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SCIENTIFIC ARTICLE

The comparison of the effects of dexmedetomidine, fentanyl and esmolol on prevention of hemodynamic response to intubation

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Esmolol

Abstract
Background and objectives: Laryngoscopy and intubation can cause hemodynamic response. Various medications may be employed to control that response. In this study, we aimed to compare the effects of dexmedetomidine, fentanyl and esmolol on hemodynamic response.
Methods: Ninety elective surgery patients who needed endotracheal intubation who were in American Society of Anesthesiology I–II group and ages between 21 and 65 years were included in that prospective, randomized, double-blind study. Systolic, diastolic, mean arterial pressures, heart rates at the time of admittance at operation room were recorded as basal measurements. The patients were randomized into three groups: Group I ($n = 30$) received 1 μg/kg dexmedetomidine with infusion in 10 min, Group II ($n = 30$) received 2 μg/kg fentanyl, Group III received 2 mg/kg esmolol 2 min before induction. The patients were intubated in 3 min. Systolic, diastolic, mean arterial pressures and heart rates were measured before induction, before intubation and 1, 3, 5, 10 min after intubation.
Results: When basal levels were compared with the measurements of the groups, it was found that 5 and 10 min after intubation heart rate in Group I and systolic, diastolic, mean arterial pressures in Group III were lower than other measurements ($p < 0.05$).
Conclusions: Dexmedetomidine was superior in the prevention of tachycardia. Esmolol prevented sytolic, diastolic, mean arterial pressure increases following intubation. We concluded that further studies are needed in order to find a strategy that prevents the increase in systemic blood pressure and heart rate both.

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PALAVRAS-CHAVE
Laringoscopia;
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Fentanil;
Esmolol

Comparação entre os efeitos de dexmedetomidina, fentanil e esmolol na prevenção da resposta hemodinâmica à intubação

Resumo
Justificativa e objetivos: Laringoscopia e intubação podem causar resposta hemodinâmica. Vários medicamentos podem ser usados para controlar essa resposta. Neste estudo, nosso objetivo foi comparar os efeitos de dexmedetomidina, fentanil e esmolol sobre a resposta hemodinâmica.
Métodos: Foram incluídos no estudo prospectivo, randômico e duplo-cego 90 pacientes programados para cirurgias eletivas, com intubação endotraqueal, estado físico ASA I-II, entre 21 e 65 anos. Pressões arteriais médias, sistólicas, diastólicas e frequências cardíacas foram medidas ao darem entrada na sala de operações e registradas como valores basais. Os pacientes foram randomizados em três grupos: Grupo I (n = 30) recebeu 1 μg/kg de dexmedetomidina com infusão em 10 min; Grupo II (n = 30) recebeu 2 μg/kg de fentanil; Grupo III (n = 30) recebeu 2 mg/kg de esmolol 2 min antes da indução. Os pacientes foram intubados em 3 min. As pressões médias, sistólicas e diastólicas e as frequências cardíacas foram medidas antes da indução, antes da intubação e nos minutos 1, 3, 5 e 10 após a intubação.
Resultados: Quando os níveis basais foram comparados entre os grupos, verificou-se que nos minutos 5 e 10 pós-intubação as frequências cardíacas no Grupo I e as pressões arteriais médias, sistólicas e diastólicas no Grupo III estavam mais baixas do que em outros tempos mensurados ($p < 0,05$).
Conclusões: Dexmedetomidina foi superior na prevenção de taquicardia. Esmolol preveniu o aumento das pressões arteriais médias, sistólicas e diastólicas após a intubação. Concluímos que estudos adicionais são necessários para descobrir uma estratégia que previna tanto o aumento da pressão arterial sistêmica quanto da frequência cardíaca.

Introduction

During general anesthesia airway control is generally provided by laryngoscopy and intubation. Laryngoscopy and intubation lead to mechanical and chemical stimuli. Mechanical stimulus causes reflex responses in cardiovascular and respiratory systems.[1] That response reaches its maximum level within 1 min and ends in 5–10 min after intubation. On the other hand, chemical stimulus results with catecholamine release via increase in sympathoadrenergic activity. Catecholamine release leads to hypertension, tachycardia and arrhythmia. Tachycardia generates a more powerful load on the heart when compared with hypertension as it increases oxygen consumption of the myocardium, decreases diastolic filling and finally reduces coronary blood supply.[2]

The degree of the reflex response of laryngoscopy and intubation is related with the deepness of anesthesia, patient's age and the presence of diabetes or heart disease. Narcotic analgesics, local anesthetics, beta-blockers, calcium canal blockers and vasodilators are employed in order to control that response.[3] Dexmedetomidine is a selective α_2 adrenergic agonist. Its effects on cardiovascular system are particularly prominent.[4,5] The effect of fentanyl on cardiovascular system is not much. The exact reason of bradycardia due to fentanyl use is not clear, but it is considered to be related with central vagal stimulation.[6] Among these agents, esmolol is a cardioselective β adrenergic blocker that has an effect with rapid onset and short duration. While it inhibits β_1 receptors of myocardium, it also inhibits β_2 receptors of smooth muscles of bronchial and vascular walls at higher doses.[7]

In this study, we aimed to compare the effects of dexmedetomidine, fentanyl and esmolol on control of hemodynamic response due to laryngoscopy and intubation.

Methods

The study was approved by Ethical Board of Ankara Numune Training and Research Hospital. Ninety elective surgery patients who were in American Society of Anesthesiology (ASA) I and II groups and whose ages were between 21 and 65 years were included in that study. The study was planned as a prospective, double blind and randomized study. Those in whom difficulty in intubation was expected, who had coronary artery disease, hypertension, chronic obstructive pulmonary disease or diabetes and who were using any cardiovascular medication were excluded.

All patients were examined one day before and their laboratory results were reviewed. Included patients received necessary information about the study and gave their written consents. Before admittance to operation room, vascular access was obtained from the back of the hand with 20G canula and 10 mL/kg/hour Ringer's lactate infusion was started. Following transferring to operation room, premedication with 0.01 mg/kg iv midazolam was performed. CAMS II (Comprehensive Anesthesia Monitor) was used for routine monitorization; ECG and heart rate (HR) were monitored at standard DII derivation; systolic (SAP), diastolic

Table 1 Patient demographics in the groups.

	Group I ($n=30$)	Group II ($n=30$)	Group III ($n=30$)
Age (years)	41.2 ± 10.6	41.5 ± 10.0	43.8 ± 12.8
Gender (F/M)	11/19	15/15	15/15
ASA (I/II)	15/15	11/19	15/15
Weight (kg)	77.9 ± 11.0	75.5 ± 12.6	77.0 ± 12.3

(DAP) and mean (MAP) arterial pressures were monitored via automatic non-invasive blood pressure measurements and peripheral oxygen saturation (SpO_2) was monitored via pulse oxymetry.

The patients were randomized into three groups. These groups were determined with closed envelopes. The subjects were blinded to the treatment they received. The anesthesiologists who prepared and administered the medications were provided to be different. Group I ($n=30$) received 1 μg/kg dexmedetomidine (Precedex®, Meditera, 200 μg/2 mL) with infusion in 10 min, Group II ($n=30$) received 2 μg/kg fentanyl citrate (Fentanyl®, Janssen-Cilag, 0.05 mg/mL) and Group III received 2 mg/kg esmolol (Brevibloc®, Eczacibasi, 10 mg/mL) 2 min before induction. Then 6 mg/kg thiopental and 0.1 mg/kg vecuronium were administered intravenously. Three minutes later laryngoscopy and intubation were performed by the same anesthesiologist. The patients in whom endotracheal intubation could not be achieved within 45 s were excluded from the study. All patients received 50%O_2 (2 L/min), 50% N_2O (2 L/min) and 1.5 MAC sevoflurane (Sevorane®, Abbott) during maintenance of anesthesia. These parameters were measured and recorded before induction (t_0), after induction (t_1) before intubation (t_2) and 1 (t_3), 3(t_4), 5 (t_5) and 10 min (t_6) after intubation in all patients. The measurements before induction (t_0) were considered as basal levels and all of other measurements were compared with these basal levels. Surgical incisions were started following completion of that data collection process. The patients were ventilated in order to maintain end tidal CO_2 levels between 30 and 35 mm Hg. During the operations HR, SAP, MAP, DAP, and SpO_2 levels were recorded with 5 min intervals. After the operations, the subjects were monitored in recovery room for 60 min following awakening and then were transferred to inpatient clinics.

Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows version 10.0 was used for statistical analysis. One-way Anova and Student's t test were used for comparison of quantitative data besides descriptive statistical methods (mean, standard deviation) in evaluation of study data. Chi-square test was employed for comparison of qualitative data. The comparisons were considered as not significant ($p>0.05$), significant ($p<0.05$) or extremely significant ($p<0.001$) in a confidence interval of 95%. A sample size of 30 achieved 100% power to detect a difference (P1−P0) of 0.2540 using a two-sided binomial test. The target significance level was 0.0500. The actual significance level achieved by this test was 0.9229 (92%).

Results

There was no difference between three groups according to age, weight, gender and ASA physiological scores ($p>0.05$ for all, Table 1).

Mean SAP decreased at t_1, t_2, t_5, and t_6 in Group I, at t_1, t_5 and t_6 in Group II, at t_2, t_5, and t_6 in Group III ($p<0.001$ for all). When the groups were compared with eachother, mean SAP was lower in Group III than other groups at t_1, t_2, t_5 and t_6 ($p<0.05$ for all, Table 2).

Mean DAP decreased at t_1, t_2, and t_6 in Group I ($p<0.001$, $p<0.001$ and $p<0.05$, respectively), at t_5 and t_6 in Group II ($p<0.001$for both), at t_1, t_2, t_5, and t_6 in Group III ($p<0.05$, $p<0.001$, $p<0.05$ and $p<0.001$, respectively, Table 3).

Mean MAP decreased at t_1, t_2, and t_6 in Group I ($p<0.001$, $p<0.001$and $p<0.05$, respectively), at t_5 and t_6 in Group II ($p<0.001$for both), at t_1, t_2, t_5 and t_6 in Group III ($p<0.05$, $p<0.001$, $p<0.05$ and $p<0.001$, respectively). When the

Table 2 The comparison of the groups according to systolic artery pressure measurements (mm Hg).

	Group I ($n=30$)	Group II ($n=30$)	Group III ($n=30$)	p
t_0	138.63 ± 16.99	141.03 ± 11.87	131.03 ± 16.55	0.066
t_1	117.00 ± 18.27[a]	123.73 ± 17.45[a]	114.27 ± 20.81	0.040[b]
t_2	115.37 ± 18.47[a]	132.83 ± 17.76	103.07 ± 17.45[a]	0.039[b]
t_3	147.13 ± 19.41	156.60 ± 16.87	147.43 ± 21.27	0.079
t_4	129.20 ± 20.72	134.63 ± 16.46	125.93 ± 23.70	0.055
t_5	119.17 ± 17.10[a]	116.67 ± 17.43[a]	111.60 ± 19.91[a]	0.037[b]
t_6	116.17 ± 17.01[a]	110.73 ± 18.05[a]	103.90 ± 22.06[a]	0.031[b]

[a] Extremely significant at the level of $p<0.001$ (inter group comparisons).
[b] Significant at the level of $p<0.05$.

Table 3 The comparison of the groups according to diastolic artery pressure measurements (mm Hg).

	Group I ($n = 30$)	Group II ($n = 30$)	Group III ($n = 30$)	p
t_0	82.03 ± 10.23	82.67 ± 9.87	80.57 ± 10.26	0.055
t_1	73.33 ± 12.07[a]	80.40 ± 9.11	71.03 ± 14.89[a]	0.040[b]
t_2	72.00 ± 13.40[c]	83.57 ± 11.93	63.73 ± 11.20[c]	0.038[b]
t_3	97.73 ± 12.28	99.23 ± 13.01	95.07 ± 13.49	0.080
t_4	83.07 ± 14.40	88.50 ± 13.97	80.83 ± 14.68	0.058
t_5	76.77 ± 12.15	75.10 ± 12.34	71.67 ± 15.61[a]	0.040[b]
t_6	74.90 ± 13.60	73.50 ± 12.16[a]	67.76 ± 16.62[c]	0.035[b]

[a] Significant at the level of $p < 0.05$ (inter group comparisons).
[b] Significant at the level of $p < 0.05$.
[c] Extremely significant at the level of $p < 0.001$ (inter group comparisons).

Table 4 The comparison of the groups according to mean artery pressure measurements (mm Hg).

	Group I ($n = 30$)	Group II ($n = 30$)	Group III ($n = 30$)	p
t_0	100.77 ± 12.23	99.97 ± 11.81	96.43 ± 11.66	0.058
t_1	87.10 ± 12.05[a]	95.60 ± 10.55	84.10 ± 16.43[b]	0.040[c]
t_2	86.63 ± 14.14[a]	121.63 ± 17.76	76.83 ± 13.02[a]	0.037[c]
t_3	114.30 ± 13.65	119.53 ± 16.87	112.33 ± 19.49	0.081
t_4	98.63 ± 15.22	102.30 ± 16.46	97.13 ± 16.85	0.056
t_5	91.90 ± 13.15	84.80 ± 17.43[a]	85.63 ± 16.88[b]	0.039[c]
t_6	90.30 ± 14.38[b]	85.73 ± 18.05[a]	80.86 ± 20.35[a]	0.035[c]

[a] Extremely significant at the level of $p < 0.001$ (inter group comparisons).
[b] Significant at the level of $p < 0.05$ (inter group comparisons).
[c] Significant at the level of $p < 0.05$.

groups were compared with eachother, mean MAP was lower in Group III than other groups at t_1, t_2, t_5 and t_6 ($p < 0.05$ for all, Table 4).

Mean HR decreased at t_1, t_2, t_4, t_5 and t_6 in Group I ($p < 0.001$for all) at t_2, t_5 and t_6 in Group II ($p < 0.001$, $p < 0.05$ and $p < 0.001$, respectively) and at t_2 and t_6 in Group III ($p < 0.05$ for both). When the groups were compared with eachother, mean HR was lower in Group I than other groups at t_1, t_2, t_5 and t_6 ($p < 0.001$ for all, Table 5).

Discussion

Pathophysiologic effects of endotracheal intubation may be encountered almost in all systems of the body and may lead to harmful consequences. The most frequent effects are cardiovascular hemodynamic responses characterized with hypertension, tachycardia, arrhythmia and increase in sympathoadrenergic activity. Although cardiovascular hemodynamic responses carry risk for all patients who receive anesthesia that risk is more prominent in those who have cerebrovascular or coronary artery disease. Thus preventing the increase in sympathoadrenergic activity due to endotracheal intubation is an important aspect.[8] Dexmedetomidine that is a selective α_2 adrenergic agonist, fentanyl that is an opioid and esmolol, that is a β adrenergic receptor blocker are generally used for that purpose. When we compared these medications with each other, we observed that dexmedetomidine controlled

Table 5 The comparison of the groups according to heart rate measurements (beat/min).

	Group I ($n = 30$)	Group II ($n = 30$)	Group III ($n = 30$)	p
t_0	87.7 ± 13.35	90.97 ± 17.40	86.34 ± 11.49	0.062
t_1	73.47 ± 6.9[a]	87.57 ± 14.17	82.00 ± 11.49	0.0048[b]
t_2	69.23 ± 8.19[a]	79.60 ± 15.16[a]	78.10 ± 9.49[c]	0.0035[b]
t_3	82.27 ± 8.25	93.20 ± 12.54	89.38 ± 10.6	0.066
t_4	76.17 ± 9.18[a]	87.53 ± 14.47	89.55 ± 10.8	0.0569
t_5	70.17 ± 14.8[a]	80.00 ± 13.44[c]	84.48 ± 10.00	0.004[b]
t_6	70.60 ± 9.03[a]	75.72 ± 12.50[a]	79.38 ± 11.005[c]	0.003[b]

[a] Extremely significant at the level of $p < 0.001$ (inter group comparisons).
[b] Extremely significant at the level of $p < 0.001$.
[c] Significant at the level of $p < 0.05$ (inter group comparisons).

heart rate and esmolol controlled blood pressure better.

Gupta et al.[6] compared the effects of 2 mg/kg esmolol and 2 μg/kg fentanyl that were administered 3 min before anesthesia induction in order to prevent hemodynamic response in patients in whom elective surgical procedures were planned. They reported that a single dose of esmolol prevented the increase in blood pressure. They also found that, although clinically insignificant, the effect of esmolol on the increase in heart rate was better than fentanyl. Atlee et al.[9] compared the effects of 1 mg/kg esmolol and 30 μg/kg nicardipine alone and in combination and reported that they did not prevent blood pressure change when they were administered solely, but were effective in combination. These drugs did not show any effect on heart rate alone or in combination. Figueredo et al.[10] performed a meta-analysis of different esmolol doses and reported that infusion was more effective than single dose administration to prevent cardiovascular stress response. We used esmolol at a dose of 2 mg/kg in this study. We observed that this level was adequate to prevent the increases in systolic, diastolic and mean arterial pressures, but did not have any effect on heart rate.

Adachi et al.[11] used 2 μg/kg fentanyl just before induction in order to prevent cardiovascular stress. They found that fentanyl was more effective in prevention of cardiovascular hemodynamic response secondary to endotracheal intubation than prevention of hemodynamic response to laryngoscopy. They reported that this effect of fentanyl was related with the interaction with plasma concentrations of the anesthetics that were used for induction. Ugur et al.[12] used 1.5 mg/kg esmolol, 1 μg/kg fentanyl and 1.5 mg/kg lidocain 2 min before intubation and found that esmolol prevented the increase in heart rate. On the other hand, Hussain et al.[7] compared the effects of 2 μg/kg fentanyl and 2 mg/kg esmolol that were administered 2 min before laryngoscopy and intubation and reported that fentanyl was inadequate to prevent the increases in heart rate and blood pressure. They also showed that esmolol prevented the increase in heart rate, but did not have any effect on blood pressure. In our study, we found that 2 mg/kg esmolol decreased systolic, diastolic and mean arterial pressures more than 2 μg/kg fentanyl, but there was not any difference between two groups according to prevention of the increase in heart rate.

Dexmedetomidine decreases arterial blood pressure and heart rate by reducing serum noradrenalin levels. Talke el al.[13] performed a placebo controlled study in vascular surgery and showed that dexmedetomidine caused less increase in heart rates and noradrenalin levels when administered at a dose of 0.8 μg/kg via intravenous infusion. Hall et al.[14] used 0.2 and 0.6 μg/kg dexmedetomidine via intravenous infusion and reported that although heart rate decreased prominently, there was not any change in mean arterial pressure. Similarly, Yildiz et al.[15] found that a single dose of 1 μg/kg dexmedetomidine prevented cardiovascular hemodynamic response and decreased the need for additional opioid during laryngoscopy and endotracheal intubation in elective minor surgery patients. It was noticed that infusion doses of dexmedetomidine used in these studies were between 0.2 and 0.8 μg/kg. Alternatively, Ozkose et al.[16] administered a single dose of 1 μg/kg dexmedetomidine 10 min before induction. They reported that when compared with control measurements, mean arterial pressures decreased up to 20% and heart rates decreased up to 15% 1 and 3 min following intubation. They observed bradycardia that necessitated atropin administration in four of their 20 patients. We administered 1 μg/kg dexmedetomidine before induction via infusion in 10 min. We did not demonstrate any difference in systolic, diastolic and mean arterial pressures between groups, but found that it was effective in preventing the increase in heart rate.

The most common side effects of dexmedetomidine are hypotension and bradycardia that occur more frequently during loading period. We suggest that reducing loading dose and slowing infusion rate may prevent cardiovascular side effects. We administered dexmedetomidine with slow infusion in our study and observed bradycardia necessitating atropin use in only one of our patients. Similarly Venn et al.[17] reported that these side effects were not observed when 2.5 μg/kg loading dose of dexmedetomidine was administered in 10 min and followed by an infusion rate of 0.2–0.5 μg/kg/min.

We concluded that esmolol was more effective than dexmedetomidine and fentanyl in prevention of the increases in systolic, diastolic and mean arterial pressures following endotracheal intubation. On the other hand, dexmedetomidine was more effective than esmolol and fentanyl in preventing the increase in heart rate. To prevent the increases in blood pressure and heart rate is particularly important from the aspect of myocardial ischemia. We considered that further studies will be suitable in which these agents are used in combination in order to prevent the increase in systemic blood pressure and heart rate both.

Conflicts of interest

The authors declare no conflicts of interest.

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