Abstract
Aim: Little is known about whether one of these agents has superiority over the other in attenuating hemodynamic responses associated with tracheal intubation. This paper aims to compare the effects of intravenous injection of low-dose esmolol, magnesium sulfate, and placebo on hemodynamic responses associated with endotracheal intubation.

Material and Methods: Sixty patients receiving elective spine surgery were randomized into three groups: esmolol group (E; 0.2 mg/kg bolus, 3 mg/kg/h infusion thereafter), magnesium sulfate group (M; 30 mg/kg bolus, 10 mg/kg/h infusion thereafter), or control (placebo) group (C). Heart rate (HR), mean arterial pressure (MAP), and systolic (SBP), and diastolic blood pressure (DBP) were recorded at baseline, after induction, intubation, prone positioning, skin incision, supine positioning, and at recovery. Differences in HR, MAP, SBP, and DBP in the three groups during anesthesia and recovery were the most important result of this work.

Results: HR, MAP, SBP, and DBP were similar in all groups following endotracheal intubation. Hypotension occurred in three patients in group M at the end of anesthesia when they were repositioned to the supine position. On the other hand, neither group E nor group C experienced hypotension (p=0.043). Bradycardia (HR < 50 bets/min) was observed in six patients in group M, in four patients in group E, and one patient in group C when the patients were placed in the prone position (p=0.043).

Discussion: Our findings show that 30 mg/kg magnesium sulfate and 0.2 mg/kg esmolol boluses and infusions (30 mg/kg bolus and 10 mg/kg/h, respectively) were not more effective than placebo in the prevention of the hemodynamic variations after endotracheal intubation. Higher magnesium sulfate and esmolol doses may blunt elevated heart rate and blood pressure following endotracheal intubation.

Keywords
Laryngoscopy; Endotracheal intubation; Esmolol; Magnesium sulfate
Introduction
Spine surgery is increasingly being performed for the management of symptomatic nerve stem and cord compression. Although congenital, oncologic, traumatic, degenerative, and infectious causes may be associated with nerve stem and spinal cord compression, the most common indication for spinal surgery is lumbar disc herniation [1].

Anesthesia aims to maintain adequate oxygenation of the brain and spinal cord while ensuring a stable hemodynamic profile during the surgical procedure. Controlling pain and muscle relaxation may complicate hemodynamic stability during induction, laryngoscopy, endotracheal intubation, prone positioning, skin incision, supine positioning, and extubation [2]. However, tachycardia, rise in blood pressure, and premature ventricular systole may further deteriorate heart rhythm and blood pressure, particularly in heart failure and ischemic heart disease, which may be encountered due to the sympathetic hyperactivity occurring during laryngoscopy, endotracheal intubation [3]. Blockage of sensory receptors and afferent nerves by local anesthetic agents, inhibition of central effects of the pain through opioids, suppression of efferent pathways by local anesthetic agents such as (e.g., lidocaine) beta-blockers, sympathetic ganglion blockers, and calcium channel blockers are utilized to prevent the development of unfavorable hemodynamic variations induced by the sympathetic hyperactivity occurring during endotracheal intubation [4, 5].

Esmolol, a short-acting beta-blocker, has been shown to attenuate hemodynamic variations after tracheal intubation in hypertensive patients [6]. Magnesium sulfate is another agent used to prevent the adrenal medulla and adrenergic nerve endings secreting catecholamines to inhibit blood pressure changes during tracheal intubation [7]. Magnesium sulfate also has vasodilator properties through blocking the calcium ion in vascular smooth muscle [8]. Although both agents have been reported to have mechanisms that attenuate the hemodynamic responses occurring during tracheal intubation, little is known about whether one of these agents has superiority over the other in minimizing the hemodynamic responses occurring during tracheal intubation.

This work aimed to compare the effects of intravenous administration of low-dose esmolol, magnesium sulfate, and placebo on hemodynamic responses associated with endotracheal intubation.

Material and Methods
Patient selection
This randomized, prospective, placebo-controlled study enrolled all consecutive patients planned to undergo elective spine surgery. The inclusion criteria included patients aged 18 years or older, and class I and II patients according to the American Society of Anesthesiologists (ASA). The exclusion criteria were as follows: administration of beta-blocker agents within the last week, Glasgow Coma Scale score of <14, body mass index of >30 kg/m2, 2nd or 3rd-degree atrioventricular block, advanced cardiac failure, coronary heart disease, chronic lung disease, systolic and diastolic blood pressure of >180/100 mmHg or <90/60 mmHg, advanced liver or kidney disease, and pregnancy. Eighty subjects were eligible for the study. Twenty subjects were excluded since they met at least one of the exclusion criteria. Remaining 60 patients were randomized into three groups as follows: Esmolol group (E) (n=20), Magnesium sulfate group (M) (n=20), Control group (C) (n=20). All participants gave their written informed consent. Before the study, approval was obtained from the local ethics committee. The study was carried out in compliance with the ethical principles specified in the Declaration of Helsinki.

Anesthesia
All patients arrived to the operating room following eight hours of fasting. A standardized general anesthesia procedure was applied to all patients. Midazolam (0.03 mg/kg) and 0.01mg/kg of atropine sulfate were administered intravenously as a premedication. Electrocardiogram, non-invasive BP measurements, and monitoring of peripheral oxygen saturation (SaO2) were performed with pulse oximetry throughout the surgery. End-tidal CO2 (EtCO2) was recorded following the induction of anesthesia. The numeric Rating Scale (NRS) (where 0 indicates no pain and 10 indicates worst possible pain) was used to monitor pain. A modified Ramsay Sedation Scale (mRSS) was used to monitor the degree of sedation. Loading doses of the study drugs were administered before the induction of anesthesia by an anesthesia team blinded to the study subject (For group E: esmolol 0.2 mg/kg, diluted with 20 mL saline applied in one minute; for group M: MgSO4 30 mg/kg, diluted with 20 mL saline applied in one minute; for group C: 20 ml of saline applied in one minute). Study drugs were then infused throughout the surgery (3 mg/kg/h of esmolol for group E, 10 mg/kg/h of MgSO4 for group M, and 20 ml/h of saline for group C).

Midazolam (0.01 mg/kg), 1 mcg/kg fentanyl, 5 mg/kg iv sodium thiopental and 0.15 mg/kg cisatracurium were administered intravenously for general anesthesia. Maintenance of anesthesia was provided using 4% desflurane, 40% nitrous oxide and 60% oxygen. Patients received ventilation at a tidal volume of 7–9 ml/kg. Also, all patients received diclofenac sodium at a dose of 75 mg intramuscularly 30 minutes before the completion of the surgery.

Primary outcome
HR, MAP, SBP,DBP and SaO2 were monitored at the following time points:
T0: Baseline value before drug administration
T1: in the fifth minute after bolus drug administration
T2-1: in the first minute after induction, T2-3: in the third minute after induction, T2-5: in the fifth minute after induction
T3-1: in the first minute after endotracheal intubation, T3-3: in the third minute after endotracheal intubation
T4-1: Prone position in the first minute, T4-3: Prone position in the third minute
T5-1: in the first minute following skin incision, T5-5: in the fifth minute following skin incision
T6-30: 30 minutes following skin incision, T6-60: 60 minutes following skin incision, T6-90: in the 90th minute following skin incision, T 6-120: in the 120th minute following skin incision
T7: End of operation
T8: In supine position and when anesthesia ends
T9-1: in the first minute after extubation, T9-5: in the fifth minute after extubation
Hemodynamic responses associated with endotracheal intubation

T10: Exit from the room
T11: Leaving the recovery unit (when the Aldrete Recovery Score is ≥ 9 points)

Differences in HR, MAP, SBP, and DBP in groups throughout the anesthesia and recovery were the primary outcome measure of this study.

Statistical analysis

The IBM SPSS 20.0 software (SPSS Inc., Armonk, NY, USA) was used for statistical analyses. The Shapiro-Wilk test was used to check the normality. Continuous variables are described using means (±) and standard deviations (SD), while categorical variables are described using numbers and percentages. Continuous variables were compared using the ANOVA test (Tukey’s Honest Significant Difference [HSD] was performed for post-hoc analyses). Variance analysis was used to compare intra-group variances (a paired samples t-test was used for posthoc analyses). Pearson’s chi-squared test was performed to compare categorical variables. Statistical significance was set at p<0.05.

Results

A total of 60 subjects (mean age 42.9 ± 11.6 years, 43.3% males) were included in the study. A comparison of the demographic characteristics of the study groups is presented in Table 1. Age, distribution of genders, body mass index, anesthesia time, operation time, and ASA class were similar.

The variations in SBP from T0 to T11 are listed in Figure 1. SBP was lower in patients receiving MgSO4 than in those receiving esmolol five minutes after induction (T2-5) and before leaving the recovery room (p=0.021, p=0.016, respectively).

The variations in DBP from T0 to T11 are listed in Figure 2. DBP was lower in patients receiving MgSO4 than in control subjects one minute after induction (T2-1) (p=0.019). DBP was lower in patients receiving MgSO4 and subjects receiving esmolol than in control subjects when the patients were repositioned to the supine position (T8) (p=0.035).

The variations in MAP from T0 to T11 are listed in Figure 3. MAP was lower in patients receiving MgSO4 than in control subjects one minute after induction (T2-1) (p=0.028) and when the patients were repositioned to the supine position (T8) (p=0.028). The MAP of the patients receiving MgSO4 was also lower than that of the subjects receiving esmolol five minutes after induction (T2-5) (p=0.046).

The variations in HR from T0 to T11 are listed in Figure 4.

<table>
<thead>
<tr>
<th>Table 1. Patients’ General Characteristics and Intraoperative Data</th>
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<tr>
<td><strong>Group E</strong></td>
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<tr>
<td>Age (y±SD)</td>
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<td>Gender (M/F)</td>
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<td>ASA I/II (n)</td>
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<td>Operation time (min)</td>
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<td>Anesthesia time (min)</td>
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Data of patients are expressed as numbers, mean ± standard deviation. BMI; body mass index. ASA; American Society of Anesthesiologists. M; Male, F; Female
Patients receiving esmolol had considerably lower HR than those receiving MgSO4 and controls five minutes after the loading dose (p<0.001 and p=0.002, respectively) and one minute following the induction of anesthesia (p=0.001 and p=0.003, respectively).

SaO2 was significantly higher in subjects receiving MgSO4 than in those receiving esmolol (p=0.014). EtCO2 was significantly higher in subjects receiving MgSO4 than in controls one minute after endotracheal intubation (p=0.033).

Hypotension (drop in SBP < 90 mmHg or > 30 mmHg reduction in SBP compared to baseline) occurred in three patients in group M at the end of the anesthesia when the patients were repositioned to the supine position. On the other hand, neither group E nor group C patients experienced hypotension (p=0.043). Bradycardia (HR < 50 bets/min) was observed in six patients in group M, in four patients in group E, and one patient in group C when the patients were placed in the prone position (p=0.043).

**Discussion**

This work was undertaken to compare esmolol and magnesium sulfate effects on hemodynamic responses during endotracheal intubation. We found that endotracheal intubation was associated with an increase in HR, SBP, DBP, and MAP. In the study, subjects receiving esmolol or magnesium sulfate gave hemodynamic responses to endotracheal intubation similar to those of control group subjects. However, SBP, DBP, and MAP were lower in subjects receiving magnesium sulfate than in those receiving esmolol during the induction phase. On the other hand, esmolol was associated with a lower heart rate during the induction phase than magnesium sulfate. Besides those receiving esmolol or control subjects, patients receiving magnesium sulfate were increasingly vulnerable to hypotension when repositioned to the supine position.

It has been shown that airway manipulation during laryngoscopy and endotracheal intubation leads to reflex sympathetic activity, characterized primarily by systemic arterial hypertension and tachycardia [9, 10]. Manipulations of the pharynx and larynx have been shown to correlate with an increase in plasma epinephrine and norepinephrine concentrations [11]. Hemodynamic variations during laryngoscopy and endotracheal intubation are transient and do not significantly affect healthy individuals. However, they may induce ischemia in patients with coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease, and may induce intracranial hemorrhage [7]. Therefore, inhibition of this transient increase in arterial pressure and pulse rate may prevent further complications in hypertension, CAD, and PAD patients, as well as in those with a history of intracranial hemorrhage.

Several agents have been administered to blunt the hemodynamic reactions occurring during laryngoscopy and endotracheal intubation. Beta-blockers, calcium channel blockers, Na nitroprusside, nitroglycerine, alpha agonists, vasodilators, fentanyl, and lidocaine have traditionally been used to prevent unfavorable hemodynamic responses occurring during endotracheal intubation [12]. Esmolol and magnesium sulfate have also been used at varying doses to inhibit hypertension and tachycardia during intubation.

Esmolol is a short-acting, cardio-selective beta-blocker used to manage hypertensive emergencies and supraventricular tachyarrhythmias [13]. Extensive data indicate that esmolol can blunt hemodynamic responses associated with endotracheal intubation. One of the earliest trials with esmolol was a Canadian multicentre trial, which found that 100 and 200 mg of esmolol effectively suppressed the increase in SBP during intubation [14]. Levitt et al., in their study, examined the effects of esmolol 2 mg/kg and lidocaine 2 mg/kg on intubated patients with isolated head injury, and reported that esmolol and lidocaine had similar efficacy in blunting the hemodynamic response to intubation in this patient population [15]. Another study by Uğur et al. compared esmolol 1.5 mg/kg, lidocaine 1.5 mg/kg, and fentanyl 1 µg/kg boluses in 120 ASA class I-and II patients [16]. The authors reported that hemodynamic responses occurring during endotracheal intubation were more effectively prevented with esmolol bolus than with lidocaine and fentanyl. Gogus et al. aimed to compare the effects of 1 µg/kg dexmedetomidine (infusion in 10 min) and 2 µg/kg fentanyl and 2 mg/kg esmolol boluses on attenuating the hemodynamic response to endotracheal intubation. The authors found that dexmedetomidine was superior to fentanyl and esmolol in preventing tachycardia and that esmolol prevented the increase in SBP, DBP, and MAP following intubation [17]. Selvaraj et al. compared dexmedetomidine 1 µg/kg (infusion in 10 min) and esmolol 0.5 mg/kg iv. bolus to prevent the hemodynamic response to laryngoscopy and endotracheal intubation. The authors reported that dexmedetomidine infusion was superior to esmolol bolus in preventing the increase in HR, SBP, and MAP following intubation [18]. More recently, Sharma et al. reported that dexmedetomidine 1 µg/kg (infusion in 10 min) was superior to esmolol 1.5 mg/kg (infusion in 10 min) in maintaining hemodynamic stability following endotracheal intubation [19].

Magnesium sulfate, another agent, used to blunt hemodynamic responses occurring during endotracheal intubation, blocks the release of catecholamines by the adrenal medulla and has a systemic and coronary vasodilator effect by antagonizing calcium ion in vascular smooth muscle [20]. Magnesium has also been shown to cause central nervous system depression by acting as an antagonist of N-methyl-D-aspartate (NMDA) receptors [21]. Panda et al. reported that 30 mg/kg bolus of magnesium sulfate could optimally control BP during intubation in hypertensive patients [7]. Nooraei et al. showed that 60 mg/kg of magnesium sulfate bolus was more effective than 60 mg/kg of lidocaine bolus in controlling blood pressure following endotracheal intubation [22]. In a study on patients undergoing elective coronary artery bypass grafting surgery, Kiae et al. used lidocaine (1.5 mg/kg) and magnesium sulfate (50 mg/kg within five minutes) to explore their impact on hemodynamic responses during endotracheal intubation. The authors found that lidocaine produced a more considerable decrease in blood pressure than magnesium sulfate [23]. Recently, Mendonca et al. reported that lidocaine 2 mg/kg and magnesium sulfate 30 mg/kg (both infused over 10 minutes) yielded similar results in preventing the hemodynamic responses occurring during endotracheal intubation [21]. Although both esmolol and magnesium sulfate have shown favorable outcomes in preventing the hemodynamic variations...
following endotracheal intubation, few data have been reported regarding the superiority of one agent over the other. Kumar et al. compared magnesium sulfate 60 mg/kg bolus, esmolol 2 mg/kg bolus, and diltiazem 0.2 mg/kg bolus and found that esmolol was the most effective of the three agents in preventing the rise in HR and BP following endotracheal intubation [24]. David et al. administered magnesium sulfate 50 mg/kg bolus and esmolol 1.5 mg/kg bolus to subjects undergoing elective ENT surgeries. The authors reported that esmolol was superior to magnesium sulfate in reducing HR, MAP, SVP, and DBP following endotracheal intubation [25]. Kumar et al. compared magnesium sulfate 60 mg/kg bolus, esmolol 2 mg/kg bolus, and diltiazem 0.2 mg/kg bolus and found that esmolol was the most effective of the three agents in preventing increases in HR and BP following endotracheal intubation. Verma et al. compared magnesium sulfate and esmolol in patients undergoing valvular heart surgery. The authors reported that esmolol 1.5 mg/kg was superior to magnesium sulfate 50 mg/kg iv. (both infused over five minutes) in minimizing hemodynamic responses occurring during endotracheal intubation. Recently, Machado et al. studied the efficacy of esmolol 1.5 mg/kg and magnesium sulfate 30 mg/kg and found that esmolol was more effective than magnesium sulfate in blunting the hypertensive response to intubation, but with more frequent hypotension [8].

Our findings show that 30 mg/kg magnesium sulfate and 0.2 mg/kg esmolol boluses and infusions (30 mg/kg bolus and 10 mg/kg/h, respectively) were not more effective than placebo in preventing hemodynamic variations after endotracheal intubation. Esmolol and magnesium sulfate doses used in our study were much lower than those used in previous studies. With this in mind, we believe that magnesium sulfate 50 mg/kg and esmolol 0.2 mg/kg do not significantly impact HR and BP following endotracheal intubation compared to placebo. According to the previous evidence of the favorable effect of the two drugs on hemodynamic responses after intubation, we suggest that the administration of magnesium sulfate and esmolol at higher doses is necessary to attenuate the increase in BP following endotracheal intubation.

Conclusion
Magnesium sulfate (30 mg/kg) and esmolol (0.2 mg/kg) boluses do not significantly impact HR and BP following endotracheal intubation compared to placebo. Administration of magnesium sulfate and esmolol at higher doses may blunt the increase in BP and HR following endotracheal intubation.

Scientific Responsibility Statement
The authors declare that they are responsible for the article’s scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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