CONSORT the effect of intraoperative dexmedetomidine on hemodynamic responses during emergence from nasotracheal intubation after oral surgery

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Abstract
Background: Dexmedetomidine provides smooth emergence with reduced agitation. The authors hypothesized low-dose dexmedetomidine infusion might contribute to hemodynamic stability during and after nasotracheal tube extubation.

Methods: Ninety-three adult patients scheduled for oral and maxillofacial surgery were enrolled in this prospective study. Patients were randomly assigned to receive normal saline (control group, n=31), dexmedetomidine at 0.2 µg/kg/h (DEX0.2 group, n=31), or dexmedetomidine at 0.4 µg/kg/h (DEX0.4 group, n=31). Mean arterial pressure (MAP), heart rate (HR), and response entropy (RE) and state entropy (SE) were recorded during emergence from anesthesia.

Results: Extubation times were similar in the 3 groups. Mean MAP was significantly lower at eye opening (T3) and immediately after extubation (T4) in the DEX0.2 (P=0.013 and .003, respectively) and DEX0.4 group (P=.003 and .027, respectively) than in the control group. At T3 and T4, mean HR was significantly higher in the control group than in the DEX0.2 (P=.014 and .022, respectively) or DEX0.4 groups (P=.003 and <.001, respectively). In the postanesthetic care unit, mean MAP and HR were significantly lower in the DEX0.2 (P=.03 and .022, respectively) and DEX0.4 groups (P=.027 and <.001, respectively) than in the control group.

Conclusion: Intraoperative dexmedetomidine infusion at rates of 0.2 or 0.4 µg/kg/h during oral and maxillofacial surgery could provide stable hemodynamic profiles during anesthetic emergence from nasotracheal intubation without delaying extubation times.

Abbreviations: HR = heart rate, MAP = mean arterial pressure, PACU = postanesthetic care unit, RE = response entropy, SE = state entropy.

Keywords: dexmedetomidine, heart rate, mean arterial pressure, nasotracheal intubation

1. Introduction
Nasotracheal intubation is required to ensure good surgical visualization and uninterrupted manipulation during oral and maxillofacial surgery. Furthermore, the use of a nasotracheal tube tends to result in fewer laryngeal and glottis mucosal injuries than an orotracheal tube, and thus, increases patient comfort and facilitates simpler, smoother extubation.[1] However, sympathetic activation during emergence from general anesthesia induces hypertension and tachycardia, which could lead to postoperative bleeding and edema at the operative site even during nasotracheal tube extubation. Stable hemodynamics during emergence and smooth emergence are especially important in patients undergoing oral and maxillofacial surgery,[2] because the operative site is an airway structure, and thus, presents risks of bloody aspiration and airway obstruction due to soft tissue edema. In addition, the routine injection of epinephrine supplemented local anesthetics to reduce incisional bleeding increases systolic blood pressure by more than 50%, and this blood pressure elevation often persists after emergence from anesthesia.[3]

Dexmedetomidine is a highly selective α2-receptor agonist and was originally introduced as a safe, effective sedative, and anxiolytic for dental procedures or intensive care.[4,5] Clinical studies have demonstrated intraoperative dexmedetomidine infusion at 0.4 µg/kg/h effectively reduces intra- and postoperative analgesic and anesthetic requirements, attenuates surgical stress response,[6,7] and provides smooth emergence with an improved recovery profile, because it reduces the incidences of agitation, postoperative pain, and postoperative nausea and vomiting during and after orotracheal extubation.[8,9] Furthermore, it has been suggested dexmedetomidine infusion without a loading dose might facilitate extubation without hemodynamic instability or respiratory depression in surgical intensive care units.[9]

We hypothesized that a dexmedetomidine dose of 0.2 µg/kg/h, which is lower than that used in previous studies (0.4 µg/kg/h), might contribute to hemodynamic stability during and after
nasotracheal extubation. Accordingly, this prospective study was undertaken to investigate the effects of dexmedetomidine on hemodynamic profiles during emergence from spectral entropy guided general anesthesia in patients that underwent nasotracheal intubation for oral or maxillofacial surgery.

2. Methods

After obtaining approval from the Institutional Review Board of Gachon University Gil Medical Center, written informed consent was obtained from eligible participants. Ninety-three adult patients, American Society of Anesthesiologists physical status class I or II, aged 20 to 60 years, and scheduled for oral or maxillofacial surgery under general anesthesia from March 2014 to July 2015 were enrolled in this prospective randomized study. The exclusion criteria applied were as follows: a history of uncontrolled diabetes mellitus, uncontrolled hypertension, or obstructive respiratory disease, history of a cerebrovascular uncompensated cardiovascular disorder, acute or chronic diabetes mellitus, uncontrolled hypertension, an

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oriented, and tranquil; 3 = responsive to verbal commands alone; 4 = asleep, but brisk response to a light glabella tap or a loud auditory stimulus; 5 = asleep and sluggish response to a glabella tap or loud auditory stimulus; and 6 = asleep or no response to a light glabella tap or loud auditory stimulus), frequency of shivering, and requirements for rescue analgesics and antiemetics. Extubation time was defined as time from the end of surgery to extubation. The primary outcome variable was MAP immediately after extubation (T4) during emergence. A sample size calculation was conducted based on the MAP results of 6 saline-administered patients (mean 98 mmHg and standard deviation 12) during a preliminary study. To demonstrate an MAP difference of 10% with a power of 80% and an α-error of 0.05, 28 patients were found to be required per group. Thus, 31 were included per group to cater for an expected dropout rate of 10%.

The statistical analysis was performed using PASW Statistics 13 (SPSS Inc, Chicago, IL), and results are expressed as means ± SDs, median (interquartile ranges), or numbers of patients. The Kolmogorov–Smirnov test was performed on the dataset to assess for normality. Normally distributed data were analyzed using one-way ANOVA for continuous variables. When intergroup differences were found to be significant, Bonferroni post-hoc testing was performed, and when data were not normally distributed, the Kruskal–Wallis test with Bonferroni correction was used. Time * group interactions for hemodynamic changes were analyzed using repeated measures ANOVA. Categorical data were analyzed using the χ² test with Bonferroni correction for multiple comparisons (P = .05/3). Statistical significance was accepted for P values < .05.

3. Results

Of the 93 patients enrolled, 1 patient in the DEX0.4 group was excluded from the analysis because orotracheal intubation was performed instead of nasotracheal intubation (Fig. 1).

Demographic and perioperative data were similar in the DEX0.2, DEX0.4, and control groups, and group extubation times were not significantly different. However, total infused remifentanil doses were significantly different among the groups (P = .014) and were significantly higher in the control group than in the DEX0.4 group (P = .013) (Table 1).

MAP and HR results obtained during emergence are summarized in Fig. 2. MAP changes over time during emergence were not significantly different between the 3 groups (P = .116). Compared with values at T1, mean MAP increased significantly at T3 and T4 in all groups (both P values < .001 in the control group, P = .006 and < .001 in the DEX0.2 group, and P = .001 and < .001 in the DEX0.4 group, respectively). Mean MAP values were significantly lower at T3 and T4 in the DEX0.2 (P = .013 and .003, respectively) and DEX0.4 group than in the control group (P = .003 and .027, respectively). Changes in mean HR during emergence were also significantly different in the groups (P = .001). As compared with mean T1 values, mean HR was significantly higher at T3 and T4 in the control group (both P values < .001), but only significantly higher at T4 in the DEX0.2 (P < .001) and DEX0.4 groups (P < .001). Furthermore, mean HR were significantly higher in the control group than in the DEX0.2 (P = .014 and .022, respectively) and DEX0.4 groups (P = .003 and < .001, respectively) at T3 and T4.

Data obtain in the PACU are provided in Table 2. In the PACU, MAP and HR were significantly lower in the DEX0.2 (P = .03 and

| Table 1 | Patient characteristics and perioperative data. |
|---------|---------------------------------------------|
|         | Control group (n = 31) | DEX0.2 (n = 31) | DEX0.4 (n = 30) |
| Age, y  | 38 ± 11 | 37 ± 12 | 37 ± 12 |
| Sex (M/F) | 24/7 | 22/9 | 21/9 |
| Weight, kg | 64 ± 11 | 67 ± 14 | 65 ± 9 |
| Height, cm | 171 ± 8 | 172 ± 10 | 169 ± 8 |
| ASA PS (I/II) | 22/9 | 21/10 | 22/8 |
| Operation time, min | 86 ± 51 | 87 ± 58 | 92 ± 48 |
| Extubation time, min | 10 [5–12] | 10 [5–14] | 10 [5–15] |
| Total dose of remifentanil, µg | 669 ± 381 | 505 ± 267 | 448 ± 141 |

Values are means ± SDs, medians (interquartile ranges), or number of patients. Control group members received intravenous normal saline infusion; DEX 0.2 or 0.4 group members received intravenous DEX infusion at 0.2 or 0.4 µg/kg/h. ASA PS; extubation time, time from end of surgery to extubation. ASA PS = American Society of Anesthesiologists physical status, DEX = dexmedetomidine, SD = standard deviation.

*P < .05 versus the control group.

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.022, respectively) and DEX0.4 groups (P=.027 and <.001, respectively) than in the control group. Other recovery profiles, such as Ramsay sedation scores, frequencies of shivering, and requirements for rescue analgesics and antiemetics, were similar in the 3 groups. There was no case of failed extubation or reintubation.

### 4. Discussion

This prospective, randomized study shows intraoperative infusion of dexmedetomidine at 0.2 or 0.4 µg/kg/h might provide stable hemodynamic profiles during anesthetic emergence without delaying extubation from nasotracheal intubation. Furthermore, dexmedetomidine infusion reduced intraoperative opioid requirements in patients undergoing oral and maxillofacial surgery, and contributed to the prevention of hypertension and tachycardia without prolonging sedation in the PACU.

Dexmedetomidine reduces the release of norepinephrine due to its presynaptic α2-receptor agonistic effect and inhibits sympathetic outflow induced by postsynaptic receptors in the central nervous system, which in concert might depress sympathetic activation and contribute to stable hemodynamics.[10,11] In the present study, MAP and HR were both lower during anesthetic emergence in the DEX0.2 and DEX0.4 groups than in the control group. In addition to its effects during anesthetic emergence, intraoperative low-dose dexmedetomidine infusion might also reduce the risks of postoperative hypertension and tachycardia.

Bekker et al.[12] demonstrated dexmedetomidine infusion during craniotomy significantly reduced hypertensive episodes without inducing side effects, such as hypotension and bradycardia, in their PACU, which concurs with our results, as we found hemodynamics in the PACU were more stable in the dexmedetomidine-infused groups than in controls.

In the present study, 0.2 or 0.4 µg/kg/h of dexmedetomidine was applied without a loading dose, because this sometimes evokes transient hypertension.[13] The continuous infusion dose of dexmedetomidine used was determined based on a previous report, in which it was found a rate of 0.4 µg/kg/h effectively reduced emergence agitation and provided smooth emergence.[7,8] However, a previous clinical study on orotracheally intubated patients failed to detect any significant positive effect for 0.2 µg/kg/h dexmedetomidine on hemodynamic profiles during emergence.[6] Nevertheless, we supposed that 0.2 µg/kg/h dexmedetomidine might be effective for stabilizing hemodynamics because nasotracheal intubation has a simpler, smoother extubation profile than orotracheal intubation.[11] This supposition was supported by our results, which showed 0.2 µg/kg/h dexmedetomidine effectively improved hemodynamic profiles during emergence from nasotracheal intubation.

In an earlier study by Iwakiri et al.[14] it was concluded the intraoperative infusion of dexmedetomidine at rates of 0.3 to 0.4 µg/kg/h might improve postoperative recovery profiles in patients after gynecologic surgery. In their study, dexmedetomidine infusion without loading only achieved a plasma concentration of 0.2 ng/mL at 1 hour after starting infusion, which is below its clinically effective plasma concentration range of 0.3 to 1.2 ng/mL.[14] Nevertheless, our results suggest the coadministration of dexmedetomidine with anesthetics, sedatives, hypnotics, and opioids may have greater effects due to pharmacodynamic interactions. In the present study, emergence hemodynamics and recovery profiles were improved in the DEX0.2 and 0.4 groups, although Stanpump simulations and Dyck kinetics[15] predicted mean concentrations ± SDs in the DEX0.2 and DEX0.4 groups at the end of surgery of only 0.14 ± 0.03 and 0.28 ± 0.07 ng/mL, respectively.

Although dexmedetomidine preserves respiratory drive,[16] its sedative and anxiolytic effects could delay time to eye opening or verbal response and prolong emergence time.[16,17] Electroencephalography (EEG)-based anesthetic monitoring has been used to prevent the risk of intraoperative awareness, to reduce anesthetic drug consumption, and to promote recovery from anesthesia.[18,15] Furthermore, SE was reported to be reliably correlated with bispectral index and less interrupted by electrocautery during surgery.[20] On the other hand, RE indicates emergence from anesthesia 11 and 12.4 seconds earlier than SE and BIS, respectively.[21] SE-guided anesthesia also helps reduce recovery times by decreasing anesthetic agent requirements.[22] A clinical study on bispectral index guided anesthesia during nasal surgery showed dexmedetomidine infusion from anesthetic induction to extubation did not delay extubation, and the authors suggested smooth emergence and a lower incidence of emergence agitation after dexmedetomidine infusion might have explained this observation.[6] In the present study, we also maintained sedation levels at a constant level in the 3 groups under SE guidance, and found extubation times, sedation scores, and hemodynamic profiles in the 2 DEX groups were similar to those in control group during emergence and recovery from anesthesia, which suggests SE-guided low-dose dexmedetomidine infusion does not delay extubation times and provides proper sedation after anesthetic recovery.

Some limitations of the present study warrant consideration. First, the effects of postoperative pain on hemodynamic profiles during emergence could not be discerned[23] although based on pain scores and analgesic requirements in the PACU, we believe pain severities during emergence were similar in all 3 groups. Second, only the short-term effects of dexmedetomidine, that is, during PACU stays, were evaluated, and it is known the effect of dexmedetomidine peaks within 15 minutes and that its elimination half-life is ~2 hours. Thus, we suggest further study be conducted to establish the time-dependence of hemodynamic suppression after the infusion of low-dose dexmedetomidine.

In conclusion, the study shows intraoperative dexmedetomidine infusion rates of 0.2 or 0.4 µg/kg/h during oral and maxillofacial surgery may result in stable hemodynamic profiles during anesthetic emergence from nasotracheal intubation without delaying extubation times. In addition, the study suggests intraoperative dexmedetomidine contributes to the prevention of hypertension and tachycardia in the PACU setting.

### Table 2

|                        | Control group (n=31) | DEX0.2 (n=31) | DEX0.4 (n=30) |
|------------------------|---------------------|---------------|---------------|
| MAP, mm Hg             | 115 ± 14            | 103 ± 17      | 106 ± 9       |
| HR, beats/min          | 105 ± 17            | 95 ± 16       | 89 ± 13       |
| Ramsay sedation score  | 2 [2–3]             | 3 [3–4]       | 2 [2–3]       |
| Shivering (n)          | 3                   | 2             | 0             |
| Rescue analgesics (n)  | 3                   | 4             | 1             |
| Rescue antiemetics (n) | 1                   | 0             | 0             |

Values are means ± SDs, medians (interquartile ranges), or number of patients. Control group members received an intraoperative normal saline infusion; DEX0.2 or 0.4, members received intraoperative dexmedetomidine infusion at 0.2 or 0.4 µg/kg/h. DEX = dexmedetomidine, HR = heart rate, MAP = mean arterial pressure, SD = standard deviation.

P < .05 versus the control group.
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