Clinical Trial/Experimental Study

Medicine®

OPEN

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

Youn Yi Jo, MD, Hong Soon Kim, MD, Kyung Cheon Lee, MD, Young Jin Chang, MD, Youseok Shin, MD, Hyun Jeong Kwak, MD, PhD*

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 ($P = .013$ 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 α_2-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.[7,8] 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

Editor: Somchai Amornyotin.

The authors have no conflicts of interest to disclose.

Department of Anesthesiology and Pain Medicine, Gachon University Gil Medical Center, Incheon, South Korea.

* Correspondence: Hyun Jeong Kwak, Department of Anesthesiology and Pain Medicine, Gachon University Gil Medical Center, 1198 Guwol-dong, Namdong-gu, Incheon 405-760, South Korea (e-mail: hyun615@gilhospital.com).

Medicine (2017) 96:16(e6661)

Received: 19 February 2017 / Received in final form: 28 March 2017 / Accepted: 29 March 2017

http://dx.doi.org/10.1097/MD.0000000000006661

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, an uncompensated cardiovascular disorder, acute or chronic obstructive respiratory disease, history of a cerebrovascular disorder, moderate obesity (body mass index $>30\,kg/m^2$), a suspected difficult airway, a history of cervical spine disease, and bleeding tendency. Patients were randomly assigned to 1 of 3 groups, that is, to a normal saline group (the control group, n = 31), a 0.2 μg/kg/h dexmedetomidine group (the DEX0.2 group, n = 31), or to a 0.4 μg/kg/h dexmedetomidine group (the DEX0.4 group, n = 31) using a randomized list generated using Excel 2007 (Microsoft Office, Redmond, WA) without stratification (Fig. 1).

All patients were premedicated with 0.2 mg of glycopyrrolate intramuscularly 30 minutes before anesthesia induction. On arrival at the operating room, standard monitors including blood pressure, EKG, and pulse oximetry were applied. In addition, a spectral entropy sensor (Entropy sensor; Datex-Ohmeda, Finland) was attached to the frontotemporal area and connected to a monitor (M-Entropy plug-in module, GE Healthcare, Helsinki, Finland). For the DEX0.2 and DEX0.4 groups, 50 mL of 2 or 4 μg/mL dexmedetomidine, respectively, were prepared by senior trainees unaware of group assignments. Controls were administered 50 mL of normal saline. Dexmedetomidine (0.2 or 0.4 μg/kg/h) or the same volume of normal saline was infused from immediately before anesthetic induction to the end of surgery. For anesthesia induction, 1.0 μg/kg of remifentanil, 1 ml/kg of lidocaine, 1.5 to 2.0 mL/kg of propofol, and 0.8 mg/kg of rocuronium were administered. Nasotracheal intubation was performed using a nasal RAE tube (Portex Polar Preformed Tracheal Tube, Smith Medical International Ltd., Hythe, Kent, UK) lubricated with a water-soluble jelly. The internal diameters of the tubes used were 7.0 mm for men and 6.5 mm for women. Anesthetic induction, maintenance, emergence, and extubation were performed by an anesthesiologist unaware of group assignments. To maintain response entropy (RE) and state entropy (SE) between 40 and 60, anesthesia was maintained with sevoflurane at 1.5 to 2 vol% and remifentanil at 0.1 to 0.3 μg/kg/min at an inspired oxygen fraction (FiO_2) of 0.5 in medical air. Patient-controlled analgesia during the first 48 hours postoperatively was performed using 100 mL of a solution of fentanyl (800 μg) in normal saline (Accufuser; Wooyoung Meditech, Seoul) via an intravenous line. To prevent postoperative nausea and vomiting, 0.075 mg of palonosetron was injected before discontinuing the dexmedetomidine or normal saline.

Mean arterial pressure (MAP), heart rate (HR), RE, and SE were recorded before anesthesia induction (baseline, T0), after stopping study drug administration at the end of surgery (T1), 5 minutes after T1 (T2), at eye opening (T3), and immediately after extubation (T4). On arrival at the postanesthetic care unit (PACU) the following were recorded; hemodynamic variables, Ramsay sedation scores (1 = anxious, agitated, or restless; 2 = cooperative,

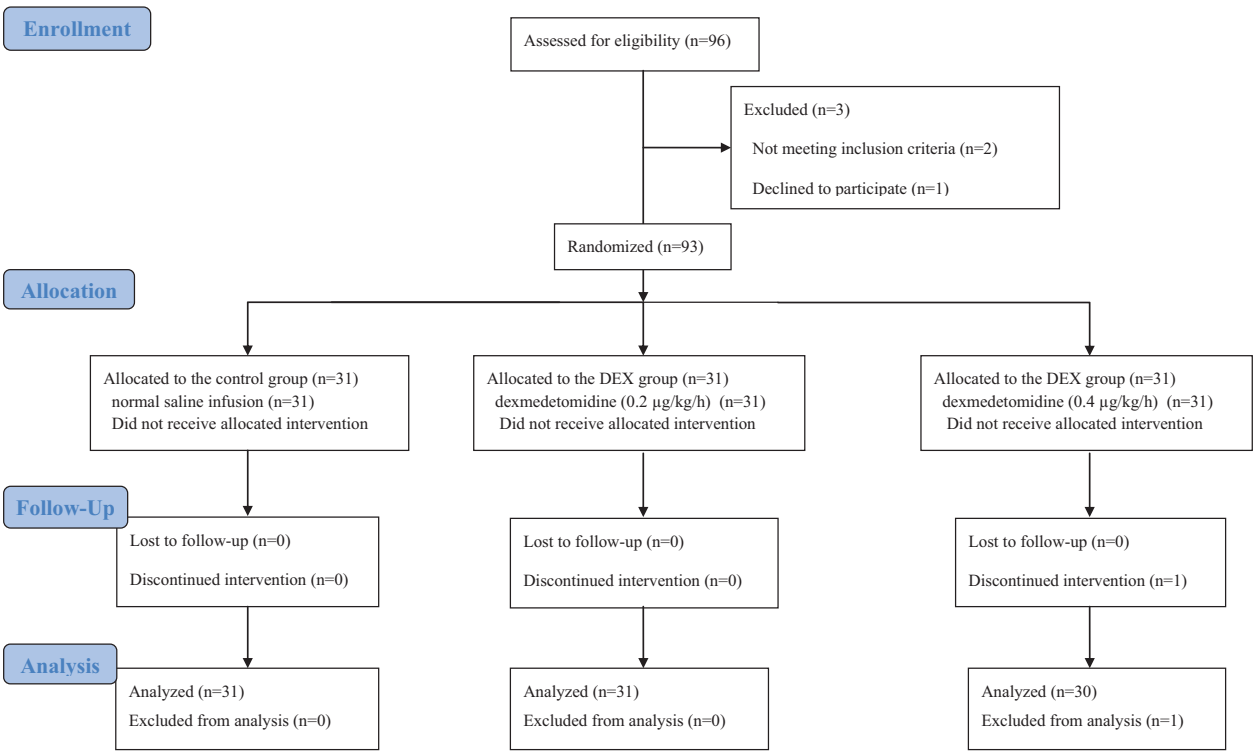

Figure 1. Patient allocation flow diagram.

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 mm Hg 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 drop-out 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 χ^2 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

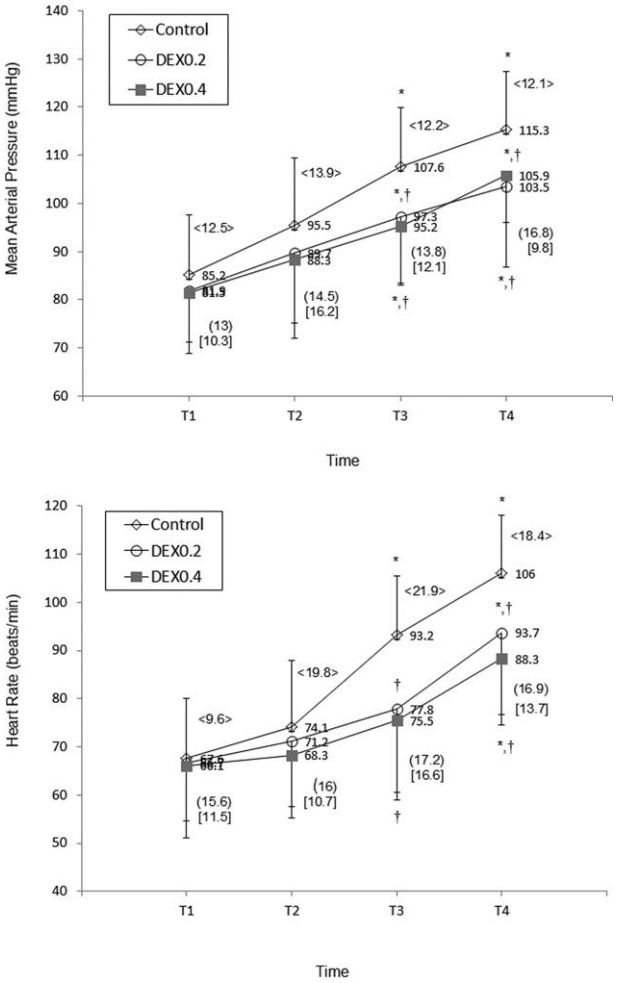

Figure 2. Changes of MAP and HR during emergence in patients that received normal saline (control group, ◊), dexmedetomidine 0.2 μg/kg/h (DEX0.2 group, ○), or dexmedetomidine 0.4 μg/kg/h (DEX0.4 group, ■) during general anesthesia for oral and maxillofacial surgery. Error bars and numbers in parenthesis (< >, ( ) and [ ] in the control, DEX0.2 and DEX0.4 groups, respectively) represent standard deviation). T1, at the end of surgery (immediately after drug administration); T2, 5 min after T1, T3, at eye opening; T4, immediately after extubation. *$P < .05$, versus T1 within the same group; †$P < .05$, versus the control group. HR = heart rate, MAP = mean arterial pressure.

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	89 ± 51	87 ± 38	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 intraoperative normal saline infusion; DEX 0.2 or 0.4 group members received intraoperative 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 Anesthesiologists physical status, DEX = dexmedetomidine, SD = standard deviation.

* $P < .05$ for all 3 groups.

† $P < .05$ versus the control group.

Table 2

Recovery profiles and hemodynamic data in the postanesthetic care unit.

	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.

.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 α_2-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.[1] 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.[8,17] 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.[18,19] 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.[8] 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.

References

[1] Holzapfel L. Nasal vs oral intubation. Minerva Anestesiol 2003;69: 348–52.

[2] Cavallone LF, Vannucci A. Review article: extubation of the difficult airway and extubation failure. Anesth Analg 2013;116:368–83.

[3] Pasternak JJ, Atkinson JL, Kasperbauer JL, et al. Hemodynamic responses to epinephrine-containing local anesthetic injection and to emergence from general anesthesia in transsphenoidal hypophysectomy patients. J Neurosurg Anesthesiol 2004;16:189–95.

[4] Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. Ann Pharmacother 2007;41:245–52.

[5] Cheung CW, Ying CL, Chiu WK, et al. A comparison of dexmedetomidine and midazolam for sedation in third molar surgery. Anaesthesia 2007;62:1132–8.

[6] Manne GR, Upadhyay MR, Swadia V. Effects of low dose dexmedetomidine infusion on haemodynamic stress response, sedation and postoperative analgesia requirement in patients undergoing laparoscopic cholecystectomy. Indian J Anaesth 2014;58:726–31.

[7] Kim DJ, Kim SH, So KY, et al. Effects of dexmedetomidine on smooth emergence from anaesthesia in elderly patients undergoing orthopaedic surgery. BMC Anesthesiol 2015;15:139.

[8] Kim SY, Kim JM, Lee JH, et al. Efficacy of intraoperative dexmedetomidine infusion on emergence agitation and quality of recovery after nasal surgery. Br J Anaesth 2013;111:222–8.

[9] Siobal MS, Kallet RH, Kivett VA, et al. Use of dexmedetomidine to facilitate extubation in surgical intensive-care-unit patients who failed previous weaning attempts following prolonged mechanical ventilation: a pilot study. Respir Care 2006;51:492–6.

[10] Gertler R, Brown HC, Mitchell DH, et al. Dexmedetomidine: a novel sedative-analgesic agent. Proc (BaylUniv Med Cent) 2001;14:13–21.

[11] Gertler R, Brown HC, Mitchell DH, et al. Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent) 2001;14:13–21.

[12] Bekker A, Sturaitis M, Bloom M, et al. The effect of dexmedetomidine on perioperative hemodynamics in patients undergoing craniotomy. Anesth Analg 2008;107:1340–7.

[13] Herr DL, Sum-Ping ST, England M. ICU sedation after coronary artery bypass graft surgery: dexmedetomidine-based versus propofol-based sedation regimens. J Cardiothorac Vasc Anesth 2003;17: 576–84.

[14] Iwakiri H, Oda Y, Asada A, et al. The efficacy of continuous infusion of low dose dexmedetomidine for postoperative patients recovering in general wards. Eur J Anaesthesiol 2012;29:251–4.

[15] Dyck JB, Maze M, Haack C, et al. Computer-controlled infusion of intravenous dexmedetomidine hydrochloride in adult human volunteers. Anesthesiology 1993;78:821–8.

[16] Hsu YW, Cortinez LI, Robertson KM, et al. Dexmedetomidine pharmacodynamics: Part I: cross-over comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology 2004;101:1066–76.

[17] Ham SY, Kim JE, Park C, et al. Dexmedetomidine does not reduce emergence agitation in adults following orthognathic surgery. Acta Anaesthesiol Scand 2014;58:955–60.

[18] Kreuer S, Biedler A, Larsen R, et al. Narcotrend monitoring allows faster emergence and a reduction of drug consumption in propofol-remifentanil anesthesia. Anesthesiology 2003;99:34–41.

[19] Myles PS, Leslie K, McNeil J, et al. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet 2004;363:1757–63.

[20] White PF, Tang J, Romero GF, et al. A comparison of state and response entropy versus bispectral index values during the perioperative period. Anesth Analg 2006;102:160–7.

[21] Vakkuri A, Yli-Hankala A, Talja P, et al. Time-frequency balanced spectral entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia. Acta Anaesthesiol Scand 2004;48:145–53.

[22] Vakkuri A, Yli-Hankala A, Sandin R, et al. Spectral entropy monitoring is associated with reduced propofol use and faster emergence in propofol-nitrous oxide-alfentanil anesthesia. Anesthesiology 2005;103: 274–9.

[23] Lepouse C, Lautner CA, Liu L, et al. Emergence delirium in adults in the post-anaesthesia care unit. Br J Anaesth 2006;96:747–53.