



ROLE OF PREEMPTIVE ORAL PREGABALIN AND ORAL GABAPENTIN FOR ATTENUATION OF SYMPATHOMIMETIC STRESS RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION IN ELECTIVE SURGICAL PROCEDURES UNDER GENERAL ANAESTHESIA

Anaesthesiology

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ABSTRACT

Background and aim:- Laryngoscopy and endotracheal intubation violate the Patient's protective airway reflexes and invariably cause hemodynamic changes associated with increased heart rate, increased blood pressure and occasional disturbance in cardiac rhythm. These hemodynamic changes arise as a form of sympathoadrenal reflex. The present study compared the efficacy of pregabalin and gabapentin for attenuation of sympathomimetic response to laryngoscopy and intubation.

Materials and Method:- Randomly selected 90 patients in between the age of 20-50 years with ASA grade I or II posted for elective surgical procedure under general anesthesia were randomly allocated in 3 groups (n=30). Group P (pregabalin group)-received 150mg pregabalin 1 hour prior to surgery and Group G (gabapentin)-received 900mg gabapentin 1 hour prior to surgery. Group C (control)-received vitamin B-complex capsule 1 hour prior to surgery. Hemodynamic parameters like heart rate (HR), systolic and diastolic blood pressure, mean arterial pressure (MAP) were recorded at baseline, during intubation and 1, 3, 5, 10, 15, 20, 25 and 30 minutes after intubation.

Results:- Pregabalin 150mg attenuated hemodynamic stress response in terms of Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Pressure and Rate Pressure Product better than Gabapentin 900mg during laryngoscopy and endotracheal intubation. Both were effective in attenuating hemodynamic response as compared to placebo. Drowsiness was the only side effect seen in few patients. But the adverse effects did not cause any harm to the patient and corrected spontaneously.

Conclusion:- Both Pregabalin and Gabapentin attenuated the hemodynamic responses to laryngoscopy and intubation. Pregabalin was more effective with minimal adverse effects.

KEYWORDS

Pregabalin, Gabapentin, Intubation, Stress response.

INTRODUCTION

Laryngoscopy and endotracheal intubation is the traditional method of securing the airway for administration of anesthesia. The influence of airway manipulation on heart rate and blood pressure was recognized more than 50 years ago and the magnitudes of the changes were observed to depend on the depth of anesthesia^[1]. It is now well established that laryngoscopy and endotracheal intubation violate patients protective airway reflexes and invariably cause hemodynamic changes associated with increase heart rate, increase blood pressure and occasional disturbance in cardiac rhythm.^{[2],[3]} These hemodynamic changes arise as a form of sympathoadrenal reflex and due to release of norepinephrine and, to a lesser extent, of epinephrine.^[4]

In normotensive subjects these hemodynamic changes are short lived.^[5] and probably of little significance. However, these hemodynamic alterations are, hazardous to the patients with hypertension, myocardial insufficiency or cerebrovascular disease.^[6] In patients with coronary artery disease it may lead to myocardial ischemia and dysrhythmia because, increase in heart rate and blood pressure associated with laryngoscopy and endotracheal intubation may result in an increase in myocardial oxygen demand and also demand for increased coronary flow. In hypertensive patients these exaggerated responses may lead to left ventricular failure, pulmonary edema and congestive cardiac failure. In patients with intracranial aneurysm or dissecting aneurysm of the aorta, the increase in systemic blood pressure may cause rupture of vessels with life threatening consequences.

So, effective prevention of the cardiovascular stress response is a prudent goal in anaesthesiology. The search for an ideal drug to attenuate the pressor response to intubation has been going on since few decades. Some of those are intubation in a deeper plane of anesthesia, topical anesthesia of the upper respiratory tract prior to laryngoscopy with lignocaine, pre-treatment with vasodilators, beta blockers, calcium channel blockers and opioids^[7,8]. But, no single drug has been proven to be the drug of choice.

Recently, gamma-amino butyric acid (GABA) analogues pregabalin

and gabapentin have gained prominence in various clinical studies, in not only alleviating peri-operative pain but also effective in attenuating pressor response to intubation and in producing peri-operative sedation and anxiolysis^[9]. This prospective, randomized, double blind, controlled study was formulated to compare the efficacy of orally administered pregabalin and gabapentin to attenuate the adverse hemodynamic response to laryngoscopy and endotracheal intubation.

MATERIAL AND METHODS

This prospective, randomized, comparative, double blind study was conducted at a tertiary care hospital in Eastern India over a period of one year (January 2013-June 2014) after approval of the Ethical cum Screening Committee. We included randomly selected 90 patients (determined by power analysis study) in between the age of 20-50 years with American Society of Anesthesiologists (ASA) physical status (PS) I and II, of either sex, weighing between 45 and 75 kg posted for elective surgical procedures under general anesthesia. Each patient received a written and verbal description of the research protocol and written informed consent was taken from all the patients in their language for inclusion in the study. Exclusion criteria for the study were patients with severe cardiovascular, respiratory, renal and hepatic diseases, patients on beta blocker therapy or alpha-2 agonist therapy, patients with anticipated difficult airway, laryngoscopy and intubation time >30sec or requiring more than two attempts.

All patients were divided in three groups (n=30)

- Group P (pregabalin group)-received 150 mg of pregabalin tablet one hour prior to surgery
- Group G (gabapentin group)- received 900 mg of gabapentin tablet one hour prior to surgery
- Group N (control/placebo group)- received capsule of vitamin B-complex one hour prior to surgery

Parameters to be studied

Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP) and Rate pressure product were recorded at baseline/pre intubation (T1), during

intubation (T2), post intubation at 1 minute (T3), 3 minutes (T4), 5 minutes (T5), 10 minutes (T6), 15 minutes (T7), 20 minutes (T8), 25 minutes (T9) and 30 minutes (T10).

Study technique

After approval of the Hospital Ethical cum Screening committee, 90 patients with the above mentioned criteria were selected for the study. On the preceding day of operation, relevant history, preanaesthetic check-up and informed consent of the patient were taken. Patients were advised to fast for 8 hours before surgery. After arrival in the operating room, patient's identity and informed consent form were checked and all requisite monitors were attached. Blinding were done by using two separate persons doing the required work. Study drugs were supplied in sealed envelope with number codes one hour prior to intubation. Anesthesiologists were chosen to conduct the procedures randomly. Later on all the data were collected from them and tabulation was done. Patients were premedicated with inj. Fentanyl (2microgram/kg) 5 min prior to intubation.

All patients received a standardized anesthetic as described- preoxygenation for 3 minutes with gas flow @ 5 liters/minute, followed by induction of anesthesia with inj. Propofol (2mg/kg I.V). Laryngoscopy (using Macintosh Laryngoscope) and intubation with appropriately cuffed endotracheal tube were facilitated with Inj. Vecuronium bromide (0.1mg/kg). Maintenance of anesthesia was done with 40% of O₂ -60% of N₂O, and Isoflurane inhalation 0.6 % MAC. Muscle relaxation was achieved with vecuronium, which was repeated at 25%-30% of the initial dose as per requirement. Ventilation was mechanically controlled and adjusted to control end tidal CO₂ concentration at 30-35 mmHg. At the end of operation residual neuromuscular blockage was antagonized with neostigmine (40 mcg/kg I.V) and glycopyrrolate (0.01mg/kg I.V). Extubation was done only after adequate reversal from general anesthesia judged on clinical basis.

Statistical Analysis:

The results of the observations thus obtained in each group of patients were tabulated, compiled and statistically analyzed using Stastica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001] and SPSS version 17 [Illinois, Chicago: SPSS Inc., 2008]. All numerical variables were mostly normally distributed by Kolmogorov-Smirnoff goodness of fits test. Results on continuous measurements were presented on Mean ± SD (Min-Max). Significance was assessed at 5 % level of significance. Analysis of variance (ANOVA) was used to find the significance of study parameters between three groups of patients. Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups.

A p value < 0.05 was considered as statistically significant and < 0.01 was considered as highly significant.

Demographic variables

The groups were statistically comparable with respect to sex, age, body weight, height and ASA grading. [Table 1] No significant differences were observed between the groups (p value > 0.05)

Table 1. Comparison of demographic variables between the study groups

DEMOGRAPHIC VARIABLES	GROUP P	GROUP G	GROUP N
SEX(M:F)	16:14	15:15	16:14
MEAN AGE(yrs)	40.6	39.9	38.6
MEAN WEIGHT(kg)	57.96	58.66	57.1
MEAN HEIGHT(cm)	157.76	159.2	158.3
ASA GRADE(I:II)	17:13	15:15	16:14

Operative Procedures

All operative procedures were elective abdominal surgeries. Calculations for statistical significance indicated that there was no difference in the types of operative procedures across the groups (p value > 0.05) [Table 2].

Table 2. Types of operative procedures in the study groups

SURGICAL PROCEDURE	GROUP P	GROUP G	GROUP N
OPEN CHOLECYSTECTOMY	6	5	6
OPEN NEPHRECTOMY	3	4	4

TAH±BSO	5	5	3
APENDICECTOMY	6	4	5
INSIONAL HERNIA REPAIR	2	3	2
MYOMECTOMY	2	2	3
MASTECTOMY	2	1	2
GASTECTOMY	1	2	1
OVARIANCYSTECTOMY	3	4	4

Comparison of Heart rate (beats/min) between groups

When the preoperative baseline Heart Rates was compared between three groups, no statistically significant difference was found (p value >.05). The HR during intubation and after intubation were significantly lower in Pregabalin compared to Gabapentin and placebo (p value < 0.001) and lower in Gabapentin compared to placebo (p value<.001) [Table-3]

Table 3:-Mean heart rate and standard deviation

TIME	GROUP P	GROUP G	GROUP N	P VALUE	REMARK
T1	85.1±2.79	83.7±1.72	83.1±1.28	>.05	IS
T2	97.9±4.9	108.7±2.42	119.7±1.76	<.001	S
T3	90±1.9	105.8±2.8	116.3±2.24	<.001	S
T4	85.4±2.25	104±2.82	109±1.9	<.001	S
T5	82±2.34	92.9±2.88	103.4±1.45	<.001	S
T6	81.6±2.40	90±2.17	100±1.65	<.001	S
T7	79.8±2.01	88.8±2.1	98.8±1.32	<.001	S
T8	78±2.12	86.4±2.3	97.7±1.36	<.001	S
T9	77.8±1.84	85.4±2.1	95.3±1.42	<.001	S
T10	77.5±1.99	84.9±1.8	93.1±1.01	<.001	S

IS=Insignificant, S=Significant

Comparison of SBP (mmHg) between groups

When the preoperative baseline SBP was compared between three groups, no statistically significant difference was found (p value >.05). The SBP during intubation and after intubation were significantly lower in Pregabalin compared to Gabapentin and placebo (p value < 0.001) and lower in Gabapentin compared to placebo (p value<.001) [Table-4]

Table 4:- Mean systolic blood pressure and standard deviation

TIME	GROUP P	GROUP G	GROUP N	P VALUE	REMARK
T1	126.6±2.943	127±2.37	126.3±2.17	>.05	IS
T2	133.5±3.45	145.3±2.21	156±1.69	<.001	S
T3	133.1±3.12	144.3±2.24	153±1.64	<.001	S
T4	132±3.04	142.2±1.755	150±2.03	<.001	S
T5	131.2±2.70	141.1±1.639	147.1±2.06	<.001	S
T6	129.1±2.52	137±1.486	143.2±1.17	<.001	S
T7	122.5±2.48	130.2±1.71	138±1.57	<.001	S
T8	121.7±2.43	128.6±1.92	135.2±1.88	<.001	S
T9	120.3±2.02	125.8±1.71	131.2±2.15	<.001	S
T10	118.1±2.14	124.3±1.535	128.8±1.7	<.001	S

IS=Insignificant, S=Significant

Comparison of DBP (mm Hg) between groups

When the preoperative baseline DBP was compared between three groups, no statistically significant difference was found (p value >.05). The DBP during intubation and after intubation were significantly lower in Pregabalin compared to Gabapentin and placebo (p value < 0.001) and lower in Gabapentin compared to placebo (p value<0.001) [Table-5]

Table 5: Diastolic blood pressure and standard deviation

TIME	GROUP P	GROUP G	GROUP N	P VALUE	REMARK
T1	81.2±2.46	81.6±1.07	80.8±1.33	>.05	IS
T2	93.4±3.72	98.4±1.886	103±1.36	<.001	S
T3	91.8±4.09	96.2±1.87	101±1.31	<.001	S
T4	87.2±3.93	92.6±1.85	97.2±1.53	<.001	S
T5	83±2.8	89.6±1.85	95±1.93	<.001	S
T6	80.3±2.3	86.3±1.68	92.2±1.54	<.001	S
T7	79±2.6	85.1±1.58	91.1±1.63	<.001	S
T8	77.2±2.4	84.2±1.289	90±1.79	<.001	S
T9	76±1.7	83±1.129	89±1.62	<.001	S
T10	74.9±1.7	81.8±.961	87.1±1.77	<.001	S

IS=Insignificant, S=Significant

Comparison of MAP (mmHg) between groups

When the preoperative baseline MAP was compared between three groups, no statistically significant difference was found (*p value* >.05). MAP during intubation and after intubation were significantly lower in Pregabalin compared to Gabapentin and placebo (*p value* <0.001) and lower in Gabapentin compared to placebo (*p value* <.001) [Table-6]

Table 6: Mean arterial pressure and standard deviation

TIME	GROUP P	GROUP G	GROUP N	P VALUE	REMARK
T1	96.4±2.18	96.5±1.333	96±1.26	>.05	IS
T2	106.4±2.5	117.4±1.478	120±1.08	<.001	S
T3	105.6±2.5	115.2±1.43	118.3±1.05	<.001	S
T4	103±3.05	109.1±1.423	114.8±1.35	<.001	S
T5	99.2±2.3	107.4±3.839	112.2±1.60	<.001	S
T6	96.6±1.5	103.3±1.202	109.2±1.10	<.001	S
T7	93.7±1.7	100±1.474	106.7±1.12	<.001	S
T8	92.2±1.6	98.4±1.189	105±1.35	<.001	S
T9	90.8±1.12	97.2±1.278	103.1±1.30	<.001	S
T10	89.5±1.13	96±.999	101.2±1.17	<.001	S

IS=Insignificant, S=Significant

Comparison of Rate-Pressure product between groups

When the preoperative baseline Rate pressure products were compared between three groups, no statistically significant difference was found (*p value* >.05). The Rate pressure product during intubation and after intubation were significantly lower in Pregabalin compared to Gabapentin and placebo (*p value* <0.001) and lower in Gabapentin compared to placebo (*p value* <.001) [Table-7]

Table 7: Rate-pressure product and standard deviation

TIME	GROUP P	GROUP G	GROUP N	P VALUE	REMARK
T1	10768.3±421.55	10633±311.57	10495.8±259	>.05	IS
T2	13033.9±791.2	15800.7±491.53	18673.4±353	<.001	S
T3	11983.4±359.58	15295.7±500.58	17799.6±407	<.001	S
T4	11278.1±420.35	14798.9±442.76	16354±345.37	<.001	S
T5	10767.5±432.89	13158.2±476.65	15161±241.33	<.001	S
T6	10310±356.96	12325.2±268.44	14147.9±203	<.001	S
T7	9791.1±356.42	11562.7±350.86	13637.2±208	<.001	S
T8	9499.6±332.67	11111.1±388.19	13211.6±280	<.001	S
T9	9392.9±276.89	10740.4±249.5	12513.9±274	<.001	S
T10	9150.3±282.86	10566.9±234.44	11987±207.6	<.001	S

IS=Insignificant, S=Significant

Perioperative complications

4 (13%) and 3 (10%) patients complained of drowsiness in pregabalin and gabapentin groups respectively. No other complications seen in this study. [Table-8]

Table 8:- Perioperative complications between groups

COMPLICATIONS	GROUP P	GROUP G	GROUP N
Drowsiness	4	3	0
Others	0	0	0

DISCUSSION

Laryngoscopy and endotracheal intubation are associated with rise in heart rate, blood pressure and occasional disturbance in cardiac rhythm.^[2,3] Although in normotensive subjects these responses of blood pressure and heart rate are transient and short lived,^[5] they may prove to be detrimental in high risk patients especially in those with cardiovascular disease, increased intracranial pressure and anomalies of the cerebral blood vessels.^[6] So, effective attenuation of hemodynamic response to laryngoscopy and tracheal intubation is of great importance in prevention of perioperative morbidity and mortality.

This randomized, double blind study was undertaken to compare the usefulness of two drugs, pregabalin and gabapentin in attenuation of the sympathomimetic stress response following laryngoscopy and endotracheal intubation.

The factors influencing the cardiovascular changes associated with laryngoscopy and intubation are age, drugs, type and duration of procedures, depth of anesthesia, hypoxia and hypercarbia. Variations in heart rate to stressful events decrease with increasing age. Young patients show more extreme changes.^[10] Marked fluctuations in hemodynamic response have been also reported in geriatric patients.^[11,12] Therefore, patients with an optimal age range of 20 to 50 years were selected for this study. Difficult intubation takes longer time and is invariably associated with marked hemodynamic changes even in well premedicated patients. So, patients with higher Mallampati class (III and IV) were excluded from this study.

The most significant factor influencing cardiovascular responses is the duration of laryngoscopy.^[13] The force applied during laryngoscopy has only minor effect. In this study the durations of laryngoscopy and intubation were limited to less than 30 seconds. During laryngoscopy adequate depth of anesthesia was maintained avoiding hypoxia and hypercarbia.

Gabapentin,^[14,15] 2-[1 (amino methyl) cyclohexyl] acetic acid, is a structural analogue of the neurotransmitter gamma amino butyric acid. It acts by selective activation of GABA-B receptors and enhancement of NMDA current at GABAergic interneurons. It is used in epilepsy, chronic pain condition, preemptive analgesia, preoperative anxiolysis, post-operative analgesia, attenuation of hemodynamic response to laryngoscopy and intubation and in post-operative nausea and vomiting.

Pregabalin, (s)-3-(amino methyl)-5-methyl hexanoic acid) is a lipophilic analogue of GABA. Although pregabalin is structurally related to GABA, it is inactive at GABA receptors and does not appear to mimic GABA physiologically. It acts by decreasing the synthesis of neurotransmitter glutamate to act on the central nervous system. It exhibits potent anticonvulsant, analgesic and anxiolytic activity^[16,17] and is effective in preventing neuropathic component of acute nociceptive pain of surgery.

Pregabalin and gabapentin reduced heart rate compared to placebo during intubation and post intubation in the present study. With gabapentin heart rate was not significantly reduced compared to pregabalin. Before intubation there was no significant difference. Ebru Salman et al^[18] showed that premedication with single dose pregabalin 150mg attenuated hemodynamic response to laryngoscopy and endotracheal intubation.

Pregabalin was more effective in lowering heart rate than gabapentin during intubation and post intubation period.

Both Pregabalin and gabapentin significantly reduced SBP, DBP and MAP compared to placebo during intubation and post intubation. Before intubation there was no significant difference. Similar to current study, Kiran S et al^[19] also observed that gabapentin attenuated the pressor response to tracheal intubation as SBP,DBP,MAP significantly as compared to placebo.

Pregabalin was more effective in lowering SBP, DBP and MAP than gabapentin during intubation a post intubation period.

Both Pregabalin and gabapentin significantly reduced rate pressure product compared to placebo during intubation and post intubation. Before intubation there was no significant difference. According to study by Eren G et al^[20] pregabalin blunted cardiovascular responses to laryngoscopy and tracheal intubation. Fassoulaki A and colleague^[21] concluded that gabapentin attenuated the pressor response to direct laryngoscopy and tracheal intubation. Pregabalin was more effective in lowering rate pressure product than gabapentin during intubation and post intubation period in current study.

Serum catecholamines are the most important markers to assess the sympathoadrenal stress response to any stimulus. But, in this study we could not measure its level in every patient due to scarcity of the resources. This is the major limitation of our study.

Regarding complications, 13% patients on pregabalin and 10% patients on gabapentin complained of drowsiness. Mellegers MA and colleague^[22] showed that most commonly observed side effect was somnolence. Ramsay had commented that severity of side effects with gabapentin was usually of minor degree^[23].

CONCLUSION

A single dose of 150mg Pregabalin attenuates sympathomimetic stress response in terms of heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product better than Gabapentin 900mg during laryngoscopy and endotracheal intubation. Both are effective in attenuating hemodynamic response as compared to placebo. Adverse effects are minimal.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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