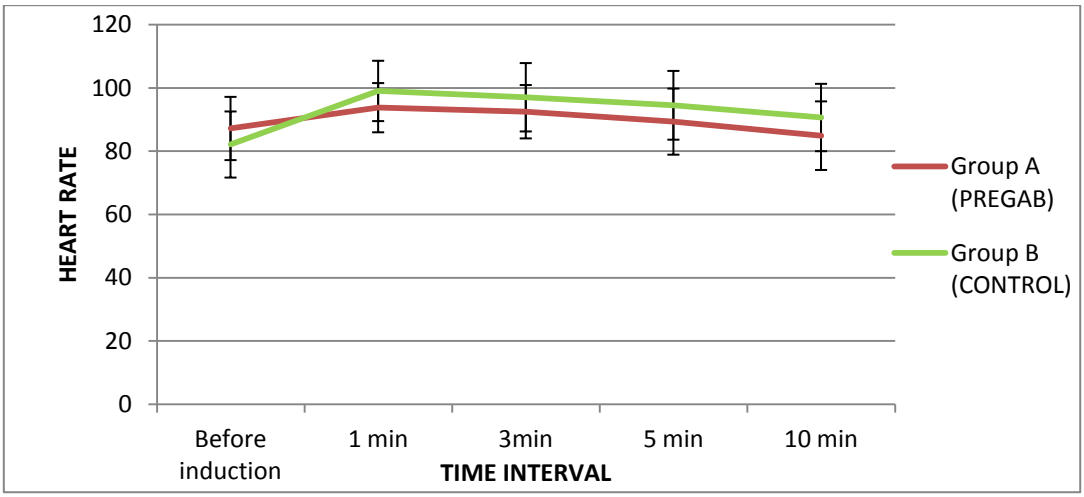

Figure 3 showing the intergroup comparison of mean heart rates with error bars showing standard deviation.

Table 1: Comparison of Mean Heart Rate (bpm)

Heart Rate (bpm)	Group A	Group B	P value
Before induction	87.2±9.99	82.13±10.45	0.0597
1 min	93.77±7.78	99.07±9.53	0.0217*
3min	92.57±8.44	97.07±10.81	0.0775
5 min	89.37±10.45	94.53±10.87	0.066
10 min	84.93±10.84	90.67±10.75	0.044*

* Statistically significant

At 1min following laryngoscopy and intubation, rise in heart rate from baseline value was lower in pregabalin group as compared to control group which was statistically significant. Both have no statistically significant effect on heart rate after 1min following laryngoscopy and intubation upto 10min. The magnitude of rise in heart rate is lower and it is falling to less than the basal value at 10 min in the pregabalin group. However, the rise in heart rate in the control group is sustained and it has not reached the basal value even by 10 minutes following laryngoscopy and intubation.

4. Mean Arterial Pressure Changes After Direct Laryngoscopy & Intubation

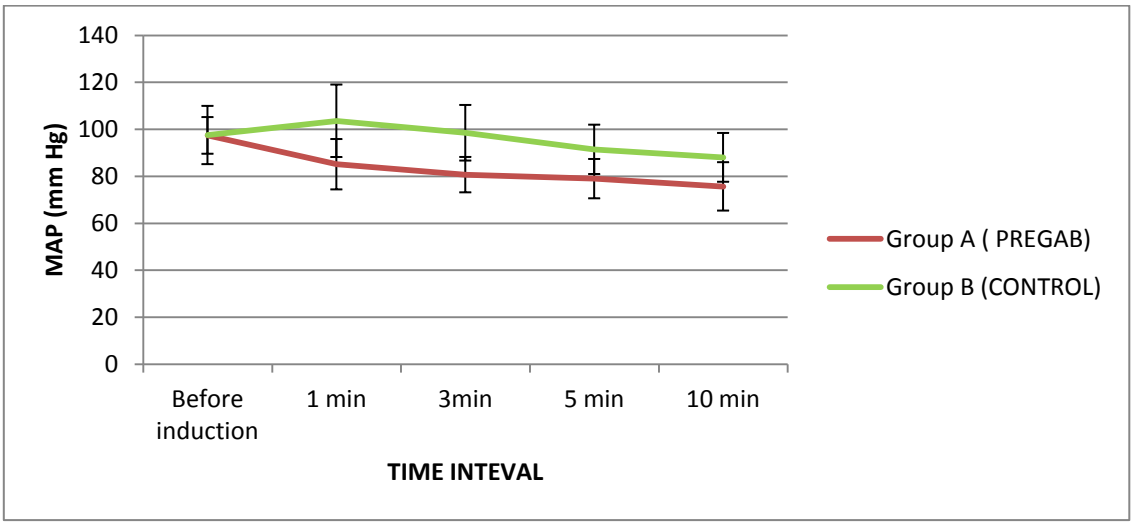

Figure 4 showing mean MAP in both groups with error bars showing standard deviation in both group

Table 2: Comparison of MAP (mm Hg)

MAP (mm Hg)	Group A	Group B	P value
Before induction	97.36±7.81	97.53±12.39	0.949
1 min	85.1±10.72	103.59±15.42	<0.001*
3min	80.66±7.53	98.49±11.83	<0.001*
5 min	78.96±8.37	91.43±10.50	<0.001*
10 min	75.67±10.30	88.02±10.39	<0.001*

*Statistically significant(Student t test)

The mean MAP at baseline are comparable in both groups.($p > 0.05$). The mean MAP at 1, 3, 5 and 10 min following laryngoscopy & intubation is clinically lower & statistically significant in pregabalin group ($p < 0.01$) when compared to control group.

5. Intraoperative Analgesic Requirement

Table 3: Intraoperative Analgesic Requirement

Rescue Analgesic	Group A (n=30)		Group B (n=30)	
	No	%	No	%
No	13	43	0	0
Yes	17	57	30	100
NIL	13	43	0	0
10 mcg	15	50	3	10
20 mcg	2	7	10	33
30 mcg	0	0	8	27
40 mcg	0	0	5	17
50 mcg	0	0	4	13
Total Requirement (mcg)	6.33±6.15	100	29±12.13	100

Unpaired t test p value <0.0001

All the patients in control group required intraoperative analgesic as compared to 57 % of the patients in pregabalin group. The total dose requirement of fentanyl intraoperatively in pregabalin group was 6.33±6.15mcg(unpaired t test, $p<0.0001$) which is significant less when compared to control group 29±12.13mcg.

6. Mean Postoperative VAS score (One hour postoperative)

The VAS score was recorded for one hour postoperatively and at the end of 1st hour was found lower in the pregabalin group as compared to control group. All the patients in pregabalin group were having VAS score of less than 4 at the end of 1st hour postoperatively while in control all the patient had VAS score of equal or more than 4.

6. Post-operative Analgesia Requirement(1st 24 Hrs postoperatively)

Table 4: Post-operative Analgesia Requirement

FREQUENCY	GROUP A	GROUP B
0	18	0
1	12	3
2	0	16
3	0	11
TOTAL	30	30

The requirement was recorded for 1st 24 hours postoperatively and was found significant lower in the pregabalin group (Mann Whitney test, P value= 0.000) as compared to control group.

DISCUSSION

The haemodynamic pressor response during laryngoscopy and intubation, in the form of tachycardia and hypertension, occurs frequently. Shribman *et al*[10] reported that laryngoscopy alone or with tracheal intubation increases the arterial blood pressure and catecholamine levels, while intubation significantly increases heart rate. Reid *et al*[1] and Hassan *et al*[11] reported high incidences of cardiac arrhythmias, myocardial ischemia, acute left ventricular failure and cerebrovascular accidents following intubation in hypertensive patients. These physiological changes are due to variation in the balance of sympathetic and parasympathetic outflow or receptor hypersensitivity. Specific measures should be taken to prevent these changes as hypertension may affect perioperative morbidity through the extent of end organ damage, like myocardial ischemia or cerebral haemorrhage. Aronson and Fontes[46] stated that rise in pulse pressure as little as 10 mmHg in both normotensive and hypertensive persons is associated with a 20% or more increased risk of renal failure, coronary events and cerebral stroke.

Many pharmacological techniques were introduced and evaluated either in the premedication or during induction to attenuate the haemodynamic pressor response to airway instrumentation. More attention is given to the use of selective beta-adrenergic blockers to prevent the reflex sympatho-adrenal discharge-mediated tachycardia and hypertension during laryngoscopy and intubation[2.] Hypotensive agents, including sodium nitroprusside, nitroglycerine, adrenoreceptor blockers, calcium channel blockers and opioids, have been used effectively to attenuate these haemodynamic responses. Intranasal nitroglycerine tends to block the hypertensive response to airway instrumentation. The intravenous lidocaine (1.5 mg/kg) prevented the increase in mean arterial pressure with no effect on heart rate. Among opioids, remifentanil (1 µg/kg), alfentanil (10–20 µg/kg) or fentanyl (0.5–1 µg/kg) have been used successfully to attenuate haemodynamic pressor response to laryngoscopy and tracheal intubation, but these are associated with bradycardia, hypotension and post-operative respiratory depression. Glossopharyngeal and superior laryngeal nerve blocks along with topical analgesia may also be effective methods.

A drug which can blunt both the heart rate response and blood pressure response of laryngoscopy and intubation, without having any adverse effects would be ideal. Pregabalin, a relatively newer anticonvulsant, has shown to attenuate hemodynamic response to direct laryngoscopy and endotracheal intubation without significant side effects.

In our study, the 150 mg oral pregabalin administered one hour before induction has sedated the patients pre-operatively and effectively attenuated the laryngoscopy and intubation induced haemodynamic pressor response intraoperatively. There was perioperative haemodynamic stability with no post-operative side-effects and respiratory inadequacy. Rastogi et

al[9] compared the onset time of sedation with different doses of pregabalin in which pregabalin 150mg had better sedation at preinduction stage as compared to control group and pregabalin 75mg. which is parallel to our study.In study by K Gupta et al[12], comparision was done between control, pregabalin and clonidine for onset time of different sedation levels in which pregabalin had better sedation level similar to our study. Sundar As et a1[13] compared sedation score of preoperative period with postoperative period, while in present study sedation score was compared in preoperative period before taking premedication and one hour after premedication. Considering that pregabalin was given an hour preoperatively and the elimination half life is 6.3 hours , the sedation may not last for more than 6 hours. All studies showed a minimal rise in heart rate with pregabalin as compared to control group. As Sundar A S et al[13] studied pregabalin in patients undergoing off pump CABG , these patients were on preoperative beta blockers and anaesthetic induction was done with higher doses of fentanyl (5mcg/kg), midazolam (50mcg/kg), thiopentone (4 mg /kg) .These drugs may play a role in producing a relatively lesser rise in heart rate when compared to other studies. However, the rise in heart rate in the present study parallels the study done by Sundar A S et al[13]. In Rastogi et al[12], there is significant rise in heart rate post intubation in pregabalin group. In his study, butraphanol was used in premedication which is less potent analgesic as compared to fentanyl used in our study, which implies that pregabalin is more effective in attenuation of haemodynamic responses when used with fentanyl. In Gupta et al[12], although there was less rise in heart rate in pregabalin group than control group post-intubation but there was significant rise in heart rate in both control and pregebalin group from the baseline. There was difference in premedication used in his study as compared to other studies as inj. midazolam was not used in his study which implies that benzodiazepines may have synergestic effect with opoids and pregabalin in attenuation of pressor response. In our study also, there was less rise in the heart rate in pregabalin group as compared to control group. There was significant difference in heart rate at 1min following intubation in pregabalin group being better when compared to control group. After 1 min, there was no significant difference in heart rate in both groups upto 10 min.

In control group, the present study show a rise in mean arterial pressure at 1min followed by falling trend in diastolic blood pressure. The study done by Sundar A S[13] is comparable with present study, whereas the studies done by Gupta[12] and Rastogi[9] also showed initial rise in the mean arterial pressure similar to our study but the rise was significant as compared to our study and Sundar et al[13].

While in pregabalin group, in studies done by Sundar AS et al[13] and Rastogi B[9], there is a fall in mean arterial pressure. However, Gupta K et al[12] study showed initial rise in the mean arterial pressure at 1 and 5 min followed by fall in mean arterial pressure. Our study results showed the decreasing trend in mean arterial pressure post intubation which are in parallel to the studies done by Sundar AS et al[13] and Rastogi B[9].

In studies done by Sundar et al[13], Rastogi B[9] and Gupta K [12], all the patients in the control group required fentanyl top ups intraoperatively for analgesia (for heart rate or blood pressure $\geq$ 20% of the baseline) while the analgesia requirement in the pregabalin group was nil or less as compared to control group. In present study, the Mean requirement of fentanyl intraoperatively in Pregabalin group was 6.33±6.15mcg which was less as compared to 29±12.13mcg in control group.The results of our study are in parallel to the others studies.

The postoperative pain score, assessed by visual analogue scale one hour postoperatively was significantly lower in the pregabalin group as compared to control group in the present study which was not compared in earlier studies. All the patients in pregabalin group were having VAS score of less than 4 at the end of 1st hour postoperatively while in control all the patient had VAS score of equal or more than 4. Inj. Tramadol

50 mg i.v. was given for rescue analgesia in post-operative period and frequency of topup was compared.

The frequency of analgesic top-up in 1st 24hrs of postoperative period when compared was much less in the pregabalin group as compared to control group. The 60% of the patients in pregabalin group did not required analgesic top up in postoperative period while 40% of the patients in pregabalin group required only once in 1st 24 hrs. With Mann Whitney test, P value is 0.000 which is statistically significant. While in control group, about 37% of the patients required analgesia thrice, 53% required twice and 3% of the patients required once in 1st 24 hrs period.

There were no significant adverse effects like nausea, vomiting, giddiness in both groups in the present study. The mechanism by which pregabalin prevents postoperative nausea and vomiting is not known, but it can be an indirect effect due to its opioid sparing action or direct action by inhibiting tachykinin activity, as postulated by Guttuso.T.Jr[14] in their study on the effect of gabapentin on chemotherapy induced nausea in breast cancer patients.

CONCLUSION

From the present study we concluded that

- A Single, Oral dose of pregabalin (150 mg) given 60 minutes preoperatively successfully attenuates the hemodynamic response associated with direct laryngoscopy and endotracheal intubation.
- Pregabalin produced better preoperative sedation after one hour of premedication, as evidenced by higher Ramsay sedation score.
- Pregabalin may have an opioid sparing effect thereby minimizing postoperative opioid related side effects.
- Pregabalin reduces the requirement of analgesia in postoperative period as evidenced by lesser consumption of Tramadol in first 24 hours of post operative period.

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