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Preliminary Report

Comparison of injection lignocaine (preservative free) 1.5mg/kg IV with oral pregabalin 150mg for attenuation of haemodynamic response to laryngoscopy and tracheal intubation

Anand T Talikoti[1], Dinesh K[2], Deepak V D[3], Ananya Nanda[3], Somasekharam P[4]

Endotracheal intubation is sine quo non for safe conduct of general anaesthesia. Pregabalin, an anticonvulsant drug is being studied for control of haemodynamic response to laryngoscopy and intubation. Some authors have found that pregabalin 150mg orally attenuates the haemodynamic response to laryngoscopy. The purpose of the present study was to compare injection lignocaine (preservative free) IV and oral pregabalin for attenuation of haemodynamic response to laryngoscopy and intubation. The study consisted of 60 patients of ASA class I, divided into two groups of 30 each. Group I received injection lignocaine (preservative free) 1.5mg/kg IV, 3 minutes prior to laryngoscopy. Group II received oral pregabalin 150 mg capsule 1hour prior to induction. The parameters recorded were heart rate, systolic BP, diastolic BP, mean BP and rate pressure product was calculated at baseline before induction and at 1, 3 and 5 minutes following laryngoscopy . The data obtained was analysed using unpaired "t" test. Lignocaine was more effective than pregabalin in controlling the heart rate at one minute following laryngoscopy. Pregabalin was more effective than lignocaine in controlling diastolic blood pressure at 1,3 and 5 minutes following laryngoscopy, and mean arterial pressure at 1and 3 minutes following laryngoscopy. There was no difference between two groups when systolic BP and rate pressure product were compared. Lignocaine (preservative free) thus, exerts better control over heart rate and pregabalin exerts better control over diastolic and mean blood pressure following laryngoscopy.

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Key words : Laryngoscopy, intubation, lignocaine, pregabalin.

Endotracheal intubation is a safe technique for conduct of general anaesthesia, in that it offers protection to the airway with endotracheal tube cuff and facilitates effective positive pressure ventilation. Since decades, reflex circulatory response to direct laryngoscopy and tracheal intubation performed during general anaesthesia have been studied and it has been found that deep anaesthesia obtunds the response to laryngoscopy and intubation[1,2]. The response to laryngoscopy and intubation can be either laryngovagal or laryngosympathetic. The laryngovagal response is generally seen in paediatric patients in the form of bradycardia, laryngeal spasm and bronchospasm. The most common laryngosympathetic response seen in adolescents and adults is tachycardia and hypertension which can be detrimental in some patients[1,2]. Many drugs have been given prior to induction of general anaesthesia to obtund the haemodynamic response to laryngoscopy and intubation like injection lignocaine (preservative free), lignocaine gargle and spray[3], β-blockers, opioids, nitroglycerine, clonidine and newer drugs like gabapentin. Gabapentin in doses of 600mg, 900mg and 1000mg has been studied by authors and has been shown to attenuate laryngoscopy and intubation response[4]. Pregabalin is an anticonvulsant drug introduced in 2005 for diabetic neuropathic pain and as an adjunct therapy for partial seizures. It's a FDA approved drug for diabetic neuropathic pain, partial seizures, fibromyalgia and generalised anxiety disorder[5]. Eren *et al*[6] have found that pregabalin in a dose of 150mg orally attenuates the haemodynamic response to laryngoscopy and intubation. There are not many studies regarding attenuation of haemodynamic response to laryngoscopy using pre-emptive oral pregabalin prior to laryngoscopy. Hence the present study is aimed at comparing injection lignocaine (preservative free) 1.5mg/kg IV and oral pregabalin 150 mg for attenuation of haemodynamic response to laryngoscopy and intubation.

Department of Anaesthesiology and Critical Care, Sri Devaraj Urs Medical College, Kolar 563101
[1]MD, Associate Professor
[2]MD, Professor
[3]MBBS, MD Resident
[4]MD, Professor and Head of the Department

IMA House, 53 Creek Row, Kolkata - 700 014 (India)
52, Raja Rammohan Roy Sarani,

Materials and Method

The objective of the present study is to determine and compare injection lignocaine (preservative free) 1.5mg/kg IV and oral pregabalin 150mg for attenuation of haemodynamic response to laryngoscopy and tracheal intubation in ASA class I patients. The study protocol was approved by the institutional ethical committee and written informed consent was obtained from all the patients.

This was a randomised double blind prospective study with 60 ASA class I patients aged 18- 60 years divided into 2 groups. Randomisation was done using random number table. All the patients were kept nil per oral 10 hours prior to surgery and were administered tablet ranitidine 150mg and tablet alprazolam 0.5mg on the night before surgery.

Patients of group I received colour matched empty capsule orally 1 hour before anaesthesia and injection lignocaine (preservative free) 1.5mg/kg IV 3 minutes prior to laryngoscopy. Injection lignocaine was injected over 10 seconds.

Patients of group II received 150 mg of oral pregabalin 1 hour prior to induction of anaesthesia and injection normal saline IV 3 minutes prior to laryngoscopy. Injection normal saline was also injected over 10 seconds.

The anaesthesiologist administering the study drug and the patients were unaware regarding the identity of the study drug.

Inclusion criteria : ASA class I patients aged 18-60 years coming for elective surgeries with no systemic illness.

Exclusion criteria : Patients with history of (1) any predicted difficult airway disease (2) hypertension and ischaemic heart disease (3) diabetes mellitus (4) any cerebrovascular diseases (5) renal and hepatic disease (6) bronchial asthma (7) drug or alcohol abuse (8) drug allergies (9) laryngoscopy time exceeding 15 seconds (10) on table >140/90 mm Hg, heart rate (HR)>100 beats/minute.

Anaesthesia technique was standardised for both the groups. Patients were randomly allocated to either group I received respective study drug. As laryngoscopy and tracheal intubation is a painful stimulus, the institutional ethical committee recommended usage of an analgesic prior to anaesthesia in both groups. Hence injection fentanyl 1µg/kg was administered IV along with injection glycopyrrolate 0.2mg IV 10 minutes prior to induction of anaesthesia. Before induction baseline heart rate, systolic and diastolic BP, mean arterial BP were recorded. Patients were induced with injection thiopentone 5mg/kg IV and injection succinylcholine 2mg/kg IV. Patients were ventilated with only 100% O_2 after administration of succinylcholine. After 60 seconds, laryngoscopy and tracheal intubation were performed by a staff anaesthesiologist. The parameters heart rate, systolic BP, diastolic BP and mean arterial BP were recorded at 1, 3 and 5 minutes after laryngoscopy. Blood pressure was recorded using non-invasive technique (NIBP). Both the baseline and the post laryngoscopy observations were recorded by a resident anaesthetist who was unaware, as to which group the patient belonged. After the parameters were recorded further analgesia was administered with injection tramadol 1.5mg/kg IV. Injection metoclopramide 0.15mg/kg IV was administered as an anti-emetic to all patients. Surgical incision was put after collection of data. Anaesthesia was maintained with oxygen and nitrous oxide in the concentration of 50 % each plus isoflurane 0.4 %. The fresh gas flow rate was O_2 and N_2O 1.5 litres/ml each in circle system initially which was later reduced to 750 ml each after 20 minutes. Muscle relaxation was obtained with injection vecuronium 0.1mg/kg IV bolus followed by 0.02mg/kg as maintenance dose. After the surgery, residual neuromuscular blockade was antagonised with injection neostigmine 0.05mg/kg and injection glycopyrrolate 0.01mg/kg. After satisfactory recovery, patients were extubated and shifted to post anaesthesia care unit (PACU).

The parameters heart rate, systolic BP, diastolic BP and mean arterial BP at baseline and at 1, 3 and 5 minutes following laryngoscopy were recorded and rate pressure product was calculated by multiplying systolic BP and heart rate. The mean±SD for the parameters were calculated and analysed using Student's "t" test. The unpaired "t" value was used to compare the difference in the mean values of parameters to arrive at significant "p" value. The software package SPSS version 16 was used for statistical analysis. P value <0.05 was considered significant. P value <0.01 was considered highly significant and p value ≤0.001 was considered strongly significant.

Observations

A total of 78 patients were assessed for eligibility from January 2010 to December 2010 out of which 60 patients received the study medication after randomisation. Six patients refused to participate in the study. Four patients had history of allergy to different drugs and were not included. Four patients had baseline blood pressure exceeding 140/90 mm Hg on table and were excluded. Four patients had baseline heart rate more than 100 beats/minute on table and were excluded. Laryngoscopy was limited to less than 15 seconds. In none of the patients laryngoscopy exceeded 15 seconds.

Comparison of gender distribution, age and weight has been presented in Table 1.

When mean heart rate was compared between the two groups, it was found that lignocaine had better control over heart rate than pregabalin (p=0.001) at 1 minute following laryngoscopy (Table 2).

When mean systolic BP was compared between the two groups there was no difference as evident from p value >0.05 at 1, 3 and 5 minutes following laryngoscopy (Table 3).

When mean diastolic BP was compared between the two groups, it was found that pregabalin was more efficient in controlling diastolic BP at 1 minute (p

minutes (p value = 0.01) and at 5 minutes (p value= 0.02) than lignocaine (Table 4).

When mean arterial pressure was compared between the two groups it was found that pregabalin was more efficient than lignocaine in controlling mean BP at 1 minute (p value=0.001) and at 3 minutes (p value =0.001) (Table 5).

When rate pressure product was compared between the two groups there was no difference at 1, 3 and 5 minutes (p value>0.05) (Table 6).

The average duration of surgery in group I was 110.86667 ± 60.01040 minutes while that in group II was 112.46667 ± 63.3570 minutes which was comparable among the two groups. The patients were assessed postoperatively for any adverse effects of drugs. It was noticed that 6 out of 30 patients (20%) who had received pregabalin complained of dizziness. None of the patients in the lignocaine group had any adverse effects. None of the patients in either group had respiratory depression (as evident by SPO_2> 90% on room air) or any other adverse effects.

Table 1 — *Showing Demographic Characteristics of Both the Groups*

Characteristics	Group I (n=30)	Group II (n=30)
Sex :		
Male	18(60%)	22(73.33%)
Female	12(40%)	8 (26.66%)
Age in years (mean)	37.0667	35.8333
Weight in kg (mean)	52.9666	55.6333

Table 2 — *Showing Comparison of Heart Rate between Two Groups*

Heart rate in beats/minute (mean)	Group I	Group II	Significance t	Significance p
Baseline	79.53	77.630	0.9530	0.345
From onset of laryngoscopy :				
1 minute	91.0667	97.5667	-3.375	0.001
3 minutes	88.9667	90.6333	-0.780	0.439
5 minutes	83.0333	81.9667	0.547	0.586

Table 3 — *Showing Comparison of Systolic Blood Pressure between Two Groups*

Systolic blood pressure in mm Hg (mean)	Group I	Group II	Significance t	Significance p
Baseline	126.20	123.33	1.011	0.316
From onset of laryngoscopy :				
1 minute	140.6	139.1333	0.512	0.611
3 minutes	136.3	132.5667	1.259	0.213
5 minutes	127.016	125.6667	1.030	0.307

Table 4 — *Showing Comparison of Diastolic Blood Pressure between Two Groups*

Diastolic blood pressure in mm Hg (mean)	Group I	Group II	Significance t	Significance p
Baseline	77.1333	74.8667	1.563	0.123
From onset of laryngoscopy :				
1 minute	89.3000	80.5000	5.24	0.001
3 minutes	82.7667	78.0000	3.565	0.01
5 minutes	79.3333	76.0660	2.360	0.02

Table 5 — *Showing Comparison of Mean Arterial Blood Pressure between Two Groups*

Mean arterial blood pressure in mm Hg (mean)	Group I	Group II	Significance t	Significance p
Baseline	92.7333	91.0000	1.005	0.319
From onset of laryngoscopy :				
1 minute	106.8567	99.4667	3.0369	0.001
3 minutes	101.0333	95.0330	3.417	0.001
5 minutes	95.2867	91.9333	2.918	0.06

Table 6 — *Showing Comparison of Rate Pressure Product between Two Groups*

Rate pressure product in mm Hg (mean)	Group I	Group II	Significance t	Significance p
Baseline	9961.133	9623.8667	0.868	0.389
From onset of laryngoscopy :				
1 minute	12823.36	13615.8	-1.766	0.083
3 minutes	12279.6	12050.73	0.476	0.636
5 minutes	10616.2	10337.5	0.717	0.0476

Discussion

The present study which aimed at comparing injection lignocaine (preservative free) 1.5 mg/kg IV and oral pregabalin 150mg for attenuation of laryngoscopy and intubation response was conducted after institutional ethical committee clearance on 60 ASA class I patients who were divided into two groups of 30 each. A total of 78 patients were enrolled for the study out of which 60 actually went through the study process.

Laryngoscopy, endotracheal intubation and other airway manipulations (placement of combitube or LMA) are noxious stimuli that induce profound changes in the cardiovascular physiology, primarily through reflex responses. Although these responses maybe of short duration and of little consequence to healthy individuals, serious complications may occur in patients with underlying coronary artery disease[2,7,8], reactive airways[2,9,10] or intracranial neuropathology[2,11,12].

The cardiovascular response to noxious airway manipulation is initiated by proprioceptors responding to tissue irritation in supraglottic region and trachea[2,13]. These proprioceptors are located in close proximity to the airway mucosa and are superficially located and that is the reason why lignocaine gargle and spray is effective in controlling the laryngoscopy and tracheal intubation response. The glossopharyngeal and vagal afferent nerves transmit these impulses to the brainstem, which in turn cause widespread autonomic activation through both sympathetic and parasympathetic nervous system. Bradycardia and bronchospasm are often noticed in infants and children due to underdeveloped sympathetic system. In adults the more common response to airway manipulation is hypertension and tachycardia mediated by cardioacceleratory nerves and sympathetic chain ganglion[2].

Many measures have been found out over a period of decades to blunt the cardiovascular response to laryngoscopy and intubation. These include intravenous lignocaine[14], opioids[15] in high doses, inhalational agents[16], diltiazem, verapamil, nicardipine[17,18,19], hydralazine[20], nitroprusside[21], nitroglycerine[22], labetolol[23], esmolol[17] and

clonidine[24]. However some of these drugs have some limitations in that they need to be used either in higher doses while others have some adverse effects when used in clinical doses.

Tam *et al*[25] have shown that the optimal time of injection of intravenous lignocaine prior to laryngoscopy is 3 minutes, to attenuate circulatory response to laryngoscopy and tracheal intubation. Therefore in this study 3 minutes was chosen as the optimal time for injection of lignocaine prior to laryngoscopy. Intravenous preservative free lignocaine has membrane stabilising action and is popularly used as an anti-arrhythmic agent[14,26]. This might be the reason that lignocaine has exerted a better effect on heart rate than pregabalin in this study.

Recently gabapentin, an anti-epileptic agent which has GABAmimetic action and is used to treat partial seizures is being extensively studied for attenuation of haemodynamic response to laryngoscopy and tracheal intubation. It has a unique effect on voltage dependant calcium channels at postsynaptic dorsal horn and may therefore interrupt series of events that possibly lead to the experience of neuropathic pain. It is especially useful in the treatment of diabetic neuropathy and post herpetic neuralgia. Bafna *et al*[4] have shown that gabapentin in doses of 1000mg is effective in attenuating haemodynamic response to laryngoscopy and intubation in normotensive patients.

Pregabalin, a successor of gabapentin was introduced and approved by the FDA in 2005 for clinical use. It is a FDA approved drug for partial seizures of temporal lobe epilepsy, diabetic neuropathic pain, fibromyalgia, generalised anxiety disorder (approved in European union)[5].

Its' mechanism of action is similar to gabapentin in that it binds to $\alpha 2$-δ site of voltage gated calcium channels in brain and exerts its antinociceptive and antiseizure properties. Pregabalin also decreases the release of neurotransmitters such as glutamate, noradrenaline and substance P which is supposed to be responsible for its antinociceptive action[5]. This property of pregabalin might account for its attenuation of haemodynamic responses to laryngoscopy. The most common adverse effect of pregabalin present in more than 10% of individuals is dizziness and drowsiness. The less common adverse effects are visual disturbances, ataxia, and dysarthria. Depression, agitation and hallucinations are seen in very high doses[5]. In this study, it was noticed that 20% of individuals in the pregabalin group complained of dizziness. None of the patients had respiratory depression or other adverse effects.

Eren *et al*[6] have compared pre-emptive oral pregabalin 150mg with placebo for attenuation of haemodynamic response to laryngoscopy and tracheal intubation. They have found that oral pregabalin 150 mg attenuates reflex tachycardia and hypertension related to laryngoscopy and intubation of the trachea.

In this study the ability of injection lignocaine (preservative free) with oral pregabalin for attenuation of haemodynamic response to laryngoscopy and intubation has been compared. It was found that lignocaine had better control over heart rate following laryngoscopy than pregabalin, while pregabalin had better control over diastolic blood pressure and mean arterial BP than lignocaine.

Limitations of present study : Non-inclusion of placebo group as the institutional ethical committee did not approve of placebo, since they felt even in normal individuals laryngoscopy might lead to dangerous consequences. Hence in this study injection lignocaine (preservative free) was used as a comparative group against pregabalin.

In this study, injection fentanyl 1.5µg/kg was used as premedication, as it was also an institutional ethical committee recommendation since neither lignocaine nor pregabalin are analgesics per se and laryngoscopy is a painful stimulus. Hence fentanyl, an opioid for analgesia was used prior to laryngoscopy. Fentanyl can suppress intubation response when used in high doses[27]. Fentanyl was used in both the groups and it was standardised. Moreover, whenever suppression of laryngeal intubation response is required in cardiovascular or cerebrovascular diseases, more than one agent is generally used to suppress intubation response and premedication with opioids is a very popular choice, as in such cases opioids offer some advantages like attenuating upper airway reflexes and helping in endotracheal tube tolerance.

The combination of lignocaine and pregabalin, would have given better control of haemodynamic response to laryngoscopy and intubation.

Further studies are needed with different doses of oral pregabalin along with a placebo group for comparison to arrive at the optimal dose of the drug for attenuation of laryngoscopy and intubation response.

Both injection lignocaine (preservative free) and oral pregabalin are effective in attenuating haemodynamic response to laryngoscopy and intubation. While lignocaine exerts better control over heart rate, pregabalin is more effective in controlling diastolic BP and mean BP.

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