The Effectiveness of Oral Pregabalin in Attenuation of Systolic Blood Pressure and Heart rate due to airway instrumentation During General Anaesthesia.A Dose Response Study

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Abstract- Introduction*:** Oral pregabalin premedication adequately sedates the patient and haemodynamic pressor response of airway instrumentation was attenuated ***Material and methods*:** The study was designed as a prospective randomized, double-blinded,placebo controlled study, which included 120 normotensive adult patients aged 24-56years of both genders,scheduled for elective surgery under general anaesthesia with ASA physical status I & II were allocated for the study.This study was done in the department of anaesthesia, and critical care,Sher-i-Kashmir institute of medical science, Srinager(J &K) after obtaining approval from ethical committee,a written informed consent was taken from the patients for participation in this study.Results*:** Systolic blood pressure increased maximally in group I(P0) and group II(P75) 1min after direct laryngoscopy and endotracheal intubation from baseline (32.1% from baseline).It gradually decreased to near baseline values over 10 minutes.In groupIII (P150) maximum rise in blood pressure was 11.1% from baseline.Among these only pregabalin 150mg attenuated the rise in blood pressure following laryngoscopy(p-value=0.001).

There was no significant difference in heart rate among groups before and after premedication.Immediately after laryngoscopy and intubation,the heart rate increased significantly in all groups, increase was least in group III.Maximum increase in heart rate from baseline was observed after 1 min of laryngoscopy.

Conclusion: There was no statistically significant difference between placebo and pregabalin 75mg in attenuation of systolic blood pressure.

No statistically significant attenuation of heart rate was observed in the premedicated group,although it remained stabilised in group III as compared with group I and II.

***Index Terms*-** Haemodynamic pressure response,oral pregabalin,gabapentin.

I. INTRODUCTION

Laryngoscopy and endotracheal intubation are the fundamental components of airway management and facilitate maximum control of ventilation and oxygenation, and form an integral part of anaesthesiologist's contribution to patient care.However laryngoscopy is a noxious and most invasive stimulus during endotracheal intubation.[1,2] Manipulation of the upper respiratory tract such as during laryngoscopy and endotracheal intubation are associated with haemodynamic and cardiovascular responses consisting of increased circulating catecholamine , heart rate , blood pressure , myocardial oxygen demand , tachycardia and dysrhythmias.[3]The majority of these stimuli arise from stimulation of supraglottic region by tissue tension induced by laryngoscopy.Placement of endotracheal tube and inflation of the cuff in the subglottic region produces a smaller additional response. Most anaesthesiologists agree that a skilled anaesthesiologist applies only a small force to the patient's larynx when using a laryngoscope and that reducing the force on larynx might prevent haemodynamic responses to endotracheal intubation.[2,4-7]

Evidence from the laboratory data demostrates that epipharyngeal and laryngopharyngeal stimulation augments cervical sympathetic activity in the efferent fibers to heart. This explains the increase in plasma levels of nor-epinephrine and to a lesser extent epinephrine which occur in response to laryngoscopy and endotracheal intubation.[8] The cardiovascular response to noxious airway manipulation are initiated by proprioceptors responding to tissue irritation in supraglottic region and trachea. These proprioceptors consist of mechano-receptors with small diameter myelinated fibers. The glossopharyngeal and vagal afferent nerves transmit these impulses to the brain stem, which in turn causes widespread autonomic activation throughout both sympathetic and parasympathetic nervous systems.

The rise in heart rate and blood pressure is usually transient occuring 30 seconds after intubation and lasting for less than 10 minutes.[1] Usually these changes are well tolerated by healthy individuals, but are of great concern in susceptible individuals particularly those with systemic hypertension, coronary artery disease, leaking abdominal aneurysm, intracranial aneurysm and recent myocardial infarction. In such patients these transient changes can result in potentially deleterious effects such as myocardial ischemia, left ventricular failure as a result of increased myocardial oxygen demand and cereberal haemorrhage.[1,8]

Control and protection of airway during general anaesthesia has been fundamental subject under consideration for the past four decades.

Many studies have therefore concentrated on the stressful stimulus of laryngoscopy and endotracheal intubation and a number of pharmacological measures have been used to attenuate the haemodynamic stress response to laryngoscopy and endotracheal intubation. No single drug or technique is completely satisfactory. These measures are :

- Inhalational anaesthetic agents are used to obtund the laryngoscopic response by increasing the depth of anaesthesia.[9] However it leads to hypotension, bradycardia and myocardial ischemia and it is dangerous in hypertensive patients.[10]
- Alpha adrenergic blocker, phentolamine was used to attenuate the laryngoscopic response.[11]
- Beta adrenergic blocking drugs are being used for blunting hemodynamic responses.[12-15]
- Directly acting vasodilators like sodium nitroprusside and nitroglycerine.[16]
- Low dose opioids like morphine and fentanyl.[17,18]
- Topical administration of local anaesthetics like lignocaine which block the sensory fibres in laryngopharynx.[19,20]
- Calcium channel blockers like nicardapine,verapamil and diltiazem.[21,22]
- Clonidine and other α2-adrenocepter agonists are under intense investigation.[23]
- Gabapentin was introduced as an anti-epileptic drug in 1993[24].Many studies are going on to prove the efficacy of gabapentin in attenuating preoperative anxiety and stress response to intubation.[25,26]
- Oral pregabalin premedication adequately sedates the patient and haemodynamic pressor response of airway instrumentation was attenuated in dose-related fashion.[27]

The present study was performed to compare the effect of oral Pregabalin premedication on modifying the hemodynamic stress response following laryngoscopy and intubation.

II. Aims and Objectives

1. To evaluate the safety and efficacy of oral Pregabalin premedication for attenuation of haemodynamic pressor response to airway instrumentation.
2. To compare the effectiveness of oral pregabalin in different doses to attenuate haemodynamic pressor response to airway instrumentation under general anaesthesia.

III. Materials and Methods

The study entitled “The Effectiveness of Oral Pregabalin in Attenuation of Systolic Blood Pressure and Heart rate due to airway instrumentation during General Anaesthesia: A dose response study” was conducted in department of anaesthesia and critical care,Sher-i-Kashmir institute of medical science, Srinager(Kashmir) after obtaining approval from ethical committee,a written informed consent was taken from the patients for participation in this study.

The study was designed as a prospective randomized, double-blinded,placebo controlled study, which included 120 normotensive adult patients aged 24-56years of both genders,scheduled for elective surgery under general anaesthesia with ASA physical status I & II were allocated for the study.The study was carried from January 2013 to November 2014.

IV. EXCLUSION CRITERIA:

Patients with anticipated difficult intubation,history of cardiac, pulmonary or renal disease,obesity, allergy to any anaesthetic medication and patients on sedatives, hypnotics or antihypertensive medication were excluded. When duration of laryngoscopy exceeding 22s or a second attempt for intubation is needed these patients were also excluded from the study.

The patients were randomly allocated into three groups of fourty patients each. Patients selected for surgery were admitted 24 hrs prior to surgery. Preanaesthetic evaluation was done at this stage.Age, gender, weight, ASA physical status was noted in all patients .A thorough history of any comorbid disease, previous anaesthetic exposure, smoking, medictions, allergy to any drugs and personal habits was elicited.

Double blinding was done by means of sealed envelope technique using fourty similar looking thick opaque envelopes and the code name I, II,or III was mentioned on top of envelope. The assistant separated the capsules of placebo, capsules of pregabalin (75mg) and capsules of pregabalin (150 mg) into three equal groups of fourty each. Thus three groups of fourty envelops were prepared containing either capsules of placebo, capsules of pregabalin 75mg or capsules of pregabalin 150mg with the same code (I or II or III) mentiond on them.Only the assistant was aware of the code identity which was revealed at the end of study.

The patients were randomly allocated to three equal groups of fourty each.

Group I (Po):Fourty patients received oral placebo (po) in the form of oral multivitamin capsules 1hr before surgery.(labeled code I)

Group II (P75): Fourty patients received pregabalin 75mg orally with sip of water 1hr before surgery.(labeled code II)

Group 3(P150): Fourty patients received pregabalin 150mg orally with sip of water 1hr before surgery.(labeled code III)

The drug from the closed envelope was drawn and given to the patient by anaesthesia technician with sip of water 60minutes before induction of anaesthesia.The identity of the capsule was not revealed to the patient.The patients did not receive any other premedication other than the study drugs mentioned.

Continous monitoring of heart rate, blood pressure(systolic in mmhg),Spo2(pulse oximetry) and EtCo2 was done using WATO EX-65 monitor.

Baseline readings of heart rate (HR), systolic blood pressure (SBP), before induction of anaesthesia.

The study parameters i.e. heart rate(HR), systolic blood pressure(SBP) were recorded at following intervals:-
1.Baseline.
2.Before induction.
3.After induction.
4.One minute after intubation i.e.T1
5.five minutes after intubation i.e.T5
6.Ten minutes after intubation i.e.T10

The analysis of data was carried out by statistical package for social sciences (spss version 14.0) U.S.A,Chicago for windows.

V. Observations & Results

120 patients undergoing elective surgery under general anaesthesia with endotracheal intubation were divided randomly into three groups with 40 patients each

Group I(P_0):Received placebo 1 hr before surgery.

Group II(P_{75}):Received oral pregabalin 75mg orally 1 hr before surgery.

Group III(P_{150}):Received oral pregabalin 150mg orally 1 hr before surgery.

TABLE 1:Comparison of heart rate(beats/min.) in three groups

Heart rate(beats/min)	I(Mean±SD)	II(Mean±SD)	III(Mean±SD)	p-value ANOVA	Intercomparison on group (post Hoc test)
Basal heart rate	79.93±4.90	80.08±3.12	80.65±2.64	0.235	IvsII 0.001 IIvsIII 1.00 IvsIII 0.001
Before induction	104.55±2.31	91.82±2.14	90.78±1.64	0.000	IvsII 0.000 IIvsIII 0.071 IvsIII 0.000
After induction	108.87±1.99	101.50±2.32	97.95±2.01	0.000	IvsII 0.000 IIvsIII 0.000 IvsIII 0.000
1 min after intubation	121.03±7.85	109.12±3.33	107.05±1.36	0.000	IvsII 0.000 IIvsIII 0.195 IvsIII 0.000
5 min after intubation	111.35±5.23	103.40±2.25	100.80±1.95	0.000	IvsII 0.000 IIvsIII 0.003 IvsIII 0.000
10 min after intubation	98.65±3.21	95.10±2.01	92.50±1.68	0.000	IvsII 0.000 IIvsIII 0.000 IvsIII 0.000
After extub.	103.62±3.66	97.57±1.95	93.50±2.91	0.000	IvsII 0.000 IIvsIII 0.000 IvsIII 0.000
Over all	103.52± 0.25	96.94± 0.25	94.75± 0.25	0.001	I vs II 0.001 IIvs III 0.001 Ivs III 0.001

In Table 1,there was a non- significant difference in the heart rate values among groups before and after premedication.Immediately after laryngoscopy and intubation,the heart rate increased significantly in all groups,but the increase was least in group III (P150) which bear a significant difference with group I and group II.The significant difference persists among the groups upto 10 minutes after intubation and even after extubation.The difference among the groups was statistically significant.

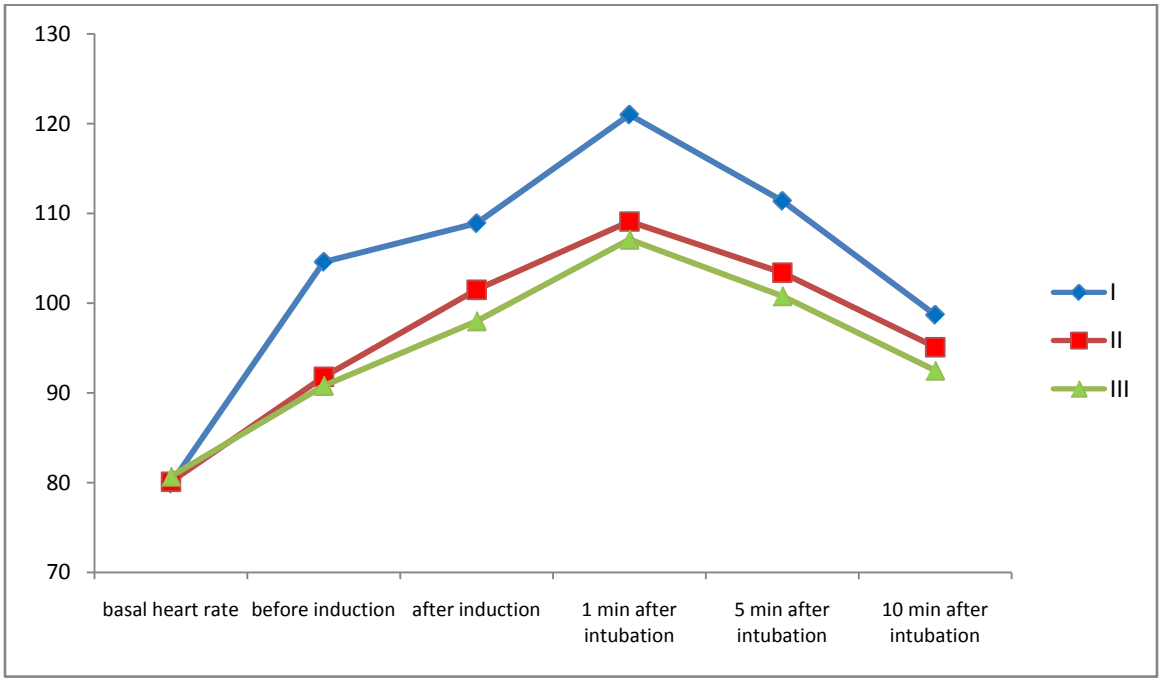

Figure 1: Line graph representing comparison of heart rate (beats/min) among three groups

TABLE 2 :Comparison of systolic blood pressure(mmhg) in three groups

	I(Mean±SD)	II(Mean±SD)	III(Mean±SD)	p-value ANOVA	Intergroup comparison (Post Hoc test)
Basal systolic BP	121.20±3.20	119.65±5.28	120.00±3.73	0.222	Ivs II 0.296 IIvs III 1.000 Ivs III 0.600
Before induction	130.43±9.23	129.20±4.50	110.63±2.56	0.000	IvsII 1.000 IIvsIII 0.000 IvsIII 0.000
After induction	129.15±2.90	128.75±3.80	106.93±3.37	0.000	IvsII 1.000 IIvsIII 0.000 IvsIII 0.000
1min after intubation	160.23±4.86	158.78±5.40	133.38±4.16	0.000	IvsII 0.547 IIvsIII 0.000 IvsIII 0.000
5min after intubation	138.10±5.25	137.72±2.21	117.65±3.37	0.000	IvsII 1.000 IIvsIII 0.000 IvsIII 0.000
10min after intubation	125.87±3.01	124.07±4.17	108.67±4.38	0.000	IvsII 0.124 IIvsIII 0.000 IvsIII 0.000

In Table 2 ,there was a non –significant difference in systolic blood pressure at baseline among the three groups.Before induction a non significant difference was observed between group I and group II,which persists upto 10min after intubation while as group III bear a significant difference with group I and group II.

Systolic blood pressure increased maximally in group I(P0) and group II(P75) 1min after direct laryngoscopy and endotracheal intubation from baseline (32.1% from baseline). In groupIII (P150) maximum rise in blood pressure was 11.1% from baseline.Among these only pregabalin 150mg attenuated the rise in blood pressure following laryngoscopy(p-value=0.001).There was no statistically significant difference between placebo and pregabalin 75mg in attenuation of systolic blood pressure.

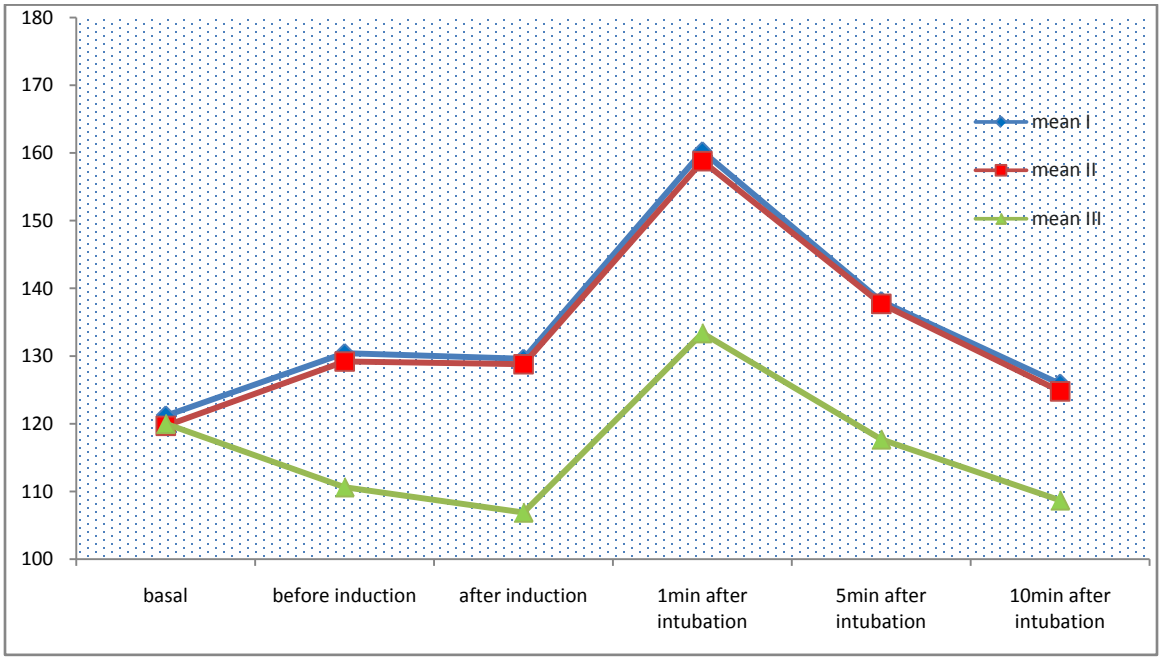

Figure 2:Line graph representing mean systolic blood pressure in mmhg among three groups.

Discussion

The present study evaluated the safe and clinically effective dose of oral pregabalin premedication for its sedative effects and for attenuation of haemodynamic response of airway instrumentation of direct laryngoscopy and intubation. .

Although,there are studies regarding pregabalin on controling the pressor response on laryngoscopy and endotracheal intubation.Our study prospective, randomised, blind, placebo controlled , is a dose response study on pregabalin

for attenuation of haemodynamic pressor respnse due to laryngoscopy and endotracheal intubation.

VI. INTRA-OPERATIVE HAEMODYNAMIC PARAMETER:

VII. HEART RATE(BEATS PER MINUTE):

In group I baseline heart rate was 79.93/min(table 5) which increased to 108.87/min immediately before intubation. The heart rate increased to 121.03/min at 1 min after intubation representing rise of 41.1/min that is 51.42% from baseline. The heart rate started settling down 5 min after intubation.By 5 min it was 111.35 and by 10 min it was 98.65/min.The increase in heart rate from baseline was statistically significant(p-value<0.05) (Table 1,figure 1)

In group II baseline heart rate was 80.08/min (table 5) which increased to 101.50/min just immediate before intubation.the heart rate increased to 109.12/min at 1min after intubation representing rise of 29.04/min(36.2%) from baseline.This was followed by gradual decline in heart rate towards baseline. By 5 min it was 103.40/min and by 10 min it was 95.10/min. The increase in heart rate was statistically significant($p<0.05$) (Table 1,figure 1)

In group III baseline heart rate was 80.65/min which increased to 90.95/min immediately before intubation.The heart rate increased to 107.05/min at 1min after intubation representing a rise of 26.4/min that is 32.7% from baseline.Subsequently the heart rate started settling down. By 5 min it was 100.80/min and by 10 min it was 92.50/min which was less compared to group I and II.

In our study,there was no significant difference in heart rate among groups before and after premedication.Immediately after laryngoscopy and intubation, the heart rate increased in all groups, increase was least in group III which bears a significant difference with group I and group II.The significant difference persisted among the groups upto 10 minutes after intubation and even after extubation.The difference among the groups was statistically
significant.

On comparing the rise in heart rate in group III with group II and group I,there was a statistically significant difference both after intubation upto 10 minutes and after extubation as well (p-value 0.001).

Our results are in agreement with the study conducted by Rastogi Bhawna et al[27] ,they studied a total of 90 normotensive adult patients aged 24-56 years,ASA grade I and II,of both gender were randomised into three groups of 30 patients each.Group I received oral placebo,Group II received oral pregabalin 75mg and Group III received oral pregabalin 150mg 1hr prior to induction.Preoperative sedation levels were higher with pregabalin premedication.Significant increase in heart rate and mean arterial pressure was observed in Group I& II after airway instrumentation,while statistically significant attenuation of mean arterial pressure was observed in Group III.No significant decrease in heart rate was observed in any group.

Our results are similar to the study of Namrath et al[28] who did a prospective randomised placebo controlled study in which 90 adult ASA I and II patients undergoing elective surgery of both sexes were divided into three groups.Group A received placebo,Group B received oral gabapentin 800 mg and Group C received pregabalin 150 mg orally .Baseline heart rate ,mean

arterial pressure and before induction,after induction,at the time of laryngoscopy and at the end of 0,1,3,5 and 10 min were recorded.Sedation score of all the three groups were recorded.They concluded that pregabalin being more sedative than gabapentin, is better than gabapentin in supressing the pressor response.

VIII. Systolic blood pressure in mmhg:

In group I the baseline systolic blood pressure was 121.20mmhg(table 6).1min after intubation it was 160.2mmhg.There was a rise of 39.0mmhg that is 32.1% from baseline.The systolic blood pressure started settling down 5minafter intubation. By 5min it was 138.10mmhg and by 10min it was 125 .8 mmhg. The increase in systolic blood pressure at 1min after laryngoscopy and intubation compared to baseline value was statistically significant($p<0.05$)(Table 2,figure 2)

In group II, the baseline systolic blood pressure was 119.65 mmhg (table 6). 1min after intubation it was 158.78 mmhg.There was a rise of 39.13 mmhg that is 32.5% from baseline. This was followed by gradual decline in systolic blood pressure towards baseline. By 5 min it was 137.72mmhg and by 10 min it was 124.07.There was a statistically significant increase in systolic blood pressure

from baseline($p<0.05$) (Table 2,figure 2).

In group III, the baseline systolic blood pressure was 120 mmhg (table 6).During pre-induction period there was a fall in systolic blood pressure with mean of 110.6mmhg.This was not observed in the other two groups.There was rise rather than fall in other two groups during pre-induction period.1min after laryngoscopy and intubation,mean systolic blood pressure was 133.38mmhg representing a rise of 13.38mmhg that is11.1% rise from baseline.Subsequently the systolic blood pressure started settling down.By 5 min it was 117.65 and by 10 min it was 108.67mmhg which is less than the baseline value.The decrease in systolic blood pressure in group III was statistically significant which was not seen in group I and group II .(Table 2,figure 2)

There was a non –significant difference in systolic blood pressure at baseline among the three groups.Before induction a non significant difference was observed between group I and group II,which persists upto 10min after intubation while as group III bear a significant difference with group I and group II.

Systolic blood pressure increased maximally in group I(P0) and group II(P75) 1min after direct laryngoscopy and endotracheal intubation from baseline (32.1% from baseline). In groupIII (P150) maximum rise in blood pressure was 11.1% from baseline.Among these only pregabalin 150mg attenuated the rise in blood pressure following laryngoscopy(p-value=0.001).There was no statistically significant difference between placebo and pregabalin 75mg in attenuation of systolic blood pressure.

Our results are in agreement with the studies conducted by Kumkum Gupta et al[29] evaluated the clinical efficacy and safety of oral pregabalin for hemodynamic stability by conducting prospective blind randomised controlled cohort observation study.They studied 80 adult patients ofASA grade I and II of either gender aged 24 -54years who were randomised to receive oral pregabalin 150mg or placebo capsule,given 60-75min before surgery.Both groups were assessed for preoperative sedation and changes in heart rate and mean arterial blood pressure before and after the induction and 1,3,5,and 10min after laryngoscopy and intubation,then at 5min intervals till end of surgery along with postoperative complications.They concluded that oral pregabalin premedication effectively leads to sedation and analgesia with successful attenuation of the adverse and deleterious hemodynamic pressor response.

Our results are also similar to Rastogi et al (2012)[27]

IX. Summary and Conclusion

1.There was no significant difference in heart rate among groups before and after premedication.Immediately after laryngoscopy and intubation,the heart rate increased significantly in all groups, increase was least in group III.Maximum increase in heart rate from baseline was observed after 1 min of laryngoscopy.No statistically significant attenuation of heart rate was observed in the premedicated group,although it remained stabilised in group III as compared with group I and II.

2. Systolic blood pressure increased maximally in group I(P0) and group II(P75) 1min after direct laryngoscopy and endotracheal intubation from baseline (32.1% from baseline).It gradually decreased to near baseline values over 10 minutes.In groupIII (P150) maximum rise in blood pressure was 11.1% from baseline.Among these only pregabalin 150mg attenuated the rise in blood pressure following laryngoscopy(p-value=0.001).There was no statistically significant difference between placebo and pregabalin 75mg in attenuation of systolic blood pressure.

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