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Comparison of Bolus and Infusion of Esmolol on Hemodynamic and Parathormone Responses to Tracheal Intubation

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Abstract

Background: We compared the effects of esmolol bolus and bolus+infusion on the haemodynamic and serum parathormone (PTH) level changes related to laryngoscopy and tracheal intubation (LTI).
Material and Methods: A total of 60 patients were enrolled to the study. The patients were randomly divided into 3 equal groups: esmolol 1.5 mg/kg as a bolus within 20 seconds (Group B), a loading dose of 0.5 mg/kg of esmolol within 20 seconds followed by esmolol was infused at a rate of 100 µg/kg/min for ten minutes (Group I) and isotonic saline (Group P). Induction of anesthesia was performed with thiopentone and rocuronium. Mean arterial pressure (MAP) and HR were recorded baseline (T0), before laryngoscopy (T1) and 1, 3, and 5 minutes after intubation (T2, T3 and T4 respectively). PTH and calcium were measured baseline, 5min and 1h after the intubation.
Results: There were significant decreases in HR at T1 (77±13 beat/min) compared to T0 (84±13 beat/min) in group I. There were significant increases in HR at T2, T3, and T4 ($p<0.001$) in group I and group P compared to T0. MAP increased significantly in all groups at T2 compared to baseline. We observed significant increases in PTH and decreases in calcium after the intubation in all groups.
Conclusion: Both dosing regimens of esmolol two minutes before laryngoscopy are insufficient in preventing pressor and hormonal responses related to LTI.

Key Words: Esmolol; tachycardia; hypertension; Intubation, Intratracheal; parathyroid hormone, calcium; adrenergic beta-Antagonists

Introduction

Laryngoscopy and tracheal intubation (LTI) lead to the increase in sympathoadrenal activity leading to increased blood pressure,tachycardia and arrhythmia (1-3). It has been known that these haemodynamic changes are closely associated with the increase in the plasma catecholamine levels (4,5). Furthermore, it has been thought that sympathetic stimulation due to LTI may causes increment of the plasma parathyroid hormone (PTH) and decrement of plasma

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calcium (6,7). Alhough the harmfull effects of LTI are transient and well tolerated by healhty people, haemodynamic control is important in patients with cardiovascular or neurosurgical diseases undergoing anesthesia (3).

Esmolol is an ultra short-acting β1-adrenoceptor antagonist to attenuate sympathetic response related to LTI related adrenergic responses depending on the dose(8,9).However, the risk of hypotension and bradycardia increases with esmolol in a dose dependent manner when combined with induction agents (8,9).

Because of its very short acting and elimination half life time, the dosing regimen (bolus or infusion) of esmolol may be important to avoid the LTI related adrenergic responses and on the occurance of the adverse reactions. Even though this subject is evaluated in several meta-analysis, there is no reported randomized controlled trial to compare bolus and infusion of esmolol in patients with ungergoing noncardiac surgery (8,10).

In this study, we aimed to compare the effectiveness of esmolol dosing regimens (bolus vs bolus + infusion) prior to intubation in preventing the hemodynamic changes associated with LTI, and to study the effects of esmolol on serum parathormone and calcium levels.

Material and Methods

Two different esmolol dosing regimens were compared in this randomized single-blind and placebo-controlled study conducted in a tertiary referral hospital in Istanbul, Turkey. The study protocol was approved by the Local Hospital Ethics Committee conducted according to the Declaration of Helsinki, and full written and verbal consent were obtained from all participants. Patients enrolled into the study were selected from 86 consecutive patients who were referred for an elective non-cardiac surgery (Fig 1).

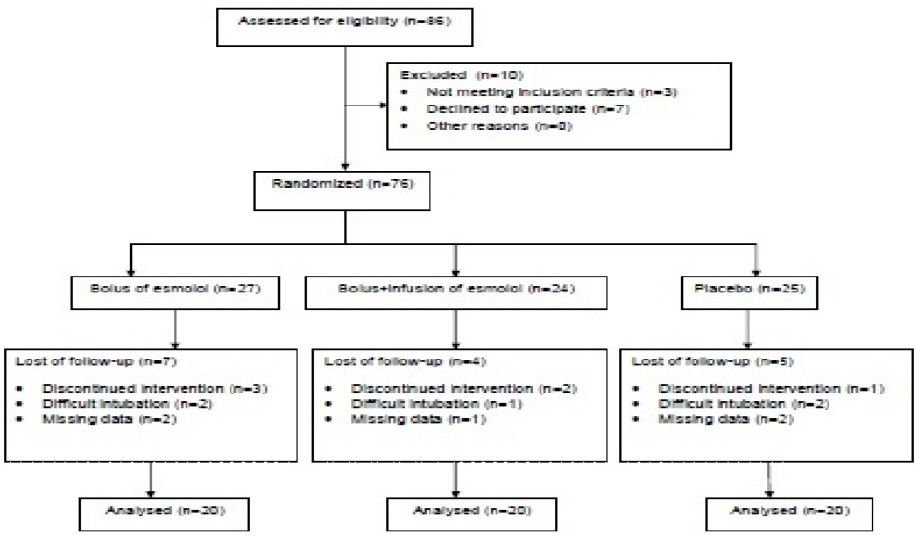

Fig 1. Flow diagram of the study.

Patients with the following characteristics were excluded from the study: bradycardia (HR < 60 beats/min), hypotension (systolic blood pressure < 100 mmHg), atrial or

ventricular arrhythmia, second or third degree A-V conduction block, hypertension, ischemic heart disease, heart failure, reactive airway disease, sedative or opioid drug use history, cardiovascular or β blocker treatment, high probability of difficult intubation Mallampati ≥ III) and a history of hypersensitivity to esmolol. Also patients whose intubation could not done at the first attempt or lasted more than 15 seconds were excluded.

No premedication was given to patients. In the operating room, all patients received intravenous isotonic saline at 8 ml/kg/h. Patients were randomly divided into three groups by computer generated randomization: to first group, esmolol 1.5 mg/kg was administered as a bolus within 20 seconds (Group B); to second group, after esmolol 500 μg/kg loading dose was given within 20 seconds, patients received an infusion for 10 minutes at 100 μg/kg/min rate (Group I); a plasebo (normal saline) 10 ml was given as bolus to 3rd Group (Group P). Esmolol was prepared as 10 mg per ml in perfusion syringe given by an infusion pump.

Anesthesia was induced with thiopentone 4-7 mg/kg and rocuronium 0.6 mg/kg to facilitate tracheal intubation. All patients were intubated by the same and experienced anesthetist 90 seconds after mask ventilation with 100% oxygen. Esmolol and placebo administration were completed two minutes prior to intubation. Maintenance of anesthesia was acheived with 2% sevoflurane in 40-60% oxygen-air mixture.

Electrocardiography (ECG), noninvasive blood pressure (NIBP), heart rate (HR), and peripheral oxygen saturation (SpO2) of all patients were monitored (Dräger Infinity Delta, Dräger Medical Systems, Inc. Danvers, MA, USA). Haemodynamic parameters (systolic, diastolic and mean arterial blood pressure and heart rate) were measured and recorded by an research resident who blinded to study with the following time points: when the patients were taken to operating room (T0), before laryngoscopy (T1) and 1 minutes (T2), 3 minutes (T3), and 5 minutes (T4) after intubation. Bradycardia (HR < 50 beats/min), hypotension (decrease of arterial pressure relatively to baseline level more than 30%), hypertension (SAP > 180 mmHg) and tachcardia (HR > 120 beats/min) were recorded. The esmolol infusion was stopped if bradycardia or hypotension occured. When SAP decreased below 90 mmHg, 5 mg of ephedrine was administrated. Bradycardia was treated with intravenous administration of 0.5 mg of atropine sulfate.

Venous blood samples were taken to cold ethylenediaminetetraacetic acid (EDTA) tubes before the operation, 5 minutes after intubation and 1 hour after intubation for PTH and calcium analysis. Plasma PTH levels were measured using a immunochemiluminescence assay with the Advia Centaur XP device by Siemens commercial kits (Siemens Healthcare Diagnostics, Deerfield, IL, USA). Plasma total calcium levels were measured with the Advia 2400 device by Arsenazo III kits (Siemens Healthcare Diagnostics, Deerfield, IL, USA) using colorimetric method. Reference range and anaylitical sensitivity for PTH 14-72 pg/ml and 2.5 pg/ml respectively. Reference range and anaylitical sensitivity for calcium 8.4-10.2 mg/dl and 1.0 mg/dl respectively.

Statistical analysis

Statistical analysis was performed by the SPSS software package for Windows

(Statistical Package for Social Sciences, version 17.0, SPSS Inc., Chicago, Illinois, USA). The power analysis with α=0.05 and β=0.2 showed us at least 16 patients are required for every treatment group for determining the 20 % decrement of the increases in heart rate and blood pressure occuring after endotracheal intubation based on previous studies (4). Chi-square testing was used to compare the categorical variables (gender, ASA, mallampati, incidence of hypotension, hypertension, bradycardia, and tachycardia) between the groups. Numerical variables (age, body weight, haemodynamic parameters and plasma PTH and calcium levels) were evaluated in terms of normal distribution by Kolmogorov-Smirnov test. In between-group comparison of parametric data, one-way analysis of variance ANOVA) was used together with postHoc Tukey test. The repeated measurements analysis of variance (RMANOVA) was used for the changes which occurred in haemodynamic data, PTH and calcium levels compared with basal values. Bonferroni test was used in postHoc multiple comparisons. Quantitative variables were expressed as mean ± standard deviation (SD), whereas categorical variables as number of patients and percentage. If p value less than 0.05 was considered as statistically significant.

Results

There were no statistically significant differences between the groups in terms of age, weight, height, gender, ASA score and mallampati classifications (Table 1).

Table 1. Characteristics of the groups.

	Group B (n=20)	Group I (n=20)	Group P (n=20)	p
Age year)	35±12	33±12	34±13	0,873
Gender M/F n)	7 / 13	10 / 10	10 / 10	0,545
Weight kg)	72±11	72±10	68±10	0,305
Height cm)	163±7	166±9	166±8	0,344
ASA I/II n)	19 / 1	16 / 4	18 / 2	0,322
Mallampati I/II n)	14 / 6	17 / 3	19 / 1	0,102

Data are given mean ± standart deviation or number of patients.

We observed significant decreases in HR immediately before the laryngoscopy compared to baseline in group I from 84 ± 13 bpm to 77 ± 13 bpm ($p < 0.001$). There were significant increases in HR at T2, T3 and T4 in group I and group P compared to

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baseline (p<0.001). But in group B we didn't find any significant change on HR compared to baseline at T2, T3 and T4 (p = 1.000, p = 0.057 and p = 0.148 respectively). No significant difference was seen between the groups for HR (Fig 2). There were statistically significant increases in MAP 1 minute after intubation compared to baseline in group B (p<0.001), group I (p=0.004) and group P (p<0.001). In all measurements of MAP there was no significant difference between the groups (T0, T1, T2, T3 and T4 respectively p=0.961, p=0.736, p=0.254, p=0.738 and p=0.556) (Fig 3).

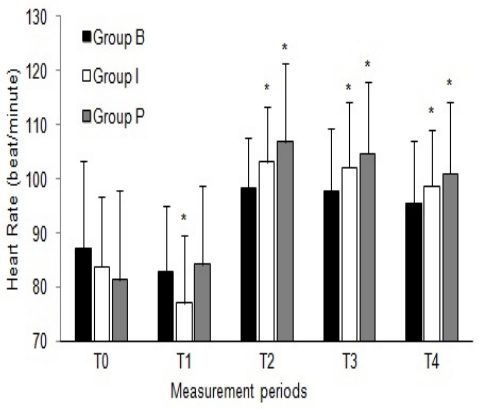

Fig 2. Heart rates during induction and endotracheal intubation. *P < 0.001 compared with T0 value (data;mean±s.d.). T0: Baseline, T1:Before laryngoscopy, T2:1 minute after intubation, T3: 3 minutes after intubation, T4:5 minutes after intubation.

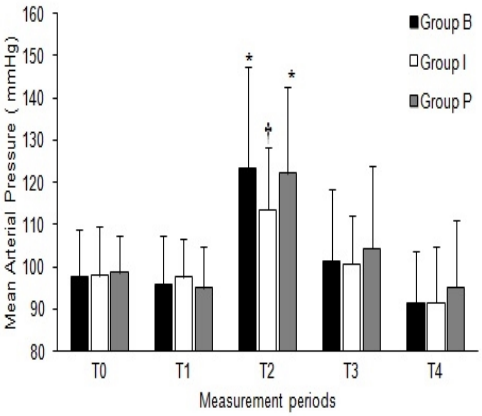

Fig 3. Mean arterial pressures during induction and endotracheal intubation.*P < 0.001 and †P=0.004, compared with T0 value (data;mean±s.d.). T0: Baseline, T1:Before laryngoscopy, T2:1 minute after intubation, T3: 3 minutes after intubation, T4:5 minutes after intubation.

Neither hypotension nor bradycardia occured in the patients. Hypertension after intubation was seen in 7 (35 %) patients of group B, 2 (10%) patients group I and 5 (25%) patients of group P but disappeared at the fifth minute in all of the patients. Tachycardia after intubation occured in 1 (5 %) patient of group B, 2 (10%) patients of group I and 5 (25%) patients of group P. Tachycardia resolved in all patient at the fifth minute excluding one patient in group P. This patient heart rate was 136 beats per minute at fifth minute but disappeared in a short time. We didn't observe any significant difference between the groups on serum parathormone at levels at T0 (p=0.287), T1 (p=0.429), and T2 (p=0.091). Similarly there were no significant differences between the groups on calcium levels at T0 (p=0.055), T1 (p=0.113) and T2 (p=0.127). There were statistically significant increases in serum parathormone levels five minutes after intubation and one hour after intubation compared to baseline values in all three groups (p < 0.001) (Fig 4). In intra-group comparison, there was a significant decrease in serum calcium levels which occurred at one hour after intubation compared to baseline values in all three groups (p < 0.001) (Fig 5).

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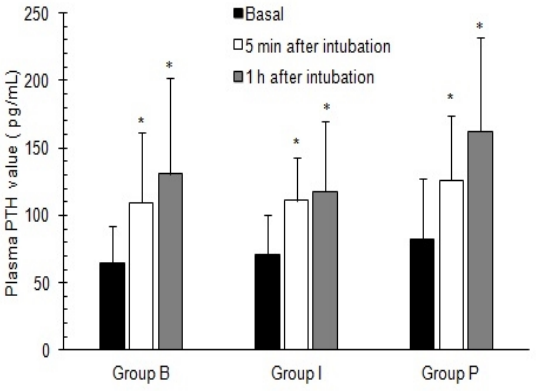

Fig 4. Plasma PTH levels after endotracheal intubation. *P < 0.001 compared with T0 value (data;mean±s.d.). T0: Baseline T1: 5 minutes after intubation, T2:1 hour after intubation.

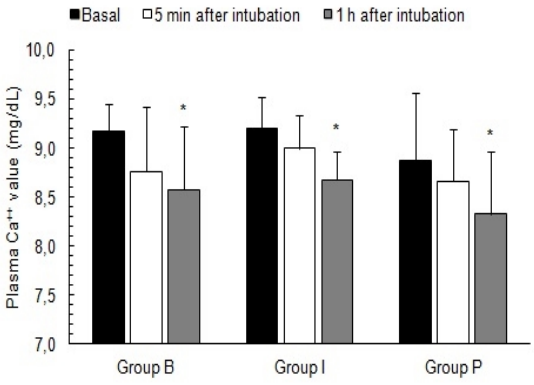

Fig 5. Plasma calcium levels after endotracheal intubation.P < 0.001 compared with T0 value (data;mean±s.d.). T0: Baseline T1: 5 minutes after intubation, T2:1 hour after intubation.

Discussion

In this study, we found that when esmolol is applied as either bolus or bolus with infusion at the given/specified doses did not prevent MAP increases induced by intubation. Furthermore, we showed that the increases which occurred in HR compared to baseline values after intubation were reduced in the single bolus dose of esmolol. In spite of this, the initial bolus dose and then infusion of esmolol are ineffective in preventing HR increases.

Esmolol is an ultra short-acting and effective β1 adrenergic antagonist, and it leads to decrease in heart rate and arterial blood pressure depending onthe dose. Accordingly, it may be a suitable option in suppressing the cardiovascular responses due to LTI (8-10).

It has been shown that esmolol 0.5 mg/kg as a single bolus is not effective in prevention of increases in both HR and arterial blood pressure after LTI(11). But esmolol 1 mg/kg is sufficient to prevent tachycardia, not enough to prevent hypertension after laryngoscopy(12). Esmolol dose required to prevent the increase in arterial pressure is higher than the dose necessary to avoid tachycardia(8-10). It has been reported on previous studies that 1.5-2 mg/kg single bolus doses of esmolol can generally provide attenuation in those hemodynamic responses but do not eliminate completely(13-15). Our results reinforce these studies. Administration of esmolol as single bolus dose is easier and simpler than administration with infusion, and is an application which requires less time. However, to the our best knowledge, there is no randomized control trial to compare bolus and infusioun of esmolol in respect to the efficacy preventing hemodynamic responses and side effects of LTI in non cardiac surgery. It has been reported that hypotension occured less freuently when esmolol given with an intial bolus dose of < 500 µg/kg before the initiation of

continious infusion and higher infusion rates associated with greater blood pressure decreases(8,10). Therefore, we chose 0.5 mg/kg of esmolol as a loading dose and later, infusion for 10 minutes at 100 µg/kg/min rate, in order to give total 1.5 mg/kg esmolol.

In studies conducted before about esmolol bolus followed by infusion, the esmolol beginning bolus doses were 0.3-2.3 mg/kg and following infusion rates were 50-300 µg/kg/min. It has been reported that HR control was better than pressor responses after LTI with this esmolol regimen (8-10,16).

The effect of esmolol on HR is directly whereas the effect on blood pressure is indirectly by gradual decreasein renin secretion. Therefore it is shown that the negative chronotropic effect of esmolol infusion is faster than hypotensive effect (4.8±3.0 *vs.* 42.5±8.9 min)(17,18).

Unlike the previous studies our results showed that esmolol applied through infusion is not sufficient in prevention the increases which occur in both HR and MAP after LTI(8,10,17,18).Furthermore, there was a tendency of decrease in HR to prior laryngoscopy through esmolol infusion like the previous studies due to fast action on the $\beta_1$receptors.(8-10,17,18).

The plasma distribution of esmolol and half life elimination rate are 2 and 9 minutes respectively. Esmolol disappears readily from plasma due to rapid and excessive hydrolysis of ester bonds in liver, leading to disappearance of effects on HR in 5 minutes after the infusion is stopped(9,17). In the present study, esmolol infusion was stopped two minutes before intubation in order to compare single bolus dose under the same conditions. Although we could not confirm this with measurements of plasma esmolol level, esmolol is quickly degraded in plasma through the hydrolysis of ester linkages, and we believe this is the reason for the ineffectiveness of esmolol in prevention of haemodynamic responses to LTI.

The secondary objective of our study was to research the effects of esmolol on serum PTH and calcium levels after LTI. We found increases of up to 1.5 to 2 times the normal serum PTH levels after the endotracheal intubation. Even if it was not statistically significant, this increase was lower in the patients who received esmolol infusion compared to the other two groups. We detected that the significant but clinically insignificant decreases occurred simultaneously in calcium levels. We obtained similar results with the limited number of studies, carried out on this subject (6,7,19).

Mahajna et al.(6) showed that significant increases occurred in PTH levels five minutes after intubation from (51±28 pg/ml to 89±35 pg/ml). In another study, it was reported that there were higher increases in PTH levels in the patients who underwent endotracheal intubation compared to patients who had laryngeal mask, and peak values were reached within six minutes(7). This increase in PTH levels, and accordingly the decrease in the calcium level, were considered to be based upon the increase in endogenous catecholamine secretion due to LTI. Although we did not encounter any study in which both catecholamine and PTH levels were measured in the plasma after intubation, it has been shown that exogenous epinephrine infusion led to temporary increase in PTH levels in normal healthy individuals(19). This increase is lower in individuals who take β blocker treatment(7,19).

Conclusion

In conclusion, 1.5 mg/kg esmolol administered as both single bolus and through infusion two minutes before laryngoscopy is insufficient in preventing pressor responses and PTH response which develop after LTI. However, while single bolus dose provided decrease in tachycardiac responses, esmolol was ineffective when applied through infusion. We found a 1.5 to 2 times increase in PTH levels, and simultaneously a significant but clinically insignificant decrease in calcium levels after intubation with and without esmolol.

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