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Attenuation of Hemodynamic Response to Tracheal Intubation with Pregabalin and Dexmedetomidine - A Prospective Randomized Double Blinded Study

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Trakeal Entübasyona Hemodinamik Yanıtın Pregabalin ve Deksmedetomidin ile Azaltılması- Prospektif Randomize Çift Kör Çalışma

ABSTRACT

Objective: *Airway manipulation during endotracheal intubation is a potential stimulus and it is associated with untoward hemodynamic changes. The aim of this study was to compare the efficacy of intravenous dexmedetomidine and oral pregabalin premedication for attenuation of hemodynamic pressor response to laryngoscopy and intubation.*
Methods: *A total of 60 patients of age group of 18-60 years scheduled for elective surgeries under general anesthesia with ASA physical status I were randomized into two groups. Group D received intravenous dexmedetomidine at a dose of 1 µg kg^{-1} over 10 minutes before induction and group P received oral pregabalin 150 mg one hour prior to intubation. The primary outcomes, heart rate and mean arterial pressure noted at serial intervals during intubation were compared between the groups. Sedation score was assessed as secondary outcome using Richmond Agitation Sedation Scale Scores (RAAS).*
Results: *Group D and P were comparable with distribution of age, sex and duration of laryngoscopy. The mean heart rates and mean arterial pressures assessed at serial measurements at 0, 1, 3, 5, 10 minutes post- intubation were statistically significant (p=0.005) in dexmedetomidine group when compared to pregabalin group. The RASS scores assessed at 15, 30 and 60 minutes post-extubation were statistically significant (p<0.05) in pregabalin group when compared to dexmedetomidine group.*
Conclusion: *Intravenous dexmedetomidine at a dose of 1 µg kg^{-1} is more effective than oral pregabalin 150 mg in attenuating hemodynamic response to laryngoscopy and orotracheal intubation. Post-procedural sedation was better achieved with oral pregabalin compared to intravenous dexmedetomidine.*

Keywords: *Dexmedetomidine, pregabalin, laryngoscopy, hemodynamic pressor response, sedation*

ÖZ

Amaç: *Endotrakeal entübasyon sırasında hava yolu manevrası potansiyel bir uyarıdır ve istenmeyen hemodinamik değişikliklerle ilişkilidir. Amaç, intravenöz deksmedetomidin ve oral pregabalin premedikasyonunun laringoskopi ve entübasyona hemodinamik cevabın azaltılmasındaki etkinliğini karşılaştırmaktı.*
Yöntem: *18-60 yaş arasında, ASA fiziksel durumu 1 olan, genel anestezi altında elektif cerrahi planlanan toplam 60 hasta randomize olarak iki gruba ayrıldı. D grubuna indüksiyondan önce 1 µg kg^{-1} intravenöz deksmedetomidin 10 dk.'da verildi ve P grubuna entübasyondan bir saat önce 150 mg oral pregabalin verildi. Primer sonuçlar, entübasyon sırasında seri aralıklarla kaydedilen kalp atım hızı ve ortalama arter basıncı gruplar arasında karşılaştırıldı. Sedasyon skoru, Richmond Ajitasyon Sedasyon Skoru (RAAS) kullanılarak sekonder sonuç olarak değerlendirildi.*
Bulgular: *Grup D ve P, yaş, cinsiyet dağılımı ve laringoskopi süresi olarak benzerdi. Entübasyon sonrası 0, 1, 3, 5, 10 dk. gibi seri aralıklarla değerlendirilen ortalama kalp hızı ve ortalama arter basıncı, deksmedetomidin grubunda pregabalin grubuna göre istatistiksel olarak anlamlıydı (p=0.005). Ekstübasyondan 15, 30 ve 60 dk. sonra değerlendirilen RASS skorları, deksmedetomidin grubu ile karşılaştırıldığında pregabalin grubunda istatistiksel olarak anlamlıydı (p<0.05).*
Sonuç: *Laringoskopi ve orotrakeal entübasyona hemodinamik yanıtı azaltmada, 1 µg kg^{-1} intravenöz deksmedetomidin, 150 mg oral pregabalin'den daha etkilidir.İntravenöz deksmedetomidine kıyasla oral pregabalin ile daha iyi İşlem sonrası sedasyon sağlandı.*

Anahtar kelimeler: *Deksmedetomidin, pregabalin, laringoskopi, hemodinamik yanıt, sedasyon*

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INTRODUCTION

Endotracheal intubation is a potent stimuli and it is associated with hemodynamic perturbation such as tachycardia and hypertension which are variable, transient and unpredictable [1]. These responses are detrimental in patients with limited cardiac reserve and potentially associated with risk of myocardial ischemia and stroke in high risk population [2]. Various pharmacological methods have been employed to attenuate the pressor response to direct laryngoscopy and endotracheal intubation. The most commonly used drugs are lidocaine, calcium channel blockers, beta blockers, opioids, and alpha-2 agonists [3,4].

Dexmedetomidine is an imidazole derivative which is a highly selective alpha-2 adrenergic receptor agonist, and is being widely used to attenuate hemodynamic response to direct laryngoscopy [2,3]. Gabapentin and pregabalin a structural analogue of gamma - aminobutyric acid originally introduced as an antiepileptic also has analgesic, anticonvulsant, and anxiolytic effects that helps in attenuation of heart rate and blood pressure following intubation [4,5]. Previous studies proved the effectiveness of dexmedetomidine in attenuating the pressor response to endotracheal intubation but there are limited studies with pregabalin. Hence we compared both the drugs to find out which drug is better in attenuating laryngoscopic response.

MATERIAL and METHODS

After obtaining approval from the hospital ethics committee and written informed consent from the patients, this prospective, double-blind randomized comparative study was performed in 60 ASA (American Society of Anesthesiology) physical status grade I patients, aged between 18-60 years scheduled for elective surgeries performed under general anesthesia requiring endotracheal intubation. Sample size was calculated to be 26 patients per group with a statistical power of 90% and an alpha error of 1% by using Master Software Version 2.0, based on the previous study [5] with the mean heart rate difference of 11, standard deviation of 10 and 10.45. Considering the possibility of dropouts, the size of sample was arbitrarily increased to 60 patients in this study. Patients who refused to participate, required emergency surgery, and more than one attempt for intubation, those with ASA physical status 2 or more, anticipated difficult airway, participants whose intubation procedure lasted more than 15 seconds, patients on gabapentin, pregabalin and allergic to study drugs were excluded from the study.

The study protocol was explained in detail to participants who met the inclusion criteria. Those who agreed to participate and accepted the informed consent forms were enrolled in the study. They were randomly allocated to two study groups using computer -generated random numbers which were contained in the sealed envelopes. Group D received IV bolus doses of 1 μg kg^{-1} dexmedetomidine over 10 minutes and Group P received pregabalin 150 mg orally. The placebo used for pregabalin group was vitamin C capsules and placebo for dexmedetomidine was normal saline. Both patients and the observers were blinded to the study drugs.

Preanesthetic assessment was done the day before surgery by an anesthesiologist not involved in the study. The study drugs received by the patients were prepared by an anesthesiologist who was not involved in the study. Patients of Group D received placebo one hour prior to the surgery in the ward and Group P patients received pregabalin 150 mg in the ward. During preoperative period baseline heart rates (HRs), blood pressures (BPs), oxygen saturations (SpO_2) were noted and preoperative sedation was also recorded using Richmond Agitation Sedation Score (RASS). Just 10 minutes prior to induction, Group D received IV bolus doses of 1 μg kg^{-1} dexmedetomidine over 10 minutes and Group P patients received normal saline (NS) over 10 minutes.

A standard anesthesia protocol was followed similarly in both groups. On arrival to the operating theatre, the patients were connected to standard monitoring devices with ECG, pulse oximetry, noninvasive blood pressure (NIBP) and preinduction values were noted. After preoxygenation and administration of fentanyl 2 μg kg^{-1}, induction of anesthesia was achieved using propofol 2 μg kg^{-1} and vecuronium 0.1 μg kg^{-1}. Adequacy of neuromuscular blockade was assessed using TOF Watch SX (Organon, Ireland).

Endotracheal intubation performed at Train of Four (TOF) count reading zero with appropriate size Macintosh blade and endotracheal tube (ETT) size 7 Fr for females and 8 Fr for males. Anesthesia was maintained using sevoflurane adjusted to MAC 1 in oxygen 40% and air mixture. At the end of the procedure, 4mg ondansetron was given to all patients and after adequate reversal of neuromuscular blockade (TOF ratio 0.9), trachea was extubated. A decrease in mean arterial pressure of 30% from baseline was treated with appropriate doses of ephedrine and bradycardia less than 40 bpm was treated with atropine and these patients were excluded from study.

The study parameters heart rate and mean arterial pressure at the time of intubation, and at 1, 3, 5 and 10 minutes post-intubation were noted. Time for intubation, i.e. the total duration of laryngoscopy was estimated from starting to use the scope to removal of the scope was measured using stopwatch. The limit for total duration was standardised in both groups to 15 seconds. The duration of intubation beyond 15 seconds were not included in the analysis. RASS scores were assessed at the time of extubation, 15, 30 minutes and 1 hour post-extubation in the PACU.

Statistical Analysis

The collected data were analyzed with IBM.SPSS Statistics Software Version 23. We used frequency analysis for descriptive statistics of descriptive variables, mean and standard deviation for continuous variables. The heart rate and blood pressure between the two groups were compared using unpaired t test and in paired groups the paired sample t-test was used. To estimate the significance in categorical data, Pearson Chi-square test was used similarly if the expected cell frequency is less than 5 in 2×2 tables then the Fisher's Exact test was used. In all the above statistical methods, the probability value $p<0.05$ was considered as the level of significance.

RESULTS

A total of 60 patients were enrolled in the study (Figure 1), and 30 patients were allocated and analy-

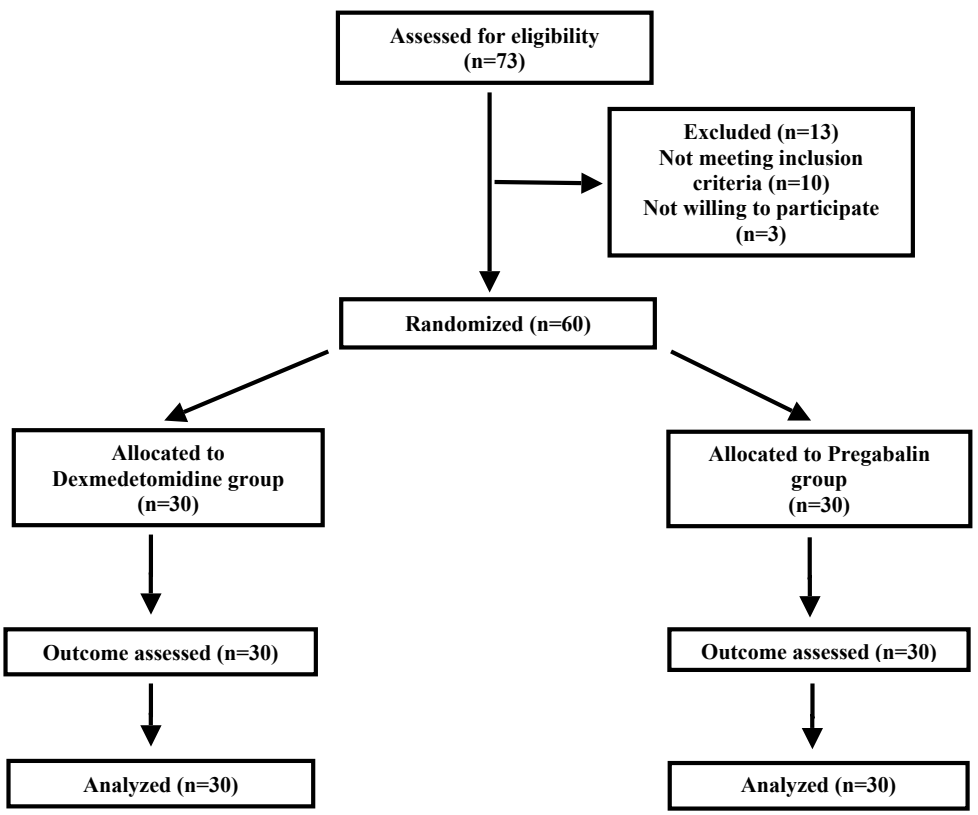

Figure 1. Study flowchart.

zed in each group. No statistical significant difference was found in age (p=0.830), weight (p=0.390) and sex (p=1.000) between the groups (Table I). The mean duration of laryngoscopy and intubation (p=0.401) in both groups were similar without any statistical significance between groups (Table I) and none of the patients were excluded from the study in view of prolonged intubation for more than 15 seconds. There were no adverse reactions in any of the patients participated in the study. The baseline heart rate (p=0.155), baseline (p=0.291) and preinduction mean arterial pressure (p=0.360) between the groups were not statistically significantly different. The heart rate and mean arterial pressure measured at serial intervals during intubation were statistically significantly different between the groups with a p value of 0.005 (Table II-III). The comparison of preinduction and postintubation heart rate (Group D, p=0.055 vs Group P, p<0.001) and mean arterial pressure at 1 minute (Group D, p=0.067 vs Group P, p<0.001) did not reveal any statistically significant difference between dexmedetomidine and pregabalin groups (Table IV). There were no variations in hemodynamic responses following intubation within

Table I. Comparison of demographic data and duration of laryngoscopy between the groups using Pearson Chi-square for categorical data and unpaired t-test for continuous data

Variables	Group D (n=30)	Group P (n=30)	p
Age (years)	30.56±5.87	30.12±7.23	0.830#
Weight (kg)	56.47±9.26	55.97±10.11	0.390#
Sex (Female: Male)	29 (96.7%): 1 (3.3%)	30 (100%): 0 (0%)	1.000#
Duration of laryngoscopy and intubation (seconds)	9.12±3.78	9.76±2.98	0.401#

#Statistically insignificant (p>0.05)

Table II. Comparison of heart rate between the groups using unpaired t-test

Time intervals	Groups (n=30 in each group)	Mean±Standard Deviation (mm Hg)	p
Baseline	D	89.27±8.395	0.291#
	P	86.97±8.311	
Preinduction	D	86.63±8.640	0.360#
	P	88.43±6.268	
0 Minute	D	85.13±8.411	
	P	97.50±6.725	0.005*
1 Minute	D	85.50±8.080	
	P	99.73±7.615	0.005*
3 Minute	D	82.43±7.546	
	P	97.03±6.901	0.005*
5 Minute	D	80.50±8.203	
	P	94.10±6.835	0.005*
10 minute	D	75.87±10.044	
	P	90.57±6.735	0.005*

*#Statistically insignificant (p>0.05) and *Statistically significant (p<0.05)*

Table III. Comparison of mean arterial pressure between the groups using unpaired t-test.

Time intervals	Groups (n=30 in each group)	Mean±Standard Deviation (beats per minute)	p
Baseline	D	77.93±9.116	0.155#
	P	81.03±7.486	
Pre induction	D	75.03±7.355	0.005*
	P	85.67±6.364	
0 Minute	D	73.20±6.020	0.005*
	P	95.20±6.020	
1 Minute	D	73.33±6.386	0.005*
	P	96.37±7.699	
3 Minute	D	71.27±5.801	0.005*
	P	92.23±7.070	
5 Minute	D	68.97±6.316	0.005*
	P	89.47±6.715	
10 minute	D	73.80±11.571	0.005*
	P	89.27±7.865	

*#Statistically insignificant (p>0.05) and *Statistically significant (p<0.05).*

Table IV. Comparison of hemodynamic variables within the groups using paired sample t-test

Variables	Group (n=30)	Pre induction values	One minute post intubation values	p
Heart Rate (beats per minute)	D	75.03±7.355	73.33±6.386	0.055#
	P	85.67±6.364	96.37±7.699	<0.001*
Mean arterial Blood pressure (mmHg)	D	86.63±8.640	85.50±8.080	0.067#
	P	88.43±6.268	99.73±7.615	<0.001*

*#Statistically insignificant (p>0.05) and *Statistically significant (p<0.05)*

Table V. Comparison of RASS between the groups using Pearson Chi-square test and Fisher's exact test

Time intervals	RASS	Group D (n=30) with % distribution	Group P (n=30) with % distribution	p
Baseline	-1	1 (3.3%)	6 (20%)	0.103#
	0	29 (96.7%)	24 (80%)	
At extubation	-2	1 (3.3%)	5 (16.7%)	0.178#
	-1	15 (50%)	15 (50%)	
	0	14 (46.7%)	8 (26.7%)	
	1	0 (0%)	1 (3.3%)	
	2	0 (%)	1 (3.3%)	
15 Minutes post extubation	-1	3 (10%)	18 (60%)	0.001*
	0	27 (90%)	11 (36.7%)	
	1	0 (%)	1 (3.3%)	
30 Minutes post extubation	-1	1 (3.3%)	14 (46.7%)	0.001*
	0	29 (96.7%)	16 (53.3%)	
At 1 hour post extubation	-1	1 (3.3%)	11 (36.7%)	0.002*
	0	29 (96.7%)	19 (63.3%)	

*#Statistically insignificant (p>0.05) and *Statistically significant (p<0.05)*

the group (heart rate, p=0.055 and mean arterial pressure, p=0.067).

The RASS scores in the preoperative period (p=0.103) and at extubation (p=0.178) were not statistically significant between the groups. The RASS scores at 15 (p=0.001), 30 minutes (p=0.001) and at 1 hour (p=0.002) post-extubation were statistically significant in the pregabalin group (Table V).

DISCUSSION

In our study, it was found that attenuation of hemodynamic response in the Dexmedetomidine group was statistically significant in comparison to the Pregabalin group. Dexmedetomidine was associated with stable hemodynamics without any perturbations during intubation when compared to pregabalin. Clinically significant sedation was achieved without any agitation, anxiety and deep sedation during preinduction and during immediate postoperative period, though sedation achieved was not statistically significant in the dexmedetomidine group.

The hypertensive-tachycardic response to airway manipulation is clinically important because it can cause myocardial ischemia in patients with coronary flow insufficiency and also it can lead to potential hazards in patients with compromised intracranial compliance [1,2]. As it is clinically imperative to achieve adequate depth of anesthesia with an intravenous or inhalational anesthetics, a variety of adjuvants like dexmedetomidine and pregabalin have been employed to potentiate the depth of anesthesia and to minimize the untoward hemodynamic responses.

Dexmedetomidine produces hyperpolarization of noradrenergic neurons, causes suppression of neuronal firing and decreases in systemic noradrenalin release leading to attenuation of sympathoadrenal response during laryngoscopy and intubation [6]. Whereas the pregabalin, a structural derivative of the inhibitory neurotransmitter γ aminobutyric acid, possesses analgesic, anticonvulsant, anxiolytic, and sleep modulating activities. Pregabalin binds to $\alpha_2\delta$ subunit of voltage sensitive calcium channels and enhance the release of neurotransmitters at the synapses of primary afferent fibers and second-order sensory neurons [7]. It is cost effective and can be administered orally with peak plasma levels reached within an average interval of 54 minutes [8]. Hence, we compared the benefits of pregabalin with another proven drug, the dexmedetomidine which is also effective in suppressing the sympathoadrenal response during intubation.

Our study outcomes were similar to those of Samal et al. [5] who compared 1 μg kg^{-1} dexmedetomidine with 150 mg pregabalin for attenuation of hemodynamic response to endotracheal intubation and found that dexmedetomidine group induced less variation in heart rate and mean arterial pressure as a response to endotracheal intubation than pregabalin group. They assessed heart rate and mean arterial pressure till 30 minutes post-intubation where the response due to surgical stimulus could affect the study. In our study, female patients were more predominantly affected which can be attributed to recruitment of patients based on the ASA physical status and the type of surgeries they onderwent during the study period. The control of hemodynamic response analysed within the group in our study proved that dexmedetomidine was better drug than pregabalin.

Kakkar et al. [8] compared 1 μg kg^{-1} clonidine, 1 μg kg^{-1}, and 0.5 μg kg^{-1} dexmedetomidine for attenuation of hemodynamic response to endotracheal intubation and found that all groups were effective in attenuating hemodynamic response. It was found that 1 μg kg^{-1} dexmedetomidine group had higher incidence of hypotension than other two groups but in our study administration of 1 μg kg^{-1} dexmedetomidine did not produce any significant hypotension.

Waikar et al. [9] proved that gabapentin, clonidine and pregabalin attenuated blood pressure and heart rate. In their study they concluded that all three drugs were very effective in relieving anxiety and improving sedation. In our study the attenuation of hemodynamic response was better with dexmedetomidine but the post-extubation RASS score was better with pregabalin which can be attributed to shorter duration of action of dexmedetomidine.

Jain et al. [10] and Vijayan et al. [11] reported similar benefits of dexmedetomidine in attenuating intuba-

tion response in patients undergoing laparoscopic Cholecystectomy when compared to pregabalin, but there were reports of bradycardia in two patients in Jain et al study which was not observed in our study.

The patients who received pregabalin had statistically significant sedation following extubation. Pregabalin group patients had a RASS score of 1 more frequently when compared to dexmedetomidine group where majority remained alert and calm with the RASS score of 0. None of the patients in the study had deeper levels of sedation leading to any complications. This can be attributed to shorter acting dexmedetomidine and the selected dose of pregabalin (150 mg) which was chosen based on the study by White et al. [12], who showed that oral pregabalin at a dose of 75 mg was not effective in attenuating preoperative anxiety, and at a dose of 300 mg, it produced increased level of sedation after surgery.

The limitation of our study was that we did not assess the PACU discharge criteria and postoperative nausea vomiting (PONV) scores in our patients which can be affected by study drugs. Further studies are required to assess the efficacies of the study drugs in high risk population who are prone for cardiovascular and neurological complications.

CONCLUSION

In our study, it was found that intravenous dexmedetomidine at a dose of 1 μg kg^{-1} was more effective than oral dose of 150 mg pregabalin in attenuating hemodynamic response to laryngoscopy and endotracheal intubation. Postprocedural sedation was better achieved with oral pregabalin compared to intravenous dexmedetomidine.

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