Original Article

Efficacy of pregabalin in attenuation of laryngoscopy and intubation reflex-A comparison with gabapentin

Muhammad Mamun Ur Rashid[1], Hasan Ali Talukder[1], Moinul Hossain Chowdhury[1], Shukha Ranjan Das[1], Md. Mozaffer Hossain[2], Taneem Mohammad[3], Nuzhat Ara[4]

[1]Anesthesiologist, Department of Anaesthesia, Analgesia, Palliative & Intensive Care Medicine, DMCH, Dhaka. [2]Professor and Head, Department of Anaesthesia, Analgesia, Palliative & Intensive Care Medicine, DMCH, Dhaka, [3]Junior Consultant, Department of Anaesthesia, Analgesia, Palliative & Intensive Care Medicine, DMCH, Dhaka. [4]Assistant Professor, Department of Anaesthesia, Analgesia, Palliative & Intensive Care Medicine, DMCH, Dhaka.

Corresponding author: Dr. Muhammad Mamun Ur Rashid, E-mail: rashidmamunur91@gmail.com

Abstract

Backgrounds: *Direct laryngoscopy and tracheal intubation are noxious stimuli that can provoke undesirable responses in the cardiovascular, respiratory and other physiologic system. These physiological changes are well tolerated by healthy individuals. However, these changes may be detrimental or even fatal in patients with coronary artery disease, hypertension, cerebrovascular disease, intracranial aneurysm, valvular heart disease.*

Many pharmacological techniques were introduced and evaluated either in the premedication or during induction to attenuate the hemodynamic pressor response to laryngoscopy and tracheal intubation, but results were controversial. 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. Gabamimetic drug like gabapentin have been successfully used as oral premedication to attenuate pressor response during airway instrumentation, to decrease the preoperative anxiety and to reduce perioperative fentanyl consumption.In contrast, newer generation Gabamimetic drug pregabalin is effective in preventing neuropathic component of acute nociceptive pain of surgery and is several times more potent than gabapentin. Pregabalin is being used as oral premedicant in some studies but very few comparative studies with gabapentin is present at time. So, there is a need to study the effectiveness of oral pregabalin in attenuating the hemodynamic response to laryngoscopy and intubation. If pregabalin is established as oral premedicant then it will bring a great benefit to peri-operative period with minimal cost.

Objectives: *To compare the efficacy of pregabalin and gabapentin in attenuation of laryngoscopy and intubation reflex (HTN & Tachycardia).*

Methods: *This is hospital based randomized double-blind control study. Eighty patients, classified by (ASA) physical status category I-II, were randomized by card method in two groups of 40 patients each. The patients were randomly allocated to receive oral Pregabalin 150mg (Group A) and Gabapentin 600mg tablet (Group B)1 hour prior to surgery. Before administration of the oral premedication, each patient's baseline heart rate, systolic and diastolic blood pressure, mean arterial pressure and oxygen saturation were recorded by an anesthesiologist who was not enrolled into the study about the occurrence. In addition, to measure anxiety and sedation Ramsay Sedation Score was completed for each patient. All measurements were repeated before induction. Grade 2 patient was selected. Systolic, diastolic and mean arterial blood pressure (SAP, DAP, MAP) and heart rate (HR), oxygen saturation (Spo2) was recorded after administration of IV anesthetics, immediately after intubation and cuff inflation, and 1, 3, 5 and 10 minutes after intubation. After tracheal extubation the patients were monitored for 24 about the occurrence of any side effects, such as nausea, vomiting, dizziness, blurred vision, respiratory insufficiency, confusion and recorded if they were present.*

Result: *Patients characteristics in respect of age, residence, other socio-demographic characteristics, ASA status and type of surgery were similar between the groups. Oral tablet Pregabalin150mg is more effective than tablet Gabapentin 600mg, in attenuation of intubation reflex. A single, oral dose of 150 mg of pregabalin premedication seems to be effective in attenuating the hemodynamic response to endotracheal intubation after the first attempt.*

Conclusion: *Pregabalin 150 mg is a better alternative to Gabapentin 600 mg in attenuation of intubation reflex without major side effect.*

Keywords: *Heart rate (HR), Systolic, diastolic and mean arterial blood pressure (SAP, DAP, MAP).*

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Introduction:

Direct laryngoscopy and tracheal intubation are noxious stimuli that can provoke undesirable responses in the cardiovascular, respiratory and other physiologic system[3]. These physiological changes are well tolerated by healthy individuals. However, these changes may be detrimental or even fatal in patients with coronary artery disease, hypertension, cerebrovascular disease, intracranial aneurysm, valvular heart disease. The sympathetic response is associated with Acute Left Ventricular Failure, ischemic ECG changes and ruptured cerebral aneurysm[4]. As today more and more patients with cardiovascular disorders are presenting themselves for surgery, anaesthesiologists are in search of safest and the most efficient drug which can prevent cardiovascular response to the laryngoscopy and tracheal intubation. Many pharmacological methods were evaluated either in premedication or during induction to attenuate the adverse hemodynamic response to laryngoscopy and intubation, such as deepening the anesthesia, pretreatment with vasodilators, adreno-receptor blocker and opioids[5]. Intranasal nitroglycerin diminished the hypertensive response but tachycardia was noted[11]. The most commonly reported adverse effects of benzodiazepines are variability of patient response and respiratory complication[12]. Opioid analgesia contributes to postoperative nausea, vomiting, bradycardia, delayed recovery of bowel function & respiratory depression[13]. Intravenous lidocaine prevented the increase in mean arterial pressure with no effect on heart rate[14]. Recently, an increasing emphasis has been made on the use of non-opioid analgesic as a part of multimodal regimen for preventing pain in the operative period, decrease anxiety and the intubation response. 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.

Pregabalin, a gabapentinoid compound, is described structurally as (S)-3 aminomethyl-5-methylhexanoic acid. Pregabalin is structurally related to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), but is not functionally related to it. It acts by decreasing the synthesis of neurotransmitter glutamate to act on the central nervous system. It is non-narcotic, with clinically important reduction in pain and adverse haemodynamic response[6]. Gabapentin is structurally related to the neurotransmitter GABA but does not modify GABA-A or GABA-B radioligand binding, it is not converted metabolically GABA-A or GABA-B agonist and it is not inhibitor of GABA uptake or degradation[7].Gabapentin has an alternative mechanism of action in CNS, it acts by decreasing the synthesis of neurotransmitter glutamate thus producing analgesia, anxiolysis, and hemodynamic stability[8].

Pregabalin and gabapentin share a similar mechanism of action, inhibiting calcium influx and subsequent release of excitatory neuro-transmitters; however, the compounds differ in their pharmacokinetic and pharmacodynamic characteristics. Gabapentin is absorbed slowly after oral administration, with maximum plasma concentrations attained within 3-4 hours. Orally administered gabapentin exhibits saturable absorption—a Nonlinear (zero-order) process—making its pharmacokinetics less predictable. Plasma concentrations of gabapentin do not increase proportionally with increasing dose. In contrast, orally administered Pregabalin is absorbed more rapidly, with maximum plasma concentrations attained within 1 hour. Absorption is linear (first order), with plasma concentrations increasing proportionately with increasing dose. The absolute bioavailability of gabapentin drops from 60% to 33% as the dosage increases from 900 to 3600 mg/day, while the absolute bioavailability of pregabalin remains at > or = 90% irrespective of the dosage. Neither drug binds to plasma proteins. Neither drug is metabolized by liver nor inhibits hepatic enzymes that are responsible for the metabolism of other drugs. Both drugs are excreted renally, with elimination half-lives of approximately 6 hours. For neuropathic pain, a pregabalin dosage of 450 mg/day appears to reduce pain comparably to the predicted maximum effect of gabapentin[9]. Therefore, its pharmacologic, analgesic and anxiolytic properties make it a useful drug for premedication. oxygen saturation (Spo 2), pre-operative anxiety and sedation.

Materials and methods:

This study was conducted at Department of Anesthesia, Analgesia, Palliative & Intensive Care

Medicine, Dhaka Medical College Hospital, Dhaka from 1st January 2016 to 30th June 2016. After taking proper approval from Ethical Review Committee, Dhaka Medical College Hospital and taking informed written consent from the participant he/she was asked to draw any one of the cards previously marked for each group. Group A were received oral Pregabalin 150mg and Group B were received Gabapentin 600mg tablet 1 hour prior to surgery. ASA status I and II underwent surgical procedure under general anaesthesia.

Before administration of the oral premedication, each patient's baseline heart rate, systolic and diastolic blood pressure, mean arterial pressure and oxygen saturation was recorded. In addition, to measure anxiety and sedation, Ramsay Sedation Score was completed for each patient. All measurements were repeated before induction. Grade 2 patients were selected. Intravenous line was secured and all patients were started on intravenous fluids. After 3 mins of pre-oxygenation with 100% oxygen, 2 ìg/kg IV Fentanyl was given for supplemental analgesia. Patient was induced with IV thiopentone 5mg/kg followed by IV suxamethonium 2mg/kg for intubation. After 60 second intubation was performed by investigator using Macintosh 3 laryngoscope blade and 7.0-8.0 mm endotracheal tube on the first attempt. The duration of laryngoscopy and intubation was limited to minimum possible time and being similar to all patients. Anesthesia was maintained with Nitrous Oxide 70%, Oxygen 30%and halothane 0.6% MAC. Muscle relaxation was achieved with IV Vecuronium 0.1mg/kg for loading dose and 0.02mg/kg for maintenance dose. Mechanical ventilation was adjusted to maintain normocarbia. Systolic, diastolic and mean arterial blood pressure (SAP, DAP, MAP) and heart rate (HR), oxygen saturation (Spo2) was recorded after administration of IV anesthetics, immediately after intubation and cuff inflation, and 1, 3, 5 and 10 minutes after intubation.

All collected data checked very carefully to identify the error in the data. Data processing work consist of registration schedules, editing, computerization, preparation of dummy table, analyzing and matching of data. After collection of all information, these data were checked, verified for consistency and edited for finalized result. After editing data directly entered into the computer by using SPSS version 16. Data cleaning validation and analysis was performed using the SPSS software and graph and chart by MS excel. The hemodynamic variables represented by mean value ± SD. The statistical significance in mean difference was performed using analysis of variance (ANOVA) and Chi Square test as appropriate. p value of < 0.05 was considered significant and < 0.001 as highly significant. The failure rate of drug was defined by operational definition.

Results:

Table 3.1 *Demographic characteristics of the patients (n=80)*

Demographic variables	Group A (n=40)	Group B (n=40)	P value
Age (years)			
Mean ± SD	26.4 ±8.2	25.3 ±9.3	0.892NS
Sex (male: female)	26 : 14	24:16	0.234NS
Weight (kg)	65 ± 13.23	67 ± 11.23	0.423NS

A total of 80 patients, 40 in each group, were evaluated. All groups were comparable with respect to the demographic and operational factors. No significant differences were found between groups.

Table 3.2 *American Society of Anesthesiologist (ASA) physical status (n=80)*

Status	Number of Patient		P value
	Group A	Group B	
ASA I	26(65%)	29(72.5%)	
ASA II	14(35%)	11(27.5%)	0.950NS

Patient distribution as regard to ASA status, there were no significant difference between the groups (p=0.950). Comparison was done by Chi-Square (÷2) test.

Table 3.3: *Types of surgery in different groups*

Types	Number of patients		Total	P value
	Group A	Group B		
Laparoscopic cholecystectomy	26(65%)	24(60%)	50	0.726^{NS}
Mastoidectomy	8(20%)	9(22.5%)	17	
Tympanoplasty	6(15%)	7(17.5%)	13	

No significant differences were found among groups with respect to type of surgery. The difference was statistically not significant (P>0.05).

Table 3.4 *Mallampati grading in different groups:*

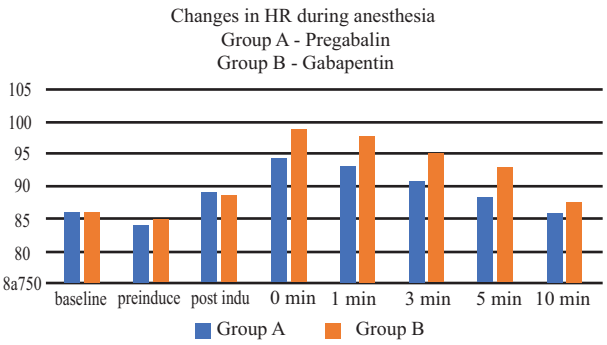
Mallampati	Number of patients		Total	P
	Group A	Group B		value
Grade 1	27(67.5%)	28(70%)	55	0.921^{NS}
Grade 2	13(32.5%)	12(30%)	25	

No significant differences were found among groups with respect to Mallampati grading. The difference was statistically not significant (P>0.05).

Table 3.5 *Changes in HR during anesthesia*

Parameters	Group A	Group B	P value
Baseline	86.05 ± 5.20	86.00 ±7.50	0.634NS
After Preme-dication	84.26 ± 5.19	85.16 ±9.29	0.543NS
After induction	89.20 ± 3.90	88.72 ±10.21	0.587NS
During laryngoscopy (0 min)	94.39 ± 3.70	98.96 ±7.23	<0.001S
1 min	93.15 ± 2.23	97.88 ± 5.33	<0.001S
3 min	90.98 ± 2.45	95.31 ± 5.34	<0.001S
5 min	88.44 ± 4.79	93.1 ± 4.32	<0.001S
10 min	85.93 ± 4.12	86.78 ± 4.68	0.872NS

There was no significant difference in the pre-anesthesia and prior of medication heart rate values between group A and group B. During laryngoscopy, at 1, 3- and 5-mins heart rate was significantly increased in group B than group A. Results showed statistically significant p value. (<0.001)



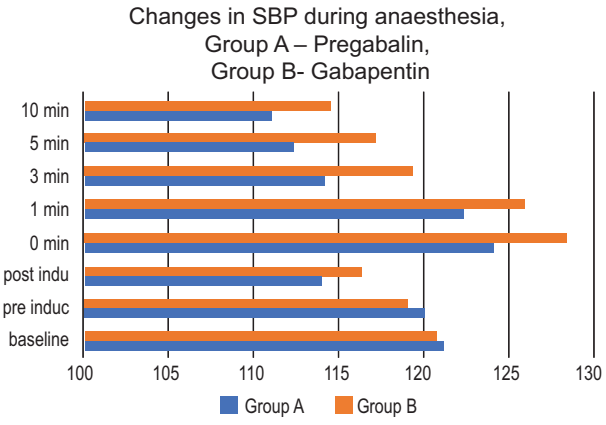
Graph 1 *Graphical presentation of changes in HR during.*

Table 3.6 *Changes in SBP during anesthesia*

Parameters	Group A	Group B	P value
Baseline	121.324±4.247	120.893±3.87	0.451NS
After Premedication	120.214±3.834	119.234±3.12	0.495^{NS}
After induction	115.121±5.664	116.45±6.125	0.231NS
During laryngoscopy (0 min)	124.324±2.34	128.634±6.43	<0.001S
1 min	122.532±3.72	126.12±5.42	<0.001S
3 min	114.231±2.67	119.521±4.21	<0.001S
5 min	112.421±3.512	117.342±5.76	<0.001S
10 min	111.122±6.167	114.64±6.32	<0.001S

There was no significant difference in the pre-anesthesia and prior of medication Systolic blood pressure values between group A and group B. During laryngoscopy, at 1,3,5, 10 mins systolic blood pressure was significantly increased in group B than group A. where p value was less than 0.001.

Changes in SBP during anaesthesia, Group A – Pregabalin, Group B- Gabapentin

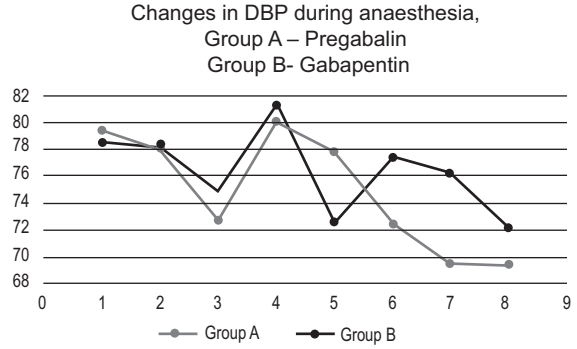


Graph 2 Graphical presentation of changes in SBP during anaesthesia.

Table 3.7 *Changes in DBP during anesthesia*

Parameters	Group A	Group B	P value
Baseline	79.231 ± 2.43	78.421 ± 3.97	0.623S
After Premedication	78.156 ± 4.752	77.94 ± 5.32	0.421S
After induction	72.451 ± 3.421	74.76 ± 6.38	0.027S
During laryngoscopy (0 min)	79.91 ± 2.26	82.18 ± 7.45	<0.001S
1 min	76.64 ± 3.89	79.35 ± 5.75	<0.001S
3 min	72.226 ± 2.43	77.275 ± 6.36	<0.001S
5 min	69.241 ± 3.49	76.134 ± 5.81	<0.001S
10 min	70.189 ± 3.61	72.02 ± 7.43	0.003NS

There was no significant difference in the pre-anesthesia and prior of medication diastolic blood pressure values between group A and group B. During laryngoscopy, at 1, 3- and 5-mins diastolic blood pressure significantly increased in group B than group A.

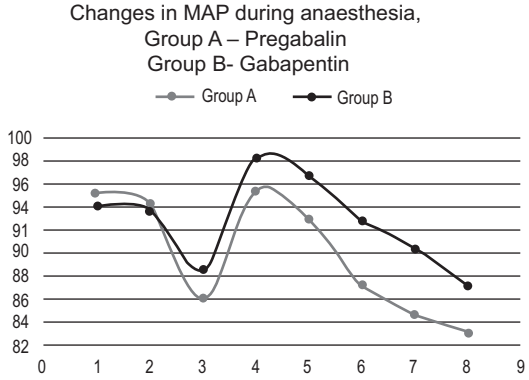


Graph 3 Graphical presentation of changes in DBP during anesthesia

Table 3.8 *Changes in MAP during anesthesia*

Parameters	Group A	Group B	P value
Baseline	95.3 ± 5.8	94.12 ± 6.7	0.812NS
After Premedication	94.2 ± 2.9	93.7 ± 7.85	0.672NS
After induction	86.1 ± 4.26	88.54 ± 8.9	0.231NS
During laryngoscopy (0 min)	95.33 ± 2.87	98.2 ±10.5	0.012NS
1 min	92.96 ± 2.9	96.7 ± 11.43	<0.001s
3 min	87.22 ± 2.5	92.8 ± 9.4	<0.001s
5 min	84.68 ± 2.12	90.43± 8.3	<0.001s
10 min	83.1 ± 3.4	87.2 ± 7.12	<0.001s

There was no significant difference in the pre-anesthesia and prior of medication mean blood pressure values between group A and group B. After laryngoscopy, at1, 3, 5and 10 mins mean blood pressure significantly increased in group B than group A. where p value was statistically significant (p<0.001).



Graph 3 Graphical presentation of changes in MAP during anesthesia

Table 3.9 *Per-operative Ramsay sedation score*

	Group A (40)	Group B (40)
Before Induction	Grade 2 -(28)	Grade 2 – (06)
	Grade 1 –(12)	Grade 1 – (34)
1 hours after	Grade 2 – (37)	Grade 3 –(16)
extubation	Grade 1 –(03)	Grade 2 –(18)
		Grade 1 –(06)

Group A patients were adequately tranquil before induction and recovery was not delayed and patients were not agitated or sleepy. Opposite situation was occurred in group B, where patients were not tranquil before induction and recovery was delayed and patient was too deep for more than hour. This was for several hours in case of patient's age from 45 yrs to 55 yrs.

Table 4.0 *Per-operative complication*

Complication	Group A (40)	Group B (40)
Hypotension	0	0
Bradycardia	0	0
Vomiting	0	0
Blurred vision	0	0
Respiratory depression	0	0

Though group B patients were too deep during recovery time, both groups showed no complications during per-operative period such as hypotension, bradycardia, vomiting, blurred vision and respiratory insufficiency. So, with pregabalin premedication near normal physiology of patients was maintained per-operatively.

Discussion:

Pregabalin administered as a premedication significantly attenuated the pressor response to tracheal intubation in adults. The elevation of the pulse rate and blood pressure may be transient, variable. Usually these changes are well tolerated by healthy individuals. Although many studies proved the efficacy of gabapentin to attenuate intubation response, but a few studies showed the efficacy of pregabalin to suppress intubation response.

In this study all 80 enrolled patients were randomized to one of the two medication treatment groups of 40 patients each. All patients were with ASA physiological status I and II. In pregabalin group 26(65%) were ASA I and 14(35%) were ASA II. In gabapentin 29(72.5%) were ASA I and 11(27.5%) were ASA II.Group A and group B patients had no significant changes in heart rate, after premedication, after induction and 10 minutes after laryngoscopy and intubation. Heart rate increased during laryngoscopy in pregabalin & gabapentin group. During laryngoscopy results were statistically significant where p value was less than 0.001. After 5 mins of laryngoscopy, pregabalin group showed stable heart rate which was near baseline but in gabapentin group heart rate was still away from baseline, where p value was statistically significant.

In a study published in Saudi Journal of Anesthesia, kumkum gupta, Deepak Sharma et al[11], presented similar result by using oral pregabalin 150mg, where heart rate was decreased slightly before induction but stable after intubation.

In journal of Anesth Essays Res, Chandrakant Waikar, Jaideep Singh Et al[21] found similar result with use of pregabalin 150 mg, showing HR was increased after intubation which was near this study result.

So, group A patient's heart rate was significantly stable during laryngoscopy, after 1 min,3 minutes and 5 minutes than group B patients which had similarity with others study published in journal. Group A and group B patient have no significant changes in Systolic blood pressure at baseline, after premedication and after induction. Systolic blood pressure in both groups increase during laryngoscopy but higher in gabapentin group. During laryngoscopy results was statistically significant where p value was less than 0.001. So, group A patient's Systolic blood pressure was significantly stable during laryngoscopy, after 1 min, which was significantly decrease after 3 minutes, 5 minutes and 10 mins than group B patients. So, in group A patient's systolic blood pressure was near normal during and after laryngoscopy

In Journal of Clinical and Diagnostic research, Shirin Parveen, Devendra Singh Negi, Rajesh Kumar and Mohd Chand Bagwan[20], presented in their study, 150mg was effective in blunting hemodynamic stress response to laryngoscopy and tracheal intubation. Systolic blood pressure was not increase after intubation; systolic blood pressure was found near normal. This finding was near same as investigator found in this study.

Group A and group B patient have no significant changes in Diastolic blood pressure at baseline, after premedication, after induction and 10 minutes after laryngoscopy. Diastolic blood pressure in each group increases during laryngoscopy which was higher in gabapentin group. During laryngoscopy results was statistically significant where p value was less than 0.001. After 5 mins of laryngoscopy pregabalin group showed diastolic blood pressure near to baseline which was less than gabapentin group, where p value was statistically significant.

In Journal of Clinical and Diagnostic research Shirin Parveen, Devendra Singh Negi, Rajesh Kumar and Mohd Chand Bagwan[20], presented in their study, 150mg was effective in blunting hemodynamic stress response to laryngoscopy and tracheal intubation. Preoperative baseline diastolic blood pressure was not increase after intubation, diastolic blood pressure was same as before laryngoscopy and intubation. This result was slightly higher than my result.

So, both groups showed stable diastolic blood pressure after laryngoscopy but in group A

patient's diastolic blood pressure was significantly less during after 1 min, 3 minutes and 5 minutes than group B patients.Group A and group B patient had no significant changes in Mean blood pressure at baseline, after premedication and after induction. Mean blood pressure was increased during laryngoscopy especially in gabapentin group. During laryngoscopy results was statistically significant. In 10 mins after laryngoscopy both groups showed stable mean blood pressure.

Another study published in Indian journal of Anesthesia, Bhawna Rastogi, Kumkum Gupta, Himanshu Chauhan[12] showed in their study no significant difference was observed in the mean arterial pressure before and after premedication with pregabalin 150 mg but after laryngoscopy and intubation, the attenuation of mean arterial blood pressure in pregabalin group was statistically significant as compared with the control group. After intubation MAP value was near to this study.

In Journal of Anaesthesia Essays and Researches, Chandrakant Waikar, Jaideep Singh Et al[21] showed in their study oral premedication with oral pregabalin 150 mg attenuate laryngoscopy and intubation reflex successfully. Mean blood pressure after intubation raised slightly higher which was near baseline.

So, group A patients mean blood pressure was significantly stable during laryngoscopy, after 1 min, 3 minutes and 5 minutes than group B patients which had similarity with others study published in journal.Investigator result correlated well with the report of Eren et al[17]. They determined the effect of a single dose of pregabalin 150 mg, administered 1 h prior to surgery on reducing the cardiovascular response and stated that 150 mg of pregabalin had significantly decreased the mean arterial pressure and heart rate response to tracheal intubation of the patients undergoing lumbar discal hernia repair under general anesthesia.

According to Ramsay sedation score, in group A maximum patients were in grade 2 sedation level before induction of anesthesia and recovery was adequate without prolonging and postoperatively patients were in grade 2 sedation level. In group B maximum patients were in grade 1 sedation level and they were anxious. After extubation many patients were too deep for more than hours, sedation score was grade 3 for maximum patients and grade 4 for some patients which were not desirable. So, pregabalin group patients were adequately sedated without prolonging recovery time, which is beneficial for many patients.

Though group B patients were too deep during recovery time, both groups showed no complications during per-operative period such as hypotension, bradycardia, vomiting, blurred vision and respiratory insufficiency. So, with pregabalin premedication near normal physiology of patients was maintained per-operatively.

Conclusions:

The results of this study indicate that oral tablet Pregabalin150mg is more effective than tablet Gabapentin 600mg, in attenuation of intubation reflex. The Heart rate and Mean blood pressure is well control in the A group (pregabalin), with less side effects. The Heart rate and Mean blood pressure increase in the group B (gabapentin), with more side effects.

Pregabalin is emerging as an effective and safe drug as it leads to sedation, analgesia and hemodynamic stability. A single, oral dose of 150 mg of pregabalin premedication seems to be effective in attenuating the hemodynamic response to endotracheal intubation after the first attempt, an effect which may be useful in patients suffering from coronary insufficiency and might enable laparoscopic cholecystectomy in obese, hypertensive, and cardiac compromised patients. As there was no postoperative respiratory depression, it may be used in asthmatic and airway compromised patients.

Study patients age was between 15 – 60 years, but elderly patients more often take drugs such as antidepressants, hypnotics and anti-hypertensives with increased sensitivity to anesthetic medications and the safety and effectiveness of pregabalin in children and adolescent has not been established.

So, further study should be encouraged to established oral pregabalin for attenuation of laryngoscopy and intubation reflex in all age group with co-existing disease.

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