RESEARCH ARTICLE

# Evaluation of Prophylactic Injection of Two Doses of Tramadol on the Heart Rate and Blood Pressure Changes after Laryngoscopy and Tracheal Intubation

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**Background:** Laryngoscopy is an invasive technique that is associated with severe cardiovascular complications. This study was designed to compare the preventing effect of two doses tramadol injection on the heart rate and blood pressure changes after laryngoscopy and tracheal intubation in elective surgical patients.

**Methods:** In this clinical trial study, 189 elective surgical patients randomly divided to three groups: Group A and Group B, received tramadol 1mg/kg, 2mg/kg iv 5 minutes before induction of anesthesia respectively; Group C, received normal saline. The heart rate(HR), systolic blood pressure(SBP), diastolic blood pressure(DBP) and mean arterial pressure(MAP) were measured just before induction of anesthesia, just before laryngoscopy, at 1, 3, 5, 10 minutes after laryngoscopy and tracheal intubation.

**Results:** Mean HR, SBP, DBP and MAP changes at 1, 3, 5, 10 minutes after laryngoscopy was significantly less in Group B, compared with Group A and Group C($P<0.05$). The incidence of tachycardia (6.3% vs. 19% and 28.6% respectively) and hypertension (4.8% vs. 15.9% and 22.2% respectively) was significantly less in Group B compared with Group A and C ($P < 0.05$).

**Conclusion:** Administration of tramadol with dosage of 2mg/kg iv 5 minutes before induction of anesthesia, significantly attenuated blood pressure and heart rate changes till 10 minutes after laryngoscopy and endotracheal intubation compared with using tramadol 1mg/kg iv.

**Keywords:** tramadol; laryngoscopy; cardiovascular complications

The laryngoscopy and tracheal intubation causes sympathetic and parasympathetic stimulation. Consequently, it increase heart rate and blood pressure after laryngoscopy. Hypertension, tachycardia, bradycardia and cardiac arrest are common complications of laryngoscopy [1]. Laryngoscopy causes hypertension, tachycardia and ST-T changes in old age group. Another complication of laryngoscopy is increase intracranial pressure and consequently intracranial hemorrhage [2]. Many drugs have been used for attenuation of sympathetic stimulation following laryngoscopy such as gabapentin, beta blockers, vasodilators, calcium channel blockers [3], magnesium sulfate [4], propofol, midazolam [5], spraying of lidocaine 10% [6] and opioids [7-8].

Tramadol hydrochloride is an analgesic drug which has very weak agonist activity at μ receptor. Tramadol has two different opioid and non-opioid effects [9]. Likewise, it inhibits the reuptake of serotonin and norepinephrine in neuron terminals [10]. In human body, tramadol converts to O-desmethyltramadol that is more potent than tramadol [11]. Tramadol is agonist of nicotinic and muscarinic receptors (types I and II) [12] and antagonist of glutamate receptors. It has 75% bioavailability and a 4-6 hours half-life. It alleviates the muscle spasms and prescribed in moderate to severe non malignancy pains, neuropathic pains and Fibromyalgia [13-14].

In a previous study it was shown that adding tramadol 2mg/kg iv to sevoflurane significantly attenuated chronotropic response to the laryngoscopy and tracheal intubation [15]. Due to low sample size in this study, the authors couldn't show the effect of tramadol on blood pressure changes after laryngoscopy. So, we designed the present study with larger sample size to investigate the effect of two different doses of tramadol (1mg/kg and 2mg/kg) on heart rate and blood pressure changes after laryngoscopy and endotracheal intubation.

## Methods

After obtaining institutional approval from the Ethics' Committee of University and taking written informed consent from the patients, this randomized double blinded clinical trial study was performed at a university hospital throughout September 2014 to December 2015. One

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hundred eighty-nine ASA I-II patients, aged 18-65 years who were candidated for surgery under general anesthesia requiring laryngoscopy and endotracheal intubation were included in this study. If there was changing in technique of anesthesia or laryngoscopy time exceeded more than 15 seconds, the patients were excluded from the study.

The included patients were randomized into three groups by using random allocation software. Group A (n =63) received tramadol 1mg/kg iv; Group B (n= 63) received tramadol 2mg/kg iv; Group C (n = 63) received normal saline. The study drugs were administrated 5 minutes before induction of anesthesia. The preparation of the study drug was done by anesthesia registered nurse in a similar syringe with respect to the shape and volume. The collection of data was performed by a physician who was not involved in preparation and administration of study drug.

After arrival of the patient in the operating room, demographic data included age, sex, weight and height were recorded. After that, the patient was transferred to the operating bed and noninvasing monitoring included heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), electrocardiogram (ECG) and oxygen saturation of arterial blood (SpO2) were performed.

The induction of anesthesia was done by using sodium thiopental 5 mg/kg iv, fentanyl 2 µg/kg iv and atracurium 0.6 mg/kg for facilitation of tracheal intubation. Anesthesia was maintained by using isoflourane 1.25% and N2O 50% in Oxygen. Morphine 0.1 mg/kg iv was administered for analgesia during the operation.

The laryngoscopy was done by an anesthesiologist with 15 years experience. The grading of laryngoscopy was done by using Cormack-Lehane score [16]. The time from beginning of laryngoscopy till filling of tracheal cuff with air was considered as duration of laryngoscopy. Hemodynamic parameters including HR, SBP, DBP, MAP and SpO2 of the patients were collected at baseline (before induction of anesthesia), just before laryngoscopy, at 1, 3, 5 and 10 minutes after laryngoscopy. If the patients developed bradycardia (HR < 60 bmp), tachycardia (HR > 100 bpm), hypotension (SBP < 90 mmHg) or hypertension (SBP > 140 mmHg and DBP > 90 mmHg), they were recorded.

The analysis of data was performed by using SPSS (version 22). The qualitative data including sex, ASA, grade of laryngoscopy were analyzed with using Chi-Square test. The quantitative data including age, weight, height, duration of laryngoscopy were analyzed by using ANOVA. The HR, SBP, DBP, MAP and SpO2 at different time intervals were analyzed by using repeated measure analysis of variance. P < 0.05 was considered as significant.

## Results

One hundred eighty-one patients were enrolled into the study. The flow diagram of randomized patients is shown in (Figure 1). There were no statistically significant differences between the three groups in terms of demographic characteristics of the patients, grading and duration of laryngoscopy (P> 0.05) (Table 1). The HR changes were significantly different between three groups at 1, 3, 5 and 10 minutes after laryngoscopy (P< 0.05). This variable was significantly less in Group B than Group A and Group C (P< 0.05) (Table 2). There was no significant difference between Group A and Group C in this respect (P> 0.05).

The SBP changes were significantly different between three groups at 1, 3, 5 and 10 minutes after laryngoscopy (P< 0.05). This variable was significantly less in Group B than Group A and Group C (P< 0.05) (Table 3). There was no significant difference between Group A and Group C in this respect (P> 0.05). The DBP changes was significantly different between three groups at 1, 3, 5 and 10 minutes after laryngoscopy (P< 0.05). This variable was significantly less in Group B than Group A and Group C (P< 0.05) (Table 4). There was no significant difference between Group A and Group C in this respect (P> 0.05).

The MAP changes were significantly different between three groups at 1, 3, 5 and 10 minutes after laryngoscopy (P< 0.05). This variable was significantly less in Group B than Group A and Group C (P< 0.05) (Table 5). There was no significant difference between Group A and Group C in this respect (P> 0.05). The incidence of hypertension and tachycardia was significantly less in Group B than Group A and Group C (P< 0.05) (Table 6). There was no significant difference between Group A and Group C in this respect (P> 0.05). The incidence of hypotension and bradycardia was not significantly different between three groups (P> 0.05) (Table 6).

**Table 1- Demographic Data of the patients in three groups**

| Variable | | Group A (n = 63) | Group B (n = 63) | Group C (n = 63) | P value |
|---|---|---|---|---|---|
| Age (years) | | 39.9 ± 12.5 | 41.1 ± 11.5 | 38.9 ± 11.8 | 0.576 |
| | Male | 38 (60.3) | 34 (53.9) | 35 (55.5) | 0.756 |
| Sex | Female | 25 | 29 | 28 | |
| Laryngoscopy grade | I | 41 | 34 | 42 | 0.630 |
| | II | 20 | 26 | 19 | |
| | III | 2 | 3 | 2 | |
| Duration of laryngoscopy(Second) | | 1.5±7.52 | 1.6±7.40 | 1.6±7.44 | 0.902 |
| Weight(Kg) | | 7.2±70.59 | 7.6±69.65 | 8.3±68.10 | 0.191 |
| Height(Cm) | | 9.9±170.22 | 9.3±171.67 | 7.8±169.90 | 0.510 |

Data are presented as mean ± SD or numbers (%). Group A and Group B, received tramadol 1mg/kg, 2mg/kg iv 5 minutes before induction of anesthesia respectively; Group C, received normal saline.

**Figure 1- Flow diagram of randomized patients.**

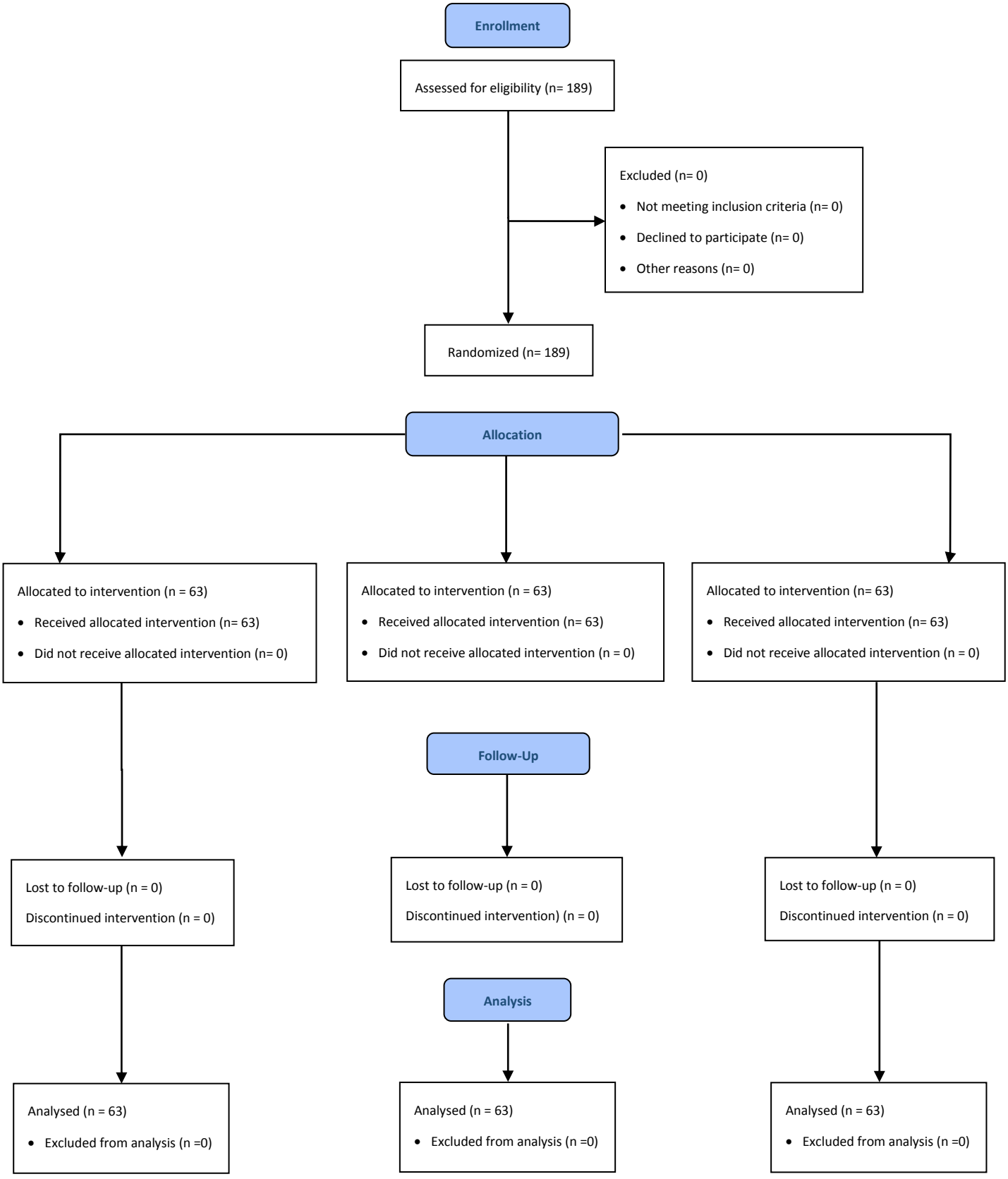

**Table 2- Heart rate changes at different time intervals in three groups**

| Timing of measurement / HR (BPM) | Group A (n = 63) | Group B (n = 63) | Group C (n = 63) | P value |
|---|---|---|---|---|
| Before anesthesia | 74.7±8.2 | 76.4±8.1 | 78.0±9 | |
| Before laryngoscopy | 83.7±3.4 | 85.4±7 | 84.6±7.9 | 0.298 |
| T-1 | 95.1±3.2 | 88.6±3.3* | 94.4±6.1 | 0.000 |
| T-3 | 93.0±3.3 | 87.2±4* | 93.4±5.6 | 0.000 |
| T-5 | 87.6±3.1 | 82.8±4.4* | 87.9±3.3 | 0.000 |
| T-10 | 80.4±3.2 | 76.3±4.6* | 81.7±4.3 | 0.000 |

Data are presented as mean ± SD. Group A and Group B, received tramadol 1mg/kg, 2mg/kg iv 5 minutes before induction of anesthesia respectively; Group C, received normal saline. HR = heart rate; BPM = beat per minute. *P < 0.05 vs. Group A and Group C. There was no significant difference between Group A and Group C.

**Table 3- Systolic blood pressure changes at different time intervals in three groups**

| Timing of measurement / SBP (mmHg) | Group A (n = 63) | Group B (n = 63) | Group C (n = 63) | P value |
|---|---|---|---|---|
| Before anesthesia | 121.6±15.5 | 120.2±10.3 | 118.1±10.3 | 0.289 |
| Before laryngoscopy | 120.9±16.3 | 117.9±17.6 | 118.7±15.8 | 0.562 |
| T-1 | 133.9±7.6 | 128.3±14.2* | 134.3±14.2 | 0.011 |
| T-3 | 131.5±6.9 | 126.8±7.4* | 130.3±7.4 | 0.001 |
| T-5 | 128.2±7.5 | 124.7±7.1* | 127.8±7.2 | 0.013 |
| T-10 | 124.6±6.7 | 120.8±6.6* | 124.3±6.8 | 0.002 |

Data are presented as mean ± SD. Group A and Group B, received tramadol 1mg/kg, 2mg/kg iv 5 minutes before induction of anesthesia respectively; Group C, received normal saline. SBP = systolic blood pressure. * P < 0.05 vs. Group A and Group C. There was no significant difference between Group A and Group C.

**Table 4- Diastolic blood pressure changes at different time intervals in three groups**

| Timing of measurement / DBP (mmHg) | Group A (n = 63) | Group B (n = 63) | Group C (n = 63) | P value |
|---|---|---|---|---|
| Before anesthesia | 78.9±10 | 80.9±9.4 | 80.10±9.6 | 0.489 |
| Before laryngoscopy | 75.6±11.1 | 77.1±11.4 | 77.04±11.8 | 0.730 |
| T-1 | 83.5±9.2 | 78.9±8.8* | 83.8±9.3 | 0.003 |
| T-3 | 82.9±9.5 | 77.2±9.3* | 81.3±9.7 | 0.003 |
| T-5 | 81.2±9.7 | 76.6±9.6* | 80.8±9.4 | 0.013 |
| T-10 | 80.9±9.6 | 76.5±9.6* | 81.3±9.7 | 0.009 |

Data are presented as mean ± SD. Group A and Group B, received tramadol 1mg/kg, 2mg/kg iv 5 minutes before induction of anesthesia respectively; Group C, received normal saline. DBP = diastolic blood pressure. * P < 0.05 vs. Group A and Group C. There was no significant difference between Group A and Group C.

**Table 5- Mean arterial pressure changes at different time intervals in three groups**

| Timing of measurement / MAP (mmHg) | Group A (n = 63) | Group B (n = 63) | Group C (n = 63) | P value |
|---|---|---|---|---|
| Before anesthesia | 93.1 ±8.5 | 94.0 ±6.6 | 92.8±6.8 | 0.623 |
| Before laryngoscopy | 90.7 ±10.6 | 90.6±7.5 | 90.9 ±10.6 | 0.987 |
| T-1 | 100.4 ±6.5 | 96.0 ±7.4* | 100.6 ±7.2 | 0.000 |
| T-3 | 99.0±6.3 | 94.4 ±6.5* | 97.7 ±6.3 | 0.000 |
| T-5 | 96.6±7.1 | 92.6 ±6.7* | 96.5 ±6.2 | 0.001 |
| T-10 | 95.5 ±6.8 | 91.6 ±6.6* | 94.9±7.1 | 0.003 |

Data are presented as mean ± SD. Group A and Group B, received tramadol 1mg/kg, 2mg/kg iv 5 minutes before induction of anesthesia respectively; Group C, received normal saline. MAP = mean arterial pressure. * P < 0.05 vs. Group A and Group C. There was no significant difference between Group A and Group C.

**Table 6- The incidence of hypertension, hypotension, tachycardia and bradycardia in three groups**

| Variable | Group A (n = 63) | Group B (n = 63) | Group C (n = 63) | P value |
|---|---|---|---|---|
| Hypertension | 10 (15.9%) | 3 (4.8 %)* | 14 (22.2 %) | 0.018 |
| Tachycardia | 12 (19.0 %) | 4 (6.3 %)* | 18 (28.6 %) | 0.005 |
| Hypotension | 2 (3.2 %) | 3 (4.8 %) | 2 (3.2 %) | 0.862 |
| Bradycardia | 1 (1.6 %) | 2 (3.2 %) | 1 (1.6 %) | 0.775 |

Data are presented as numbers (%). Group A and Group B, received tramadol 1mg/kg, 2mg/kg iv 5 minutes before induction of anesthesia respectively; Group C, received normal saline. * P < 0.05 vs. Group A and Group C. There was no significant difference between Group A and Group C.

## Discussion

Opioids are used before and during the anesthesia. Opioids decrease the threshold of excitation on cardiac receptors. As a result it decreases the cardiac output, systolic and diastolic blood pressure. Many studies have shown that opioids are useful in attenuating the hemodynamic changes during laryngoscopy [17]. Tramadol is a kind of analgesic with central effect which is structurally like codeine and morphine. It has a methyl component which gives the adhesion characteristic to drug in order to bind to μ receptors more effectively. Tramadol has two active optical isomers. Through monoaminergic pathway, the analgesic features of tramadol influences the central nervous system (CNS). Tramadol inhibits epinephrine reuptake in alpha 2 adrenergic receptors. Also it was shown that tramadol inhibits reuptake of serotonin in CNS [18].

The analgesic potency of tramadol is one tenth of its metabolite, des methyl tramadol. Tramadol is a weak agonist of opioid receptors. The analgesic effects of tramadol can be one of the reasons for its role to reduce the adverse effects of laryngoscopy. Many analgesic effects of tramadol could be due to interaction between tramadol and specific inner peptide receptors in CNS and peripheral organs. Many of these inner peptides are beta endorphin which are produced in perikaryon and after that stored in the terminal related neuron [19].

Tramadol reduces the pain by indirect effect on pain modulator neurons in midbrain, medulla oblongata and locus coeruleus. This effect can be due to inhibitory effect on posterior spinal cord horn [20]. The chemical structure of tramadol contains a positively charged nitrogen which is connected to a lipophilic ring with a few carbon atoms distance apart [21]. This kind of structure leads to local anesthetic effects and nervous conduction block. In our study the best control of hypertension and tachycardia was in Group B. Group A and Group C had significant rise in BP and HR after laryngoscopy. Regarding HR changes, Group B showed the best decrease in HR at 1, 3, 5, 10 minutes after laryngoscopy and tracheal intubation. SBP, DBP and MAP changes after laryngoscopy were significantly less in Group B in comparison with Group A and Group C. The number of patients who developed tachycardia and hypertension were significantly less in Group B in comparison with the other two groups.

In a study to evaluate the attenuating effect of tramadol 2 mg/kg on the pressor responses after laryngoscopy and tracheal intubation, Huda et al. [15] showed that addition of tramadol to the 1 MAC sevoflurane decreased further the chronotropic response to the laryngoscopy compared with using sevoflurane alone. Their study didn't show the attenuating effect of tramadol 2 mg/kg on blood pressure changes. It is assumed that low sample size (17 patients in each group) could be the reason for this conclusion. In our study, the sample size was 63 patients in each group. Using higher sample size in our investigation can be the reason for the difference between the results of our study with that of Huda et al.

We didn't measure the plasma concentration of tramadol

in our patients. It is recommended to design future studies in this respect. This point was the limitation of our study. In conclusion, our study showed that using tramadol 2 mg/kg 5 minutes before induction of anesthesia attenuated the inotropic and chronotropic response after laryngoscopy and tracheal intubation better than using tramadol 1 mg/kg without significant adverse effect.

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