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ORIGINAL ARTICLE

Preoperative dexmedetomidine attenuates hemodynamic responses to hydrodissection in patients undergoing robotic thyroidectomy

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Abstract
Purpose Percutaneous tunneling (hydrodissection) in the neck and anterior chest in patients undergoing robotic thyroidectomy leads to significant hemodynamic responses such as increases in blood pressure and heart rate. We evaluated whether a single preoperative dexmedetomidine injection attenuated hemodynamic responses to hydrodissection by reducing the half-maximal effective concentration (EC50) of remifentanil needed to maintain hemodynamic stability during hydrodissection.
Methods Forty-one patients undergoing robot-assisted endoscopic thyroidectomy were randomly allocated to one of the two groups—group D ($n = 22$) and group C ($n = 19$) patients received dexmedetomidine 1 μg/kg and normal saline for 10 min before anesthetic induction, respectively. The EC50 of remifentanil for hemodynamic stability during hydrodissection was determined using Dixon's up-and-down method with initial dose (4 and 5 ng/mL in groups D and C, respectively). The concentration of remifentanil for consecutive patients in each group was determined by the response of the previous patient, using increments or decrements of 0.5 ng/mL. Hemodynamic stability during hydrodissection was defined as increased systolic blood pressure <20 % of baseline.
Results The EC50 of remifentanil for maintaining hemodynamic stability during hydrodissection was 0.8 ng/mL in group D and 7.3 ng/mL in group C ($p = 0.002$).
Conclusions A single preoperative dexmedetomidine injection attenuated hydrodissection-induced hemodynamic responses in patients undergoing robotic thyroidectomy.

Keywords Dexmedetomidine · Robot-assisted thyroidectomy · Hemodynamic response · Remifentanil · Hydrodissection

Introduction

Dexmedetomidine (DEX) is a recently released and approved alpha 2 agonist with a relatively high ratio of α_2/α_1-activity and an almost four-fold shorter half-life than clonidine [1]. It has sympatholytic, sedative, and analgesic properties. DEX administration in the perioperative period is associated with blunted hemodynamic responses to noxious stimuli, effective postoperative analgesia, and reduced anesthetic requirements [2]. This makes DEX a useful anesthetic adjuvant for general anesthesia. While there are some reports of the beneficial effects of DEX on anesthetic requirements and hemodynamic responses to endotracheal intubation [3–6], the effect of a single preoperative injection of DEX in terms of attenuating hemodynamic responses to surgical stimulation in robot-assisted thyroidectomy is unknown.

Trial Registration Identifier: NCT02102139 (www.clinicaltrials.gov).

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When a robotic thyroidectomy using the bilateral axillary breast approach (BABA) technique is performed, subcutaneous tunneling in the neck and anterior chest, which is defined as hydrodissection, is mandatory. Unfortunately, the procedure leads to significant hemodynamic responses, such as increases in blood pressure (BP) and heart rate (HR).

We hypothesized that preoperative DEX administration would attenuate the hemodynamic responses to hydrodissection. This study was designed to evaluate the effects of a single preoperative administration of DEX on hemodynamic responses to hydrodissection in robotic thyroidectomy by comparing the half-maximal effective concentration (EC50) of remifentanil needed to maintain hemodynamic stability during hydrodissection between DEX and control groups. We also investigated the effects of preoperative DEX administration on total doses of remifentanil and propofol administered intraoperatively.

Methods

Setting and study design

This study was approved by the Institutional Ethics Committee of Seoul National University Hopspital. After obtaining written informed consent, we prospectively enrolled ASA physical status I–II patients aged 20–60 years and scheduled for general anesthesia for robotic thyroidectomy between June 2012 and August 2012. Patients with an allergy to α_2-adrenergic agonists or propofol, current antihypertensive medication, heart block greater than first degree, severe cardiorespiratory dysfunction, a history of alcohol or drug abuse, or had received opioid analgesic medication within the previous 24-h period before the operation were excluded.

Group assignment

Patients were allocated to one of two groups based on the use of DEX or not in a double-blind manner. Randomization was accomplished using random, computer-generated numbers. The assignments were concealed in opaque envelopes and opened immediately before induction by a nurse who was blinded to this study and was responsible for preparing the study drugs. In group D, DEX (1 μg/kg) was loaded intravenously for 10 min before anesthesia induction. The same volume of 0.9 % normal saline was administered in the same manner to group C. During DEX or saline loading, the depth of anesthesia was monitored using a bispectral index (BIS) monitor (A-2000 XP BIS monitor; Aspect Medical Systems, Newton, USA). Electrocardiogram, HR, pulse oximetry, and non-invasive arterial BP were monitored at 2-min intervals.

Anesthetic induction and maintenance

Anesthesia was induced with propofol 3.5 μg/mL and remifentanil 5 ng/mL at an effect-site concentration using a target-controlled infusion (TCI) device (Orchestra; Fresenius-Vial, Brezins, France). After mask ventilation was confirmed, rocuronium (0.9 mg/kg) was administered to facilitate tracheal intubation in both groups. After tracheal intubation, volume-controlled ventilation with an air/O_2 mixture (fraction of inspired oxygen: 0.5) was followed with a tidal volume of 7 mL per ideal body weight and a respiratory rate to maintain end-tidal CO_2 at 30–35 mmHg with an inspiratory/expiratory ratio of 1:2. After Allen's test, a 20G catheter was inserted into the radial artery of the non-dominant hand for direct arterial BP monitoring. Anesthesia was maintained with propofol and remifentanil continuous infusions. Apart from the study period, propofol and remifentanil doses were adjusted during surgery to maintain a BIS value of 40–60 and systolic BP (SBP) within ±20 % from baseline, respectively.

Study protocol

After surgical draping, diluted epinephrine (1:200,000) solution was injected in the working area under the platysma in the neck and subcutaneously in the anterior chest. Bilateral axillary and circumareolar incisions were made. Blunt dissections using a tunneler (hydrodissection) were performed in the flap. After elevating the flap, the ports were inserted through the incisions.

The effect-site propofol concentration was fixed at 5.0 μg/mL at the time of diluted epinephrine injection and was unchanged during the entire hydrodissection period in all patients. The remifentanil concentration was adjusted through a TCI device to the predetermined effect-site concentration at the time of diluted epinephrine injection. We used the Minto pharmacokinetic model ($k_{e0} = 0.60$/min) and the Schnider pharmacokinetic model ($k_{e0} = 0.46$/min) for remifentanil and propofol, respectively. After equilibration of plasma and effect-site propofol and remifentanil concentrations, hydrodissection was started. The first patients received effect-site concentrations of remifentanil of 4 and 5 ng/mL in groups D and C, respectively. The response of each patient determined the effect-site concentration of remifentanil of the next patient. The response to hydrodissection was classified as 'success' or 'fail' by a member of the an anesthesiology staff who entered the operating room immediately before hydrodissection to blind him to the group assignment. Success was defined as the SBP being within ±20 % from baseline SBP

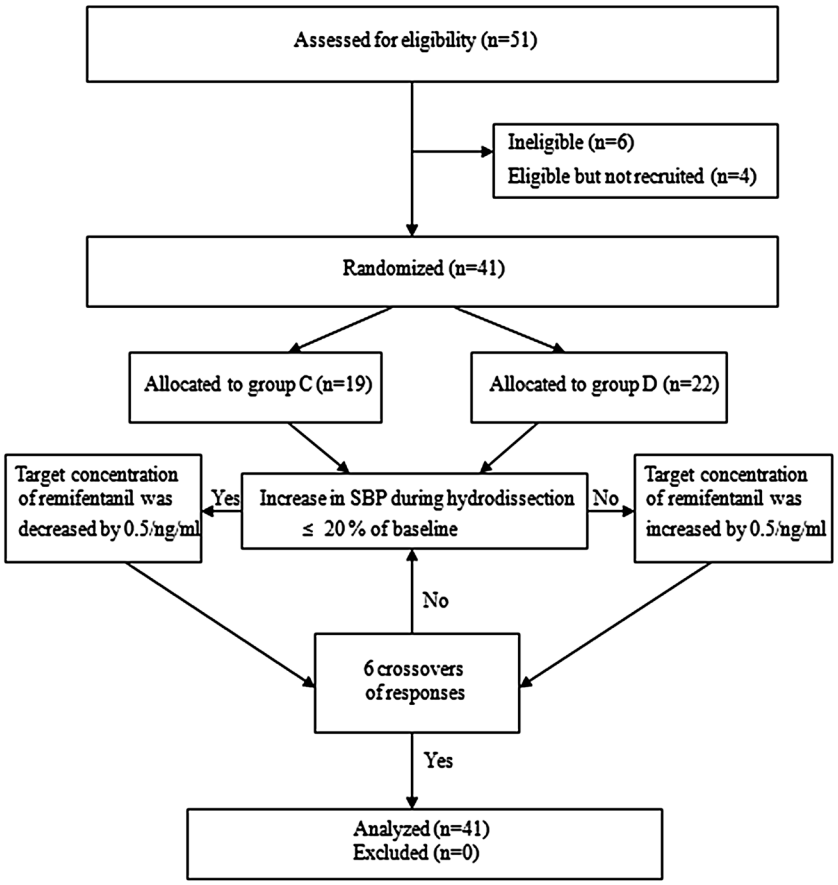

Fig. 1 Flow chart for the Dixon up-and-down method

during the entire hydrodissection period, which was measured immediately before hydrodissection. Fail was defined as SBP being over ±20 % from baseline. The EC50 of remifentanil for stable hydrodissection was determined by a modification of Dixon's up-and-down method [7]. A flow chart for the Dixon up-and-down method is shown in Fig. 1. If the response was 'success', the next target concentration of remifentanil was decreased by 0.5 ng/mL. If the response was 'fail', the target concentration was increased by 0.5 ng/mL. The process was repeated until the sixth cross-over point (fail/success) was obtained. The midpoint was defined as the mean cross-over concentration. The EC50 was defined as the mean cross-over midpoint in each group.

Measurements

SBP, mean BP (MBP), HR, and BIS were recorded before hydrodissection, every minute during the 10-min period of hydrodissection, and at the end of hydrodissection. Propofol and remifentanil requirements, eye opening time, and extubation time were recorded at the end of surgery. The primary measurement in this study was remifentanil EC50 for maintaining hemodynamic stability during hydrodissection. Secondary measurements were total doses of remifentanil and propofol administered intraoperatively.

Statistics

Pace and Stylianou [8] indicated that a total of 20–40 subjects were generally needed in the up-and-down method, but when the sixth cross-over point (fail/success) was achieved, subject enrolment to complete a study was not needed anymore. In this study, a total of 48 patients (24 patients in each group) were originally needed to compensate a drop rate of 20 %, but 41 patients (22 in group D and 19 in group C) were enrolled because the sixth cross-over point (fail/success) was achieved in each group.

Statistical analysis was performed using the SPSS software (ver. 19.0 for Windows; SPSS Inc., IL, USA). Hemodynamic data and BIS during DEX or saline infusion were analysed by repeated-measures ANOVA. If the difference between the two groups was significant, an independent *t* test was used to determine the difference at each time point with the *p* value adjustment to compensate for multiple comparisons. To indicate the significance of $p < 0.05$ and $p < 0.01$, the original *p* value should be <0.006 and 0.001, respectively. Intraoperative propofol and remifentanil requirements were analysed

by independent *t*-test. Mann–Whitney test was used to compare remifentanil EC50 for maintaining hemodynamic stability during hydrodissection. *P* values <0.05 were considered to indicate statistical significance.

Results

A total of 51 patients were assessed for eligibility. Of these, 10 patients were excluded (3, refusal; 3, uncontrolled hypertension; 1, coronary heart disease; 1, atrial fibrillation; 1, severe asthma; 1, cancelled surgery). Finally, six pairs of success−failure crossovers were obtained in 22 and 19 in groups D and C, respectively.

There was no statistically significant difference in demographics. The recovery profiles, the time to eye opening and to extubation, or operative or anesthetic times between the groups were similar between the two groups (Table 1). However, the total amounts of remifentanil [12.2 (2.6) vs 5.5 (2.6) μg/kg/hr, $p < 0.001$] and propofol [12 (2.4) vs 10.1 (1.1) mg/kg/hr, $p = 0.003$] infused intraoperatively were significantly lower in group D than in group C.

From 8 min after loading of each treatment drug to immediately after intubation, BIS values were lower in group D than in group C (Fig. 2). From 2 min after loading of each treatment drug to immediately after intubation, HRs were significantly lower in group D. However, adverse effects, such as severe hypotension or bradycardia, were not observed in either group.

The BIS value, SBP, MBP, and HR at the predetermined effect-site concentration of remifentanil before hydrodissection were 33.9 (9.5), 110.0 (15.2) mmHg, 72.5 (9.6) mmHg, and 65.0 (9.1) beats/min in group C, respectively, while the values were 31.4 (7.4), 124.9 (16.2) mmHg, 89.9 (13.0) mmHg, and 71.4 (7.8) beats/min in group D, respectively. Hydrodissection times were 12.3 (4.5) and 14.2 (5.5) min in groups C and D, respectively. The sequence of patients with hemodynamic stability during hydrodissection and those with increased hemodynamic responses in both groups are shown in Fig. 3. The EC50 of remifentanil for maintaining hemodynamic stability during hydrodissection was 0.8 (0.8) ng/mL in group D and 7.33 (0.2) ng/mL in group C, respectively ($p = 0.002$).

Table 1 Demographic and intraoperative data

Variables	Group C ($n = 19$)	Group D ($n = 22$)	*P* value
Sex (F/M)	17/2	17/5	0.419
Age (yers)	38.1 (9.7)	38.7 (9.4)	0.823
BMI (kg/m^2)	22.8 (3.4)	23.7 (3.5)	0.409
Total amount of infused propofol (mg/kg/h)	12.0 (2.4)	10.1 (1.1)	0.003
Total amount of infused remifentanil (μg/kg/h)	12.2 (2.6)	5.5 (2.6)	<0.001
Time to eye opening (min)	12.0 (3.6)	13.4 (5.6)	0.350
Time to extubation (min)	14.0 (4.0)	14.8 (5.4)	0.587
Anesthetic time (min)	195.8 (24.8)	197.1 (29.1)	0.888
Surgery time (min)	146.1 (24.1)	152.5 (25.8)	0.416

Data are mean (SD) except for gender (*n*)

Group C control group, *Group D* dexmedetomidine group

Discussion

This study showed that a single preoperative administration of DEX effectively reduced hemodynamic responses to surgical stimulation and total doses of remifentanil and propofol administered intraoperatively in patients undergoing robotic thyroidectomy without delaying postoperative recovery.

This is the first report of the beneficial effect of DEX in attenuating surgical stimuli-induced hemodynamic responses in robot-assisted thyroidectomy. BABA robotic thyroidectomy has been used successfully for various thyroid diseases with a low incidence of complications and good cosmetic results. BABA robotic thyroidectomy also provides optimal visualization of the operative field and major structures, such as the recurrent laryngeal nerve and parathyroid glands during dissection [9]. Despite the tiny incision, the mechanical stimulation during hydrodissection in BABA robotic thyroidectomy is extremely painful because sufficient working space for the large robotic arms and instruments has to be made in a small, limited field. Hydrodissection-induced sympathetic nervous system stimulation can lead to tachycardia, hypertension, and arrhythmias. Hypertension may lower the quality of the dissection in that it can cause the engorgement of blood vessels and interfere with the surgeon's view because of an increase in oozed blood. In our clinical practice, anesthesiologists commonly deepen anesthesia to reduce these hemodynamic changes by increasing the remifentanil infusion rate. This study showed that a single preoperative intravenous administration of DEX provided a reduction in the remifentanil requirement by >90 % to maintain hemodynamic stability during hydrodissection. This is comparable with a previous report that DEX reduced opioid requirements to blunt cardiovascular responses to stressful stimuli, such as endotracheal intubation [4]. Furthermore, a recent study demonstrated that DEX attenuated sympathoadrenal responses to skin incision and sternotomy in patients undergoing cardiac surgery [10]. Although the analgesic effect of DEX is not as strong as that of opioids,

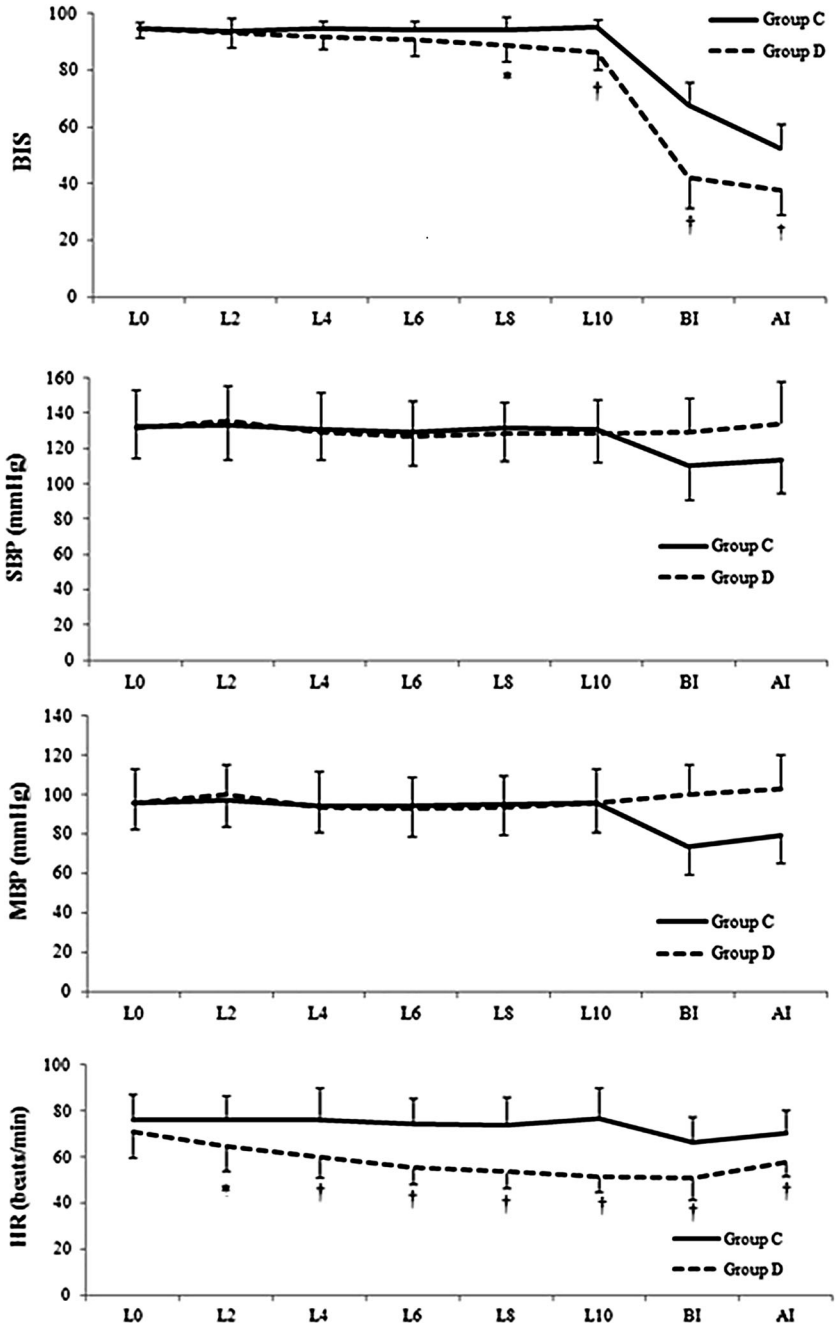

Fig. 2 BIS and hemodynamic variables. Data are mean ± SD. *L*0, *L*2, *L*4, *L*6, *L*8, and *L*10 indicate before loading of dexmedetomidine (group D) or saline (group C), 2, 4, 6, 8, 10 min after loading of dexmedetomidine or saline. *BI* before intubation, *AI* after intubation, *BIS* bispectral index, *SBP* systolic blood pressure, *MBP* mean blood pressure, *HR* heart rate. *p <0.05 compared with group C, $^{\dagger}p$ <0.01 compared with group C

DEX has some analgesic effects. Moreover, DEX induces a centrally mediated reduction of sympathetic nervous system activity and diminishes catecholamine release [11]. We considered that the combined analgesic and sympatholytic effects of DEX could be responsible for a significant reduction in the remifentanil requirement to maintain hemodynamic stability during hydrodissection in group D. Moreover, the pharmacokinetics of DEX should be taken into consideration to explain the remifentanil-sparing effect of DEX during hydrodissection. In this study, hydrodissection time, which is defined as the time from cessation of DEX administration to initiation of hydrodissection, was within about 20 min. A previous study [12] showed that plasma concentration of DEX at 10 and 60 min after intravenous injection of DEX 1 μg/kg was approximately 0.9 and 0.3 ng/ml, respectively. From 10−60 min after cessation of DEX administration (1 μg/kg), plasma norepinephrine level, MBP and HR were significantly lower than their baseline values [12]. Therefore, we believed that DEX exerted analgesic and sympatholytic effects during hydrodissection and thereby blunted hemodynamic responses to hydrodissection.

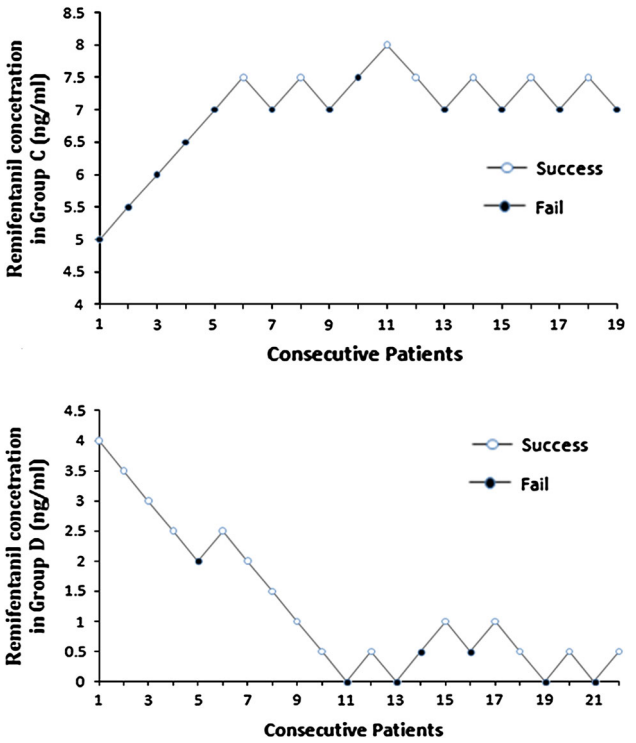

Fig. 3 Consecutive target remifentanil concentrations to maintain hemodynamic stability during hydrodissection in patients with dexmedetomidine (group D) or saline (group C)

In this study, preoperative DEX administration also decreased intraoperative remifentanil and propofol requirements, by approximately 50 and 15 %, respectively, compared with saline administration. Consistent with our results, previous reports indicated that a single administration of DEX reduced intraoperative fentanyl requirement by 12–82 % [6, 13, 14]. A recent study [15] showed that DEX at 1 μg/kg significantly reduced the amounts of propofol and remifentanil at intubation, at the start of surgery, and at the end of surgery in patients undergoing suspension laryngoscopy. DEX also decreased the intraoperative isoflurane requirement in major spine surgery and decreased the total cumulative intraoperative consumption of sevoflurane in gynecological surgery [16, 17]. Other investigations showed a 30–50 % reduction in the propofol requirements with DEX coadministration [18–20]. Patients who received thoracic epidural DEX after induction of general anesthesia required significantly less supplementary fentanyl during thoracic surgery [21]. The addition of intravenous or intrathecal DEX has been shown to prolong the duration of spinal anesthesia and to increase maximum upper levels of sensory block in spinal anesthesia [22–24]. Therefore, preoperative and/or intraoperative DEX can markedly reduce the total anesthetic requirements in a variety of surgeries, regardless of anesthetic type, suggesting that DEX is a useful and effective anesthetic adjuvant.

In this study, a single dose of 1 μg/kg DEX was administered over a 10–min period preoperatively. DEX has commonly been reported to increase the risk of hypotension and bradycardia during the loading phase due to activation of central α2 receptors, leading to inhibition of sympathetic outflow [11]. Rapid bolus administration of DEX often induces these adverse effects in healthy young volunteers with high levels of vagal tone [25, 26]. Additionally, these side-effects are observed more frequently when large doses of DEX are administered [14]. In our study, the HR was significantly slower in group D from 2 min after DEX loading, but neither severe hypotension nor bradycardia (>30 % decline from baseline values) occurred in either group. It is important to determine the injection dose and/or the infusion rate that generates the maximum anesthetic and analgesic-sparing effects while minimizing the incidence of hypotension and bradycardia.

In this study, the remifentanil-sparing effect of DEX was significant on attenuating hemodynamic responses during hydrodissection in robot-assisted thyroidectomy. Inadvertent remifentanil overdose administration during hydrodissection may result in hemodynamic instability. Remifentanil is known to increase the incidence of dose-dependent, vagally mediated hypotension and bradycardia [27]. Moreover, intraoperative remifentanil administration, although it is a short-acting opioid, may be associated with opioid-related complications such as postoperative respiratory depression, nausea, and vomiting. Preoperative DEX administration may reduce the incidence of opioid-related side-effects by decreasing intraoperative remifentanil requirements.

This study had some limitation. In this study, most subjects were middle-aged females simply because thyroid cancer is more prevalent in females in this age group [28]. Gender and age differences in the autonomic nervous system may cause differences in hemodynamic responses to surgical stimulation, especially in older patients with comorbidities. Thus, we should recognize the potential effects of gender and age on the outcomes. In addition, plasma concentrations of catecholamines as the primary marker for the magnitude of hemodynamic response were not directly measured in our study. Baseline SBP was different, although statistically non-significant, between two groups. Different baseline SBP can affect the decision of 'success' or 'fail' response because the response was based on percentage change, not the absolute value, from baseline SBP. Finally, the postoperative opioid-sparing effect of DEX was not investigated in this study. A recent meta-analysis showed that perioperative DEX or clonidine administration decreased postoperative opioid consumption and pain intensity [29].

In conclusion, we found that a single preoperative administration of DEX significantly reduced remifentanil

requirements to maintain hemodynamic stability during hydrodissection in patients undergoing robotic thyroidectomy, suggesting that DEX can attenuate untoward hemodynamic responses to brief but strong surgical stimuli during a robotic thyroidectomy. Preoperative DEX infusion also significantly decreased the total amounts of propofol and remifentanil infused intraoperatively with no apparent adverse effect.

Conflict of interest There is no conflict of interest.

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