Background: In the present study, we investigated the effect of dexmedetomidine on the intubating conditions and hemodynamic changes during endotracheal intubation following anesthetic induction performed using propofol and remifentanil without a neuromuscular blocking agent.

Methods: We selected 70 adult patients aged 20 to 65 years scheduled to undergo general anesthesia. Induction was performed using 2 mg/kg of propofol and 1.5 μg/kg of remifentanil. The patients were divided into two groups, a dexmedetomidine group (Group D) and a control group (Group C). Group D received an infusion of dexmedetomidine 1 μg/kg for 10 minutes before induction, and Group C received the same volume of normal saline infused in the same manner. Intubating conditions were evaluated and blood pressure and heart rate were recorded at various time points to assess hemodynamic stability.

Results: Intubating conditions were evaluated as excellent for 34 patients and good for 1 patient in Group D, and excellent for 4 patients, good for 20 patients, poor for 4 patients, and bad for 7 patients in Group C (P < 0.001). The heart rate was significantly lower in Group D than in Group C at all measurement times. The mean arterial blood pressure was significantly lower in Group C than in Group D at 10 minutes after dexmedetomidine administration (P = 0.049), after the induction of anesthesia (P < 0.001), immediately after endotracheal intubation (P = 0.008), and 3 minutes after endotracheal intubation (P < 0.001).

Conclusions: Dexmedetomidine 1 μg/kg improved the intubating conditions and stabilized hemodynamic changes following anesthetic induction performed using propofol 2 mg/kg and remifentanil 1.5 μg/kg without a neuromuscular blocking agent. (Anesth Pain Med 2017; 12: 56-61)

Key Words: Dexmedetomidine, Intratracheal, Intubation, Propofol, Remifentanil.

INTRODUCTION

Neuromuscular blocking agents are frequently used to facilitate endotracheal intubation during the induction of anesthesia [1]. However, neuromuscular blockers are associated with prolonged neuromuscular blockade, histamine release, and anticholinesterase-mediated side effects [2-5]. Furthermore, the use of neuromuscular blockers is either avoided or contraindicated in some patients. Therefore administration of a proper induction agent and adjuvant to provide good intubating conditions without the use of a neuromuscular blocker may be an important consideration [2-4].

Propofol and remifentanil (2–4 μg/kg) are known to be able to induce a condition appropriate for endotracheal intubation without a neuromuscular blocking agent [6]. According to a previous study, the effective doses of remifentanil in 50% (ED50) and 95% (ED95) of patients were 1.4 μg/kg and 2.4 μg/kg, respectively, during induction of anesthesia with propofol 2 mg/kg without a neuromuscular blocker [7]. Remifentanil may improve the intubating conditions in a dose-dependent manner, but adverse effects such as hypotension, bradycardia, and muscular stiffness may occur as the dose is increased [6]. If administered with propofol, remifentanil may cause hypotension and bradycardia requiring rescue medication in 50% of patients who receive doses as low as 1 μg/kg [8]. Moreover, bolus injection of a large dose of remifentanil may result in muscle rigidity, which makes
mask ventilation difficult [6]. Thus, doses of over 2 μg/kg of remifentanil, although known to be able to induce a relatively appropriate condition for endotracheal intubation without a neuromuscular blocker, also result in unavoidable adverse effects [6].

Dexmedetomidine, a highly selective α2-adrenoreceptor agonist, has good analgesic and sedative effects [9,10] to decrease the maximum alveolar concentration (MAC) of inhalational anesthetics; for example, it can decrease the MAC of sevoflurane by 17% [11] and decrease the demand for propofol and opioid in total intravenous anesthesia [12,13]. In addition, when used as an adjuvant for induction of anesthesia, dexmedetomidine improves hemodynamic stability by decreasing the hemodynamic changes caused by endotracheal intubation [14]. Furthermore, dexmedetomidine is known to have sedative and airway reflex blunting effects, providing better conditions for awake fiberoptic intubation, awake blind nasotracheal intubation, and laryngeal mask airway placement when used with propofol [15–17].

Thus, when performing endotracheal intubation without a neuromuscular blocker, dexmedetomidine may provide good intubating conditions without the use of a relatively high dose of remifentanil.

In the present study, we investigated the effect of 1 μg/kg dexmedetomidine on the intubating conditions and hemodynamic changes during endotracheal intubation following anesthetic induction performed using propofol 2 mg/kg and remifentanil 1.5 μg/kg without a neuromuscular blocking agent.

**MATERIALS AND METHODS**

The subjects of the present study were adult patients aged between 20 and 65 years, classified as American Society of Anesthesiologists Physical Status 1 or 2, who were scheduled to undergo an operation under general anesthesia. Patients with a history of sensitization to dexmedetomidine, hypertension, left ventricular ejection fraction of 40 or lower, ischemic heart disease, asthma, respiratory diseases, liver or renal function abnormalities, history of heavy alcohol consumption, or history of chronic hypnotic or analgesic use were excluded. Patients whose physical characteristics suggested difficulties in intubation (modified Mallampati score III or IV) and those who had a previously documented failed intubation were also excluded. The study was approved by the Hospital Ethics Committee, and written informed consent was obtained.

All patients were administered midazolam 2 mg and glycopyrrolate 0.2 mg by intramuscular injection and famotidine 20 mg by intravenous injection as premedication 30 minutes before arrival in the operating room. The noninvasive blood pressure, electrocardiogram, peripheral pulse oxygen saturation, end-tidal CO₂, and bispectral index (BIS) measurements of the patients were obtained with standard monitoring. Group D received 1 μg/kg dexmedetomidine (100 μg/ml; Precedex, Hospira Inc., USA) diluted to a total volume of 10 ml and infused over 10 minutes using a calibrated electronic infusion pump (Braun Infusomat, Braun, Germany). Group C received saline solution of equal volume to that of Group D. Preoxygenation was performed for 3 minutes with 5 L/min of 100% oxygen. Anesthesia was induced in an identical manner in both groups using 2 mg/kg propofol and an IV bolus dose of remifentanil 1.5 μg/kg. Tracheal intubation was performed 1 minute after the administration of remifentanil. After consciousness and the lid reflex were lost and the BIS value dropped below 50, endotracheal intubation was performed using a No. 7.5 endotracheal tube for male patients and a No. 7 tube for female patients. For all patients, intubation was performed by the same anesthesiologist, who had not been informed of the drug being used.

The drugs used in the experiments were prepared by nurses of the Department of Anesthesiology and Pain Medicine who did not participate in the present study. A double-blind method was maintained by ensuring that the doctors who were in charge of the anesthesia, the assessment of the endotracheal intubating conditions, and the measurement of vital signs were not cognizant of the study plan or the drugs used.

Based on the criteria developed by Cooper et al. [18] for assessing intubating conditions, the ease of laryngoscopy, the condition of the vocal cords, and the response to endotracheal intubation were evaluated on a four-point scale (0–3), and the total scores were added together to give an overall intubation score for each patient (Tables 1 and 2). A score of 8–9 was considered excellent, 6–7 good, 3–5 poor, and 0–2 bad; scores of good and excellent were considered clinically acceptable. Poor and bad scores were defined as failed intubations. Patients with poor or bad conditions underwent intubation after the administration of rocuronium 0.6 mg/kg. Patients who received rocuronium to facilitate intubation were included in the bad or poor class and were analyzed for every measurement performed in the present study.

After confirmation of a successful endotracheal intubation, the balloon was carefully inflated until the moment when the leaking sound was no longer heard at the neck and the mouth.
The tubing position was fixed with bilateral auscultation of pulmonary sounds. Following the endotracheal intubation, anesthesia was maintained using sevoflurane 1.5-2 vol%, and an oxygen-air mixture (2 L/min:2 L/min). The systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, and heart rate were recorded at baseline, 10 minutes after the administration of dexmedetomidine, immediately after the induction of anesthesia, immediately after the endotracheal intubation, 3 minutes after the intubation, and 5 minutes after the intubation.

Atropine 0.5 mg was prepared for intravenous injection if the heart rate decreased to 45 beats/min or lower, and ephedrine 5 mg was prepared for intravenous injection if the systolic blood pressure decreased to 80 mmHg or lower. Hypertension (≥ 20% baseline for > 1 minute) and tachycardia (≥ 20% baseline for > 1 minute) were managed by injection of nicardipine (2–10 μg/kg/min) or labetalol 5–10 mg.

Based on the assumption of an 80% possibility that the use of dexmedetomidine may improve the endotracheal intubation condition to an excellent level, the number of samples was determined using the Epicalc package of the R statistical software (ver. 3.0.0, The R Foundation for Statistical Computing, Vienna, Austria; Chi-square, effect size 0.35). The alpha error was determined as 0.05, and the power as 0.8 for the calculation. When the same number of samples were allocated to each group, 35 samples were required for each group.

The statistical analysis was performed by using the R software (ver. 3.0.2, The R Foundation for Statistical Computing, Vienna, Austria) for Windows. A Shapiro-Wilk test was performed as the normality test if the data were continuous variables. A parametric test was performed if the data showed a normal distribution. For the parametric test, a test for equality of variance was performed with respect to the two groups. If a group satisfied equality of variance, a two-sample t-test was performed. Otherwise, Welch’s test was performed. When a variable did not show a normal distribution, a non-parametric test was performed. If there was not a tie value, the Wilcoxon rank sum test was performed or, if there were more than two groups, the Kruskal-Wallis test was performed. If there was a tie value, Yuen’s test was performed to compare the 20% trimmed mean. Comparison of the hemodynamic changes between the two groups was tested by performing analysis of covariance (ANCOVA). The significance level (P value) was set at 0.05.

RESULTS

All enrolled patients were included in the analysis. There were no significant differences among age, weight, height, and sex between the two groups (Table 3).

In the classification of endotracheal intubating conditions according to the endotracheal intubation score, the condition was excellent in 4 patients, good in 20 patients, poor in 4 patients, and bad in 7 patients in Group C, while the condition was excellent in 34 patients and good in 1 patient in Group D (P < 0.001), indicating that the endotracheal intubating conditions were significantly better in the group in which dexmedetomidine was used (Table 4). The endotracheal intubation failed in 11 patients in Group C, whereas the endotracheal intubation was successful in all patients in Group D.

Hemodynamic changes for Groups C and D are shown in Figs. 1 and 2. For Group D, compared to the baseline value,
Table 4. Intubating Conditions Classification

|                      | Group C (n = 35) | Group D (n = 35) |
|----------------------|------------------|------------------|
| Excellent            | 4                | 34               |
| Good                 | 20               | 1                |
| Poor                 | 4                | 0                |
| Bad                  | 7                | 0                |

Values are number of patients. $P < 0.001$ between group C and D. Group C: The group injected with 0.9% normal saline. Group D: The group injected with dexmedetomidine 1 $\mu$g/kg.

significant decreases in heart rate were observed at all measurement times. The heart rate was significantly lower in Group D than in Group C at 10 minutes after dexmedetomidine administration ($P < 0.001$), immediately after the induction of anesthesia ($P = 0.007$), immediately after endotracheal intubation ($P = 0.007$), at 3 minutes after endotracheal intubation ($P = 0.002$), and at 5 minutes after endotracheal intubation ($P = 0.014$), indicating that there were significant differences between the groups at all measurement times (Fig. 1).

In Group C, the mean arterial pressure (MAP) was significantly decreased at the times after the induction of anesthesia, immediately after endotracheal intubation, and at 3 and 5 minutes after endotracheal intubation compared to baseline ($P < 0.001$). In Group D, the MAP was significantly decreased only at 5 minutes after endotracheal intubation compared to the baseline value ($P < 0.001$). The MAP was significantly lower in Group C than in Group D at 10 minutes after dexmedetomidine administration ($P = 0.049$), after the induction of anesthesia ($P < 0.001$), immediately after endotracheal intubation ($P = 0.008$), and at 3 minutes after endotracheal intubation ($P < 0.001$) (Fig. 2).

During the induction of anesthesia, ephedrine was administered to two patients in Group C and one patient in Group D at 3 minutes after endotracheal intubation, and atropine was administered to one patient in Group D at 10 minutes after the administration of dexmedetomidine.

**DISCUSSION**

The results of the present study showed that dexmedetomidine 1 $\mu$g/kg improved the intubating conditions and stabilized hemodynamic changes during endotracheal intubation following anesthetic induction performed using propofol 2 mg/kg and remifentanil 1.5 $\mu$g/kg.

The administration of remifentanil together with propofol in the absence of a neuromuscular blocker may have different effects on intubating conditions and result in different adverse effects depending on the remifentanil dose. Stevens reported that, in endotracheal intubation performed using propofol 2 mg/kg and different doses of remifentanil including 1 $\mu$g/kg, 2 $\mu$g/kg, 3 $\mu$g/kg, and 4 $\mu$g/kg in the absence of a neuromuscular blocker, the intubating conditions were excellent in 35% of patients at 1 $\mu$g/kg, in 75% of patients at 2 $\mu$g/kg, and in
most patients in 3 μg/kg and 4 μg/kg, while the incidence of hypotension and bradycardia was also increased [1].

Demirkaya et al. [7] reported that the effective dose (ED50) of remifentanil at which acceptable intubating conditions were observed in 50% of patients was 1.4 μg/kg during induction of anesthesia with propofol 2 mg/kg without a neuromuscular blocker. The dosage of the low-dose remifentanil in the present study was determined with reference to the previous study of Demirkaya et al. [7].

The improvement of the intubating conditions by dexmedetomidine observed in the present study may be attributable to the increase of the hypnotic depth, the increased effect of remifentanil, and the blunting of the airway reflex. Le Guen et al. [19] studied the administration of dexmedetomidine in combination with propofol and reported that dexmedetomidine decreased the propofol requirement. Various other researchers have also reported that dexmedetomidine decreased the MAC of inhalational anesthetics [8,20,21].

There are also other reports demonstrating the opioid-sparing effect of dexmedetomidine. It is known that dexmedetomidine significantly enhances the analgesic effect of opioid and thus decreases the opioid requirement [22,23]. In addition, there is a report that dexmedetomidine has the effect of preventing muscular stiffness, which is one of the adverse effects of opioids [24].

Such effects of dexmedetomidine may prevent muscle rigidity caused by bolus injection of high-dose opioid during an endotracheal intubation performed without the administration of a neuromuscular blocker, and thus reduce the risk of hypoxemia.

Hanci et al. [25] reported that the incidence of airway reflexes, such as coughing, and diaphragmatic movement during endotracheal intubation without a neuromuscular blocker was lower in patients administered propofol and dexmedetomidine than in patients administered propofol and fentanyl. In addition, it has been found in animal and human studies that α2 agonists such as dexmedetomidine attenuate airway constriction [26,27].

Although it was reported that dexmedetomidine may cause hypotension at a low loading dose, and hypertension and bradycardia at a high loading dose, no hemodynamic changes were observed when dexmedetomidine was administered slowly over 10 minutes at a low loading dose of 1 μg/kg [28].

Regarding the hemodynamic changes found in the two groups in the present study, Group C displayed a 16% decrease in MAP after administration of the induction agent, while there were no changes from baseline in Group D. Group C also showed a 20% decrease in MAP at 3 and 5 minutes after endotracheal intubation, while Group D showed 10% and 15% decreases in MAP at 3 and 5 minutes, respectively, after endotracheal intubation. These findings are consistent with previous studies reporting that dexmedetomidine contributes to hemodynamic stability during anesthetic induction, a result also observed in the present study [29,30].

In conclusion, dexmedetomidine 1 μg/kg improved the intubating conditions and stabilized hemodynamic changes in endotracheal intubation following anesthetic induction performed using propofol 2 mg/kg and remifentanil 1.5 μg/kg without a neuromuscular blocker.

REFERENCES

1. Stevens JB, Wheatley L. Tracheal intubation in ambulatory surgery patients: using remifentanil and propofol without muscle relaxants. Anesth Analg 1998; 86: 45-9.
2. Collins L, Prentice J, Vaghadia H. Tracheal intubation of outpatients with and without muscle relaxants. Can J Anaesth 2000; 47: 427-32.
3. Durmus M, Ender G, Kadir BA, Nurcin G, Erdogan O, Ersoy MO. Remifentanil with thiopental for tracheal intubation without muscle relaxants. Anesth Analg 2003; 96: 1336-9.
4. Stevens JB, Vescovo MV, Harris KC, Walker SC, Hickey R. Tracheal intubation using alfentanil and no muscle relaxant: is the choice of hypnotic important? Anesth Analg 1997; 84: 1222-6.
5. Shields JA. Heart block and prolonged Q-Tc interval following muscle relaxant reversal: a case report. AANA J 2008; 76: 41-5.
6. Alexander R, Olufolabi AJ, Booth J, El-Moalem HE, Glass PS. Dosing study of remifentanil and propofol for tracheal intubation without the use of muscle relaxants. Anaesthesia 1999; 54: 1037-40.
7. Demirkaya M, Kelsaka E, Sarilhasan B, Bek Y, Üstün E. The optimal dose of remifentanil for acceptable intubating conditions during propofol induction without neuromuscular blockade. J Clin Anesth 2012; 24: 392-7.
8. Thompson JP, Hall AP, Russell J, Cagney B, Rowbotham DJ. Effect of remifentanil on the haemodynamic response to orotracheal intubation. Br J Anaesth 1998; 80: 467-9.
9. Kim KH. Safe sedation and hypnosis using dexmedetomidine for minimally invasive spine surgery in a prone position. Korean J Pain 2014; 27: 313-20.
10. Park JW, Han JU, Shin HK, Jung JK, Cha YD, Kang SA, et al. The effect of intravenous dexmedetomidine on the duration of brachial plexus block. Anesth Pain Med 2012; 7: 307-11.
11. Fagen RJ, Fitzgerald PC. Effect of dexmedetomidine on the minimum alveolar concentration (MAC) of sevoflurane in adults age 55 to 70 years. J Clin Anesth 1999; 11: 466-70.
12. Kang WS, Kim SY, Son JC, Kim JD, Muhammad HB, Kim SH,
et al. The effect of dexmedetomidine on the adjuvant propofol requirement and intraoperative hemodynamics during remifentanil-based anesthesia. Korean J Anesthesiol 2012; 62: 113-8.

13. Gurbat A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anaesth 2006; 53: 646-52.

14. Yildiz M, Tavlan A, Tuncer S, Reisli R, Yosunkaya A, Otelcioglu S. Effect of dexmedetomidine on haemodynamic responses to laryngoscopy and intubation: perioperative haemodynamics and anaesthetic requirements. Drugs R D 2016; 32: 54-8.

15. Li CW, Li YD, Tian HT, Kong XG, Chen K. Dexmedetomidine-midazolam versus sufentanil-midazolam for awake fiberoptic nasotracheal intubation: a randomized double-blind study. Chin Med J (Engl) 2015; 128: 3143-8.

16. Kwak HJ, Min SK, Yoo JY, Park KH, Kim JY. The median effective dose of dexmedetomidine for laryngeal mask airway insertion with propofol 2.0 mg/kg. Acta Anaesthesiol Scand 2014; 58: 815-9.

17. Cooper R, Mirakhur RK, Clarke RS, Boules Z. Comparison of intubating conditions after administration of Org 9246 (rocuronium) and suxamethonium. Br J Anaesth 1992; 69: 269-73.

18. Le Guen M, Liu N, Tounou F, Augé M, Tuil O, Chazot T, et al. Dexmedetomidine reduces propofol and remifentanil requirements during bispectral index-guided closed-loop anesthesia: a double-blind, placebo-controlled trial. Anesth Analg 2014; 118: 946-55.

19. Thornton C, Lucas MA, Newton DE, Doré CJ, Jones RM. Effects of dexmedetomidine on isoflurane requirements in healthy volunteers. 2: Auditory and somatosensory evoked responses. Br J Anaesth 1999; 83: 381-6.

20. Segal IS, Vickers YG, Maze M. Dexmedetomidine decreases halothane anesthetic requirements in rats. Acta Vet Scand Suppl 1989; 85: 55-9.

21. Lin TF, Yeh YC, Lin FS, Wang YP, Lin CJ, Sun WZ, et al. Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. Br J Anaesth 2009; 102: 117-22.

22. Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anaesth 2006; 53: 646-52.

23. Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anaesth 2006; 53: 646-52.

24. Weinger MB, Segal IS, Maze M. Dexmedetomidine, acting through central alpha-2 adrenoceptors, prevents opiate-induced muscle rigidity in the rat. Anesthesiology 1989; 71: 242-9.

25. Hanci V, Ergoğun G, Oktay RD, Yurtlu BS, Ayoğlu H, Baydilek Y, et al. Effects of fentanyl-lidocaine-propofol and dexmedetomidine-lidocaine-propofol on tracheal intubation without use of muscle relaxants. Kaohsiung J Med Sci 2010; 26: 244-50.

26. Grundström N, Andersson RG, Wikberg JE. Presynaptic alpha 2 adrenoceptors inhibit contraction of tracheal smooth muscle by inhibiting cholinergic neurotransmission. Life Sci 1981; 28: 2981-6.

27. Lou YP, Franco-Cereceda A, Lundberg JM. Variable alpha 2-adrenoceptor-mediated inhibition of bronchoconstriction and peptide release upon activation of pulmonary afferents. Eur J Pharmacol 1992; 210: 173-81.

28. Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. Ann Pharmacother 2007; 41: 245-52.

29. Lawrence CJ, De Lange S. Effects of a single pre-operative dexmedetomidine dose on isoflurane requirements and peri-operative haemodynamic stability. Anaesthesia 1997; 52: 736-44.

30. Keniya VM, Ladi S, Naphade R. Dexmedetomidine attenuates sympathoadrenal response to tracheal intubation and reduces perioperative anaesthetic requirement. Indian J Anaesth 2011; 55: 352-7.