Pregabalin Blunts Cardiovascular Response to Laryngoscopy and Tracheal Intubation

Pregabalin Laringoskopi ve Trakeal Entubasyona Kardiyovasküler Cevabı Baskılar

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ABSTRACT Objective: Pregabalin, like gabapentin, is an amino acid derivative of gamma-amino butyric acid and is being used exclusively in the treatment of neuropathic pain besides as an anticonvulsant. Many studies have recently been done to diminish the reflex responses to laryngoscopic intubation with the use of a variety of agents including anaesthetics, antihypertensives, beta blockers and gabapentin. In this study we aimed to show if pregabalin attenuates the cardiovascular response to tracheal intubation of the patients udergoing lumbar discal hernia repair under general anaesthesia. **Material and Methods:** 50 patients were allocated to receive 150 mg pregabalin p.o or placebo capsules one hour before the surgery. Patients did not receive any premedication. After the induction of anaesthesia with 2 mg kg^{-1} propofol and 0.1 mg kg^{-1} vecuronium, laryngoscopy and tracheal intubation was performed and mean arterial pressure (MAP) and heart rates (HR) were evaluated in response to laryngoscopy. **Results:** The mean blood pressure and heart rates before induction and after induction did not differ significantly between groups. MAP and HR were significantly low in pregabalin group during and after intubation. Four patients in control group and none in pregabalin group had hypertension during intubation which was treated with additional bolus doses of propofol administration. **Conclusion:** This study shows that preoperatively given pregabalin 150 mg depresses reflex tachycardia and hypertension related to laryngoscopy and prevents the pressor responses to laryngoscopy and intubation of trachea.

Key Words: Pregabalin; anesthesia, general; laryngoscopy; intubation, intratracheal

ÖZET Amaç: Pregabalin, gabapentin gibi, gamma-amino butirik asitin bir amino asit türevidir ve antikonvulsan olarak kullanımının yanında nöropatik ağrı tedavisinde de yoğun olarak kullanılmaktadır. Trakeal entübasyon refleks olarak sempatik aktivitede artışa sebep olabilir. Laringoskopik entubasyona refleks cevabı azaltmak adına şimdiye kadar anestezik ajanlar, antihipertansifler, beta blokerler ve gabapentin gibi çok çeşitli ajanlarla birçok çalışma yapılmıştır. Bu çalışmada genel anestezi altında disk hernisi onarımı yapılan hastalarda pregabalinin trakeal entubasyona kardiyovaskuler yanıtı baskılayıp baskılamadığını araştırmayı amaçladık. **Gereç ve Yöntemler**: Çalışmaya 50 hasta dahil edildi ve hastalara operasyondan bir saat önce oral 150 mg pregabalin ya da plasebo kapsülleri verildi. Premedikasyon uygulanmayan hastalara 2 mg kg^{-1} propofol ve 0.1 mg kg^{-1} vecuronium ile anestezi indüksiyonu sonrasında laringoskopi ve trakeal entübasyona ortalama arteryel basınç (OAB) ve kalp hızı (KH) cevapları değerlendirildi. **Bulgular:** İndüksiyon öncesi ve sonrası ortalama arteryel basınç ve kalp hızı değerleri açısından gruplar arasında istatistiksel olarak anlamlı farklılık gözlenmedi. Entübasyon esnasında ve sonrasındaki OAB ve KH değerleri ise pregabalin grubunda istatistiksel olarak düşük bulundu. Plasebo grubunda dört hastada entübasyon esnasında, ek propofol boluslarıyla tedavi edilmesi gereken hipertansiyon gelişirken, pregabalin grubunda ise hiçbir hastada entübasyonda hipertansiyon gözlenmedi. **Sonuç:** Bu çalışmaya göre, preoperatif olarak verilen 150 mg pregabalin laringoskopi ve entübasyona ilişkin taşikardi ve hipertansiyonu baskılamakta ve sempatik yanıtı önlemektedir.

Anahtar Kelimeler: Pregabalin; genel anestezi; laringoskopi; intratrokeal entübasyon

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In 1940, Reid and Brace first described haemodynamic response to laryngoscopy and intubation.[1] Tracheal intubation causes a reflex increase in sympathetic activity that may result in hypertension, tachycardia and arrhythmia.[2] Although in the majority of patients undergoing anaesthesia, these responses are transient and probably of little consequence, they may be harmful to some patients, mainly those with myocardial or cerebro vascular diseases.[3]

One of the main goals of the anaesthesiologist is to prevent or minimize all of these adverse effects.

Many studies have recently been done to diminish these reflex responses to laryngoscopic intubation with the use of a variety of agents including anaesthetics, antihypertensives and beta blockers.[4-12]

Few studies have shown that gabapentin is effective in blunting pressor response to laryngoscopy and endotracheal intubation.[13,14] Pregabalin, like gabapentin, is an amino acid derivative of gamma-amino butyric acid (GABA analogue). Pregabalin is the pharmacologically active S-enantiomer of 3-aminomethyl-5-methyl-hexanoic acid. It is an α_2-delta ligand that has analgesic, anticonvulsant and anxiolytic activity.[15,16] Alpha2-delta is an auxiliary protein associated with voltage-gated calcium channels and pregabalin binds potently to the α_2-delta subunit resulting in modulation of calcium channels and reduction in the release of several neurotransmitters.[17,18]

Recently pregabalin has been shown in studies to provide equivalent analgesic efficacy to gabapentin, however, at much lower doses.[19] But, to our knowledge, it's not been shown yet if it attenuates hemodynamic responses following tracheal intubation, as gabapentin does. And we designed this study to investigate the effect of pregabalin on the changes in blood pressure and heart rate observed during laryngoscopy and tracheal intubation.

PATIENTS AND METHODS

After obtaining hospital ethics committee approval and patient consent, 50 ASA I adult patients undergoing elective lumbar disc surgery under general anaesthesia were selected. Patients having hypertension, bronchospastic disease, cardiac problems, anticipated difficult airway, hepatic or renal failure, allergies to any of the study drugs and those who were receiving medications known to affect blood pressure and heart rate and administration of sedative or narcotic drugs in the previous 24 hours were excluded. At the preoperative visit the difficulty of the airway was graded by the Mallampati test.

Patients did not receive any premedication. Placebo capsules were prepared after emptying of the pregabalin capsules and filled with thin sugar. All patients were randomly allocated using computerized randomization to receive pregabalin capsules 150 mg (Group I, *n*= 25) (Lyrica, Pfizer, Goedecke GmbH, Germany) or placebo capsules (Group II, *n*= 25) 1 h prior to the induction of anaesthesia.

Upon arrival in the operating room, a 18G catheter was inserted in a peripheral vein and an Isolyte solution 6-8 ml kg^{-1} was started. Standard monitoring including electrocardiography (ECG), noninvasive mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2) was used. After 3 min of preoxygenation anaesthesia was induced with propofol 2 mg kg^{-1} iv and vecuronium 0.1 mg kg^{-1} was administered to produce neuromuscular block, fentanyl in induction was omitted in order to prevent the misinterpretation of the parameters in response to laryngoscopy. Tracheal intubation was performed 3 min after loss of verbal contact. All intubations were performed by the same anaesthesiologist blinded to the study. The duration of laryngoscopy and intubation was limited to the minimum possible time to all patients and did not exceed sixty seconds.

Mean arterial blood pressure (MAP) and heart rates (HR) were recorded before and after induction, during laryngoscopy, 1, 3, 5 and 10 min after intubation. Ephedrine 5 mg was administered for hypotension with a decrease of >30% from baseline values for >60 s; and atropine, for bradycardia (heart rate <45 beats min-1). For hypertension (an increase of >30% above baseline for >60 s) or tach-

ycardia (heart rate >130 beats min-1 for >60 s), 20 mg incremental bolus doses of propofol was used.

STATISTICS

Power calculations based on previous data suggested that 25 patients per group would detect a 20% difference in MAP or heart rate between the groups after intubation (α= 0.05, power of 80%). All analyses were performed using SPSS for Windows computer software (release 10.0) (SPSS Inc., Chicago, IL, USA).

Descriptive statistics are expressed as means ± standard deviation unless otherwise stated. Student's t-test was used for comparison of the means of continuous variables and normally distributed data. The Mann-Whitney U-test was used otherwise. Individual inter-group comparisons, where appropriate, were done using Paired sample t test and Wilcoxon test.

The qualitative data were evaluated using Chi-square test. Results were given in 95% confidence interval and significance was accepted at p< 0.05 level.

RESULTS

There were no significant differences between the group 1 and group 2 with respect to age, height, body weight or gender (Table 1).

Changes in mean arterial pressure (MAP) (mmHg) in group 1 and 2 was shown in Figure 1.

The mean blood pressure before induction and after induction did not differ significantly between group 1 and group 2. MAP values were significantly low (p< 0.01) in the pregabalin group compared to the control group during intubation; again

TABLE 1: Patient characteristics in each group: Values are mean ± standard deviation. There was no statistical significance between groups.

	Group 1 (n:25)	Group 2 (n: 25)
Age (yr)	40 ± 11	41 ± 12
Height (cm)	167 ± 7	166 ± 7
Body weight (kg)	70 ± 9	69 ± 10
Female (n)	16	18
Male (n)	9	7

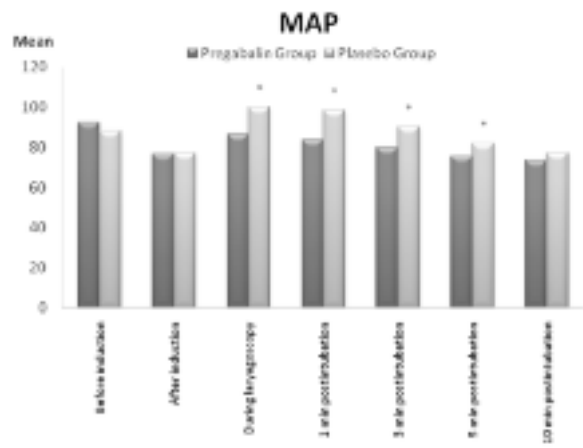

FIGURE 1: Changes in mean arterial pressure (MAP)(mmHg) in groups.
* p< 0.05.

in the pregabalin group MAP values at the 1st, 3rd and 5th minute measurements after intubation have been detected to be significantly low (p< 0.01); but 10th minute measurements after intubation did not show significant difference between groups (p> 0.05).

Heart rate recordings are shown in Figure 2. Before and after induction, values did not show a significant difference between groups (p> 0.05). During intubation the HR measurements of pregabalin group have been detected to be significantly lower compared to the placebo group (p< 0.01); 1st, 3rd, 5th and 10th minutes measurements after intubation have also been detected to be significantly low in the pregabalin group (p< 0.01).

Four patients in control group and none in pregabalin group had hypertension during intubation which was treated with additional bolus doses of propofol administration. We did not see any side effects, such as dizziness, somnolence, nausea, hypersensitivity, peripheral edema or blurred vision.

DISCUSSION

Laryngoscopy and intubation are mandatory for most patients undergoing operation under general anaesthesia, which is invariably associated with certain cardiovascular changes such as tachycardi-

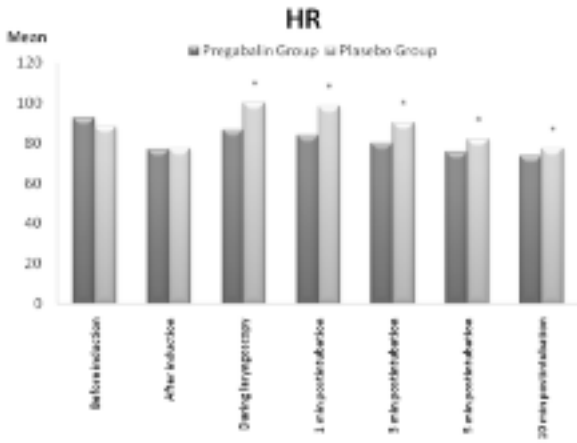

FIGURE 2: Changes in heart rate (beats/minute) at various instances in groups.
* p<0.05.

a or bradycardia, rise in blood pressure and a wide variety of cardiac arrythmias.[20] Many pharmacologic interventions have been suggested to attenuate these reflex responses to laryngoscopic intubation. These include the use of a variety of inhaled and intravenous anaesthetics, neuromuscular blockers, opioids, lidocaine, beta adrenergic antagonists, antihypertensives, nitroglycerin and magnesium.[4-12] Unfortunately, none of these pharmacological manipulations can consistently and effectively attenuate these adverse responses, nor are they free from complications. Short-acting opioids appear to have a reliable and constant effect but they may contribute to postoperative respiratory depression. Lidocaine is the drug used most often, but its efficacy has been questioned in recent studies.[8,12] Beta-blockers with bradycardic, antihypertensive, antiarrhythmic and antiischaemic properties have been advocated. As opposed to lidocaine, these agents are more effective in preventing the changes in heart rate than the pressor response.[8,9] Because of their depressor effects on the myocardium, their place still remains to be defined, especially in the cardiac risk patients. Nitroglycerin is specifically indicated in coronary artery disease; however it causes tachycardia. Clonidine and calcium channel blockers seem to be less effective in preventing haemodynamic alterations.[10,21] The risk of hypotension from calcium channel blockers such as nicardipine and verapamil when used with inhalation agents for maintenance of anaesthesia should be constantly borne in mind. Similar to gabapentin, which is effective in the treatment of neuropathic pain, pregabalin specifically targets an important pronociceptive site of the central sensitisation cascade.[22-24] Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally-related to pregabalin indicate that selective binding to the α_2-delta protein is required for analgesic, antiepileptic and anxiolytic action in animal models. Also the mechanisms of action of pregabalin have also been linked to the L-amino asid transporter, alpha-amino-3-hidroxy-5-methyl-4-izoxazolepropionic acid (AMPA) receptors, N-methyl-D-aspartate (NMDA) receptors and ATP-sensitive potassium channels. Only few data in the literature are available regarding the effect of pregabalin on the cardiovascular system. No significant effects on cardiovascular parameters were observed in vitro with oral doses up to 300 $mg.kg^{-1}$ or IV doses of 15-150$mg.kg^{-1}$ in rats.[25] Although ECG was only evaluated visually for rate and rhythm abnormalities in safety pharmacology studies, a comprehensive evaluation, including measurement of QT interval, was conducted in monkeys given pregabalin for up to 69 weeks.[25] Daily oral administration of pregabalin for 65 to 69 weeks at doses up to 500 $mg.kg^{-1}$ produced no cardiac changes attributable to drug treatment.

Reuben et al reported in their study, which compared the analgesic efficacy of celecoxib, pregabalin and their combination in 80 patients undergoing elective decompressive lumbar laminectomy with posterior spinal fusion, that 150 mg of pregabalin administered 1 h before surgery had no effect on arterial blood pressure or heart rate.[26]

To the best of our knowledge no randomized controlled study evaluated the effect of pregabalin on tracheal intubation. In our study, given 1 h before operation pregabalin 150 mg resulted in significant decreases in MAP values in the first five minutes, and in HR values in the first ten minutes. Measurements in MAP values just before and after induction did not differ significantly between pregabalin and control group (p> 005). MAP va-

lues have been detected to be significantly low ($p< 0.01$) in the pregabalin group compared to the control group during intubation; again in the pregabalin group the 1st, 3rd and 5th minute measurements after intubation were significantly low ($p< 0.01$). In our study none of the patients in the pregabalin group exhibited severe hypotension. The 10th minute measurements after intubation did not show significant difference between groups. Four patients in control group had hypertension during intubation which was treated with additional bolus dose of propofol administration. HR values before and after induction did not show significant differences between groups ($p> 005$), but during intubation and at the following measurements until 10 minutes the pregabalin group has been detected to be significantly low compared to the placebo group ($p< 0.01$). There were no incidences of bradycardia, tachycardia, arrhythmias, ST segment, or other ECG changes observed during the study.

The mechanism by which pregabalin attenuates the pressor response to laryngoscopy and intubation is unknown. As pregabalin and gabapentin share the same mechanism of action through inhibition of voltage-gated calcium channels, it might most probably be the same way as was shown in the studies of Memis et al and Fassoulaki et al.[13,14] Both of these two studies explanied the effectivity of gabapentin in blunting the pressor responses to laryngoscopy by inhibition of calcium efflux from muscle cells.

The most frequent side effects of pregabalin are dizziness and somnolence which are of minor or moderate degree of severity. In our study groups no patients complained of these or any side effects.

Despite the evidence in the literature and the monographic information of the agent regarding the null effect on cardiovascular parameters, this study shows that preoperatively given pregabalin 150 mg depresses reflex tachycardia and hypertension related to laringoscopy and prevents the pressor responses to laryngoscopy and intubation of trachea. However more detailed studies planned to reveal its effects on stress mediators and consequent cardiovascular responses are needed for an accurate and clear-cut conclusion on that issue.

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