Effects of Low versus Intermediate Doses of Dexmedetomidine Infusion on Blood Loss, Hemodynamics, and Operative Time in Transsphenoidal Pituitary Tumor Removal: A Prospective Randomized Study

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Abstract

Background Dexmedetomidine, an alpha-2 agonist, has been widely used as an anesthetic adjunct for transsphenoidal pituitary resection. However, there is no consensus on the appropriate infusion dosage. This study aimed to compare the effects of low (0.2 mcg/kg/h) and intermediate (0.5 mcg/kg/h) dexmedetomidine infusions during anesthetic maintenance on blood loss, hemodynamics, and operating time.

Methods A randomized controlled trial involving two centers was conducted. Between December 2015 and November 2019, 80 patients (40 in each group) who underwent elective transsphenoidal pituitary tumor resection were recruited. Dexmedetomidine was administered to group I at a loading dose of 0.5 mcg/kg, followed by 0.2 mcg/kg/h, and to group II at the same loading dose, followed by 0.5 mcg/kg/h. Comparative analyses were performed using the Student's *t*-test, repeated-measures analysis of variance, and Mann–Whitney *U* test; *p*-values < 0.05 were considered statistically significant.

Results Eighty patients were analyzed. Patient demographics were comparable. The difference in intraoperative blood loss between both groups (320 [220–525] vs. 250 [100-487] mL, $p = 0.070$) was not statistically significant. There were no differences in blood pressure or heart rate between the groups. In group II, the procedure took significantly less time (179 vs. 142 minutes, $p = 0.018$), with more episodes of transient hypotension ($p = 0.034$).

Conclusion When maintaining anesthesia for transsphenoidal pituitary resection, dexmedetomidine infusions of 0.2 and 0.5 mcg/kg/h showed the same effect on blood loss and hemodynamics; however, significantly more episodes of transient hypotension and shorter operating times were noted with the latter.

Keywords
- operative time
- blood pressure
- dexmedetomidine

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Introduction

Tumors of the pituitary gland are found in approximately 10% of brain tumor cases, and approximately 20% of all intracranial operations are performed for the removal of these tumors.[1] Such procedures cause wide fluctuations of hemodynamic variables, particularly in heart rate and blood pressure (BP). There are several intense noxious stimuli during these surgeries, including the use of sympathomimetic drug-soaked nasal packing, insertion of a nasal speculum, sphenoid drilling and cutting, and resection of the sellar and suprasellar regions.[2,3] Anesthesia for transsphenoidal sinus surgery of the pituitary gland aims to maintain hemodynamic stability, optimize cerebral oxygenation, promote a bloodless surgical field, prevent perioperative complications, and facilitate rapid smooth emergence for early neurological examination.[4,5]

Dexmedetomidine is a selective alpha-2 agonist with sedative and analgesic properties, inducing anesthetic- and opioid-sparing effects.[6–8] Owing to its properties of early postoperative pain prevention, reduction of nausea and vomiting events, and decreased shivering, it has been widely accepted as an adjunct to general anesthesia in various surgical procedures and intensive care.[9] The hemodynamic effects of dexmedetomidine cover both central and peripheral mechanisms. In the central nervous system, the activation of alpha-2 adrenoreceptors causes a reduction in sympathetic outflow and significant decrease in both heart rate and BP.[5] In the peripheral mechanism, dexmedetomidine causes peripheral vasoconstriction, inducing early-phase hypertension,[5] yet it does not cause respiratory depression at therapeutic doses. It has the potential to reduce intraoperative anesthetic drug requirements and, thus, reduce hemodynamic instability intraoperatively.[2–5,10] Nevertheless, a conclusion has not been reached, especially regarding the appropriate dosage for its continuous intravenous infusion.

In the authors' own research, we used dexmedetomidine as an adjunct to propofol for awake craniotomy[11] and in combination with desflurane anesthesia for cervical spine surgery.[12] A loading dose of dexmedetomidine of 0.5 mcg/kg in 30 minutes provided very good sedation with stable hemodynamics.[11,12] However, dexmedetomidine infusion doses vary from 0.2 to 0.7 mcg/kg/h.[2–12] Therefore, we aimed to compare the effects of low (0.2 mcg/kg/h) and intermediate doses (0.5 mcg/kg/h) of dexmedetomidine during maintenance of anesthesia on the amount of blood loss (primary objective) and compare the hemodynamics and operative times (secondary objectives) of patients undergoing transsphenoidal pituitary tumor removal with the aforementioned doses.

Methods

After obtaining institutional research committee approval from two institutes (approval numbers: Si302/2016 and NIT 027/2017), we conducted a double-blind, randomized, and controlled study on 80 patients (40 in each group) who underwent elective pituitary tumor removal via the transsphenoidal approach at two tertiary hospitals between December 2016 and November 2019. After enrolment, all patients were followed up until discharge.

We enrolled patients aged 18 to 65 years with American Society of Anesthesiologists (ASA) physical status grades I and II diagnosed with pituitary tumors who underwent elective transsphenoidal tumor removal. Exclusion criteria included the following: preoperative opioid use, preoperative Glasgow Coma Scale score < 15, bradycardia (heart rate < 50 beats/min), uncontrolled hypertension (systolic BP [SBP] > 160 mm Hg), ongoing treatment with beta-blockers or other alpha-agonists, uncontrolled or severe cardiovascular disease, liver or kidney disease (estimated glomerular filtration rate < 60 mL/min/1.7 m^2), obesity (body mass index > 30 kg/m^2), pregnancy, allergy to dexmedetomidine, and refusal to participate in the study.

Patients were randomized into two groups. Randomization was conducted using a block of four computer-generated numbers, and these group numbers were placed inside concealed envelopes, which were subsequently opened by the researchers who prepared the study drug but were not involved in patient care processes or outcome measurement.

On the morning of surgery, every patient received 0.9% sodium chloride (0.9% NaCl) at 80 mL/h with a loading dose of 100 mg of hydrocortisone, followed by 200 mg of hydrocortisone for a 24-hour infusion to account for the prophylaxis of adrenal insufficiency after pituitary tumor removal. Endocrinologists were consulted for every case, and hydrocortisone prophylaxis was administered for every case of pituitary surgery. In the operating room, standard monitoring comprising an electrocardiogram, noninvasive BP, and pulse oximeter was conducted. An arterial line was used in some cases, as indicated, and the bispectral index (BIS; Medtronics, United States) was used to monitor the depth of anesthesia. BIS was used to improve anesthetic delivery and ensure prompt recovery.[13] Anesthesia was induced with 1.5 mcg/kg of fentanyl and1.5 to 2.0 mg/kg of propofol. The dose was titrated until a verbal response was lost. Tracheal intubation was facilitated with 0.15 mg/kg of intravenous cisatracurium and subsequently continuously dripped at a rate of 0.06 to 0.1 mg/kg/h and terminated at least 30 minutes before the end of operation. Anesthesia was maintained using a mixture of air, oxygen, and desflurane to maintain a BIS level of 40 to 60. Intermittent doses of fentanyl (0.5 mcg/kg) were added according to the intensity of stimuli. Group I patients received dexmedetomidine (Precedex, Abbott, Chicago, Illinois, United States) with a loading dose of 0.5 mcg/kg in 30 minutes (started at nasal preparation), followed by 0.2 mcg/kg/h intraoperatively, while group II patients received the same loading dose, followed by 0.5 mcg/kg/h intraoperatively. Later, dexmedetomidine was stopped after complete tumor resection in both groups. The study drugs were prepared at different concentrations according to the group allocation; however, both study drugs looked alike, and the rate of infusion was based on the patient's weight. Patients, surgeons, and anesthesiologists were blinded to the dose and concentration of the study drug.

BP was controlled within 20% of the baseline BP or SBP at 90 to 140 mm Hg. If hypotension (SBP < 90 mm Hg) occurred, the percentage of desflurane decreased to a BIS of 60 followed by administration of fluid and vasopressors (ephedrine or norepinephrine) or atropine (for bradycardia). If hypertension (SBP > 140 mm Hg) occurred, patients were treated by increasing the percentage of desflurane to a BIS of 40, administering more fentanyl and nicardipine if the expected BP was not achieved. However, in cases with severely unstable hemodynamics, the in-charge anesthesiologists could terminate the study and stop the study drug infusion; unstable patients were still included as this is an intention-to-treat analysis. The total gas flow rate was kept constant at 1 L/min. All patients received dexamethasone (10 mg) and ondansetron (8 mg) as antiemetic prophylaxis. The ventilator was set with FiO_2 0.5 and a tidal volume of 8 mL/kg with positive end-expiratory pressure of 5 cm H_2O, and the respiratory rate was adjusted to maintain an end-tidal CO_2 concentration of 35 to 40 mm Hg (►**Fig. 1**).

At the end of the operation, desflurane was stopped, and the patient was ventilated with 100% oxygen (fresh gas flow of 6 L/min). Neuromuscular blockade was antagonized with the injection of 2.5 mg of neostigmine and 1.2 mg of atropine. Extubation was performed after clinical signs of adequate reversal (adequate tidal volume and minute ventilation, full awakening, return of reflexes, and ability to follow simple commands). Extubation time was defined as the time between desflurane discontinuation and extubation. Sedation level was assessed using the Riker sedation score after extubation, with scores ranging from 1 (unarousable) to 7 (dangerous agitation), with a score of 4 indicating calm and cooperation.

All patients were transferred to the neurointensive care unit for postoperative care. All surgeries in both groups were performed by experienced neurosurgeons (> 10 years' experience). Although this study was conducted at two institutes, both groups of surgeons performed the same standard operation, including nasal preparation and nasal packing.

Outcome measurements included patients' demographics, hemodynamic parameters (BP and heart rate at baseline before induction and subsequently every 5 minutes until the end of the operation), episodes of hypotension, blood loss, fluid, operative time (time from nasal preparation to finishing nasal packing at the end of operation), recovery profiles

At the ward: the day before surgery, the researcher accessed for eligibility and obtained informed consent. In the morning, 0.9% NaCl (1,000 mL) was infused for maintenance fluid. The hydrocortisone 100 mg was given as an iv push and then 200 mg was mixed with 0.9% NaCl 250 ml for a 24 hour infusion.

In the operating room:

1. Standard monitoring was applied and Bispectral index (BIS) was used for anesthetic depth monitoring.
2. General anesthesia was induced with propofol 1.5–2.0 mg/kg, fentanyl 1.5 mcg/kg, and then cis-atracurium 0.15 mg/kg.
3. Maintain anesthesia with desflurane (Bispectral index (BIS) 40-60), intermittent iv fentanyl (0.5-1.0 mcg/kg), cisatracurium infusion (0.06-0.1 mg/kg/hr) (stop half an hour before the end of the operation).
4. Dexmedetomidine loading dose of 0. 5 mcg/ kg in 30 minutes (started at nasal preparation), followed by 0.2 mcg/kg/hr (group I) or 0.5 mcg/kg/hr (group II) (stop after complete tumor removal).
5. Maintain a blood pressure of 20% of the baseline or a systolic blood pressure of 90-140 mmHg. Hypotension was treated with decreasing desflurane at a BIS of 60, a vasopressor, and fluid. Hypertension was treated with increasing desflurane at a BIS of 40, fentanyl, and antihypertensive drugs.
6. Ventilator setting: FiO_2 0.5, tidal volume of 8 ml/kg, and respiratory rate was adjusted to maintain end tidal CO_2 of 35–40 mmHg.
7. At the end of the operation, desflurane was stopped, then the patient was ventilated with 100% oxygen (fresh gas flow of 6 L/min). The neuromuscular blockade was antagonized with neostigmine 2.5 mg and atropine 1.2 mg. Extubation was performed after clinical signs of adequate reversal.
8. The sedation level was assessed by the Riker sedation score.

Postoperative period: Patient was taken care of in the neuro-intensive care unit, then went back to the surgical ward.

Fig. 1 Study protocol.

(extubation time and Riker sedation score), doses of anesthetic agents, and perioperative complications. The outcome assessors were blinded to group allocation. Estimated blood loss was calculated by subtracting the irrigating fluid from the volume of blood in the suction bottles and swabs, and the in-charge anesthesiologists administered fluid replacement according to the standards of good practice. Desflurane consumption was measured by the end-tidal percentage of desflurane every 15 minutes. In-charge anesthesiologists who were blinded to group allocation assessed all intraoperative outcomes.

Statistical Analysis

On the basis of a previously published study,[2] the sample size was calculated according to the difference in blood loss between both groups (135 ± 94 vs. 225 ± 129 mL), with alpha errors of 0.05 and beta errors of 0.1. Thirty-four patients in each group were required according to the n4 studies version 1.4.1. To avoid possible dropouts, the authors intended to include 40 patients in each group. Statistical analysis was performed using SPSS software version 18.0 (IBM Corporation, United States). Chi-square tests were performed to compare categorical data. Continuous variables were compared using Student's *t*-test for normally distributed data and the Mann–Whitney *U* test for nonnormally distributed data. Repeated-measures analysis of variance was used to compare BP and heart rate. A *p*-value of < 0.05 was considered statistically significant.

Results

A total of 80 patients were analyzed (►**Fig. 2**). Demographic data such as age, weight, height, and sex were comparable. Pituitary tumors were mostly nonfunctional. The most common underlying disease was hypertension, which was comparable between groups (►**Table 1**).

No significant difference in intraoperative blood loss was observed between the groups (group I = 320 [220–525] mL vs. group II = 250 [100–487] mL, $p = 0.070$). However, patients in group I received more fluids than those in group II (1983 ± 1084 vs. 1530 ± 824 mL, $p = 0.039$). At several different time points between both groups (►**Supplementary Fig. S1**, available in the online version), there were no differences in the intraoperative BP or heart rate. However, there were significantly more episodes of hypotension in group II than in group I (►**Table 2**).

With comparable tumor volumes (►**Table 2**), group II (intermediate-dose infusion) had shorter operative times

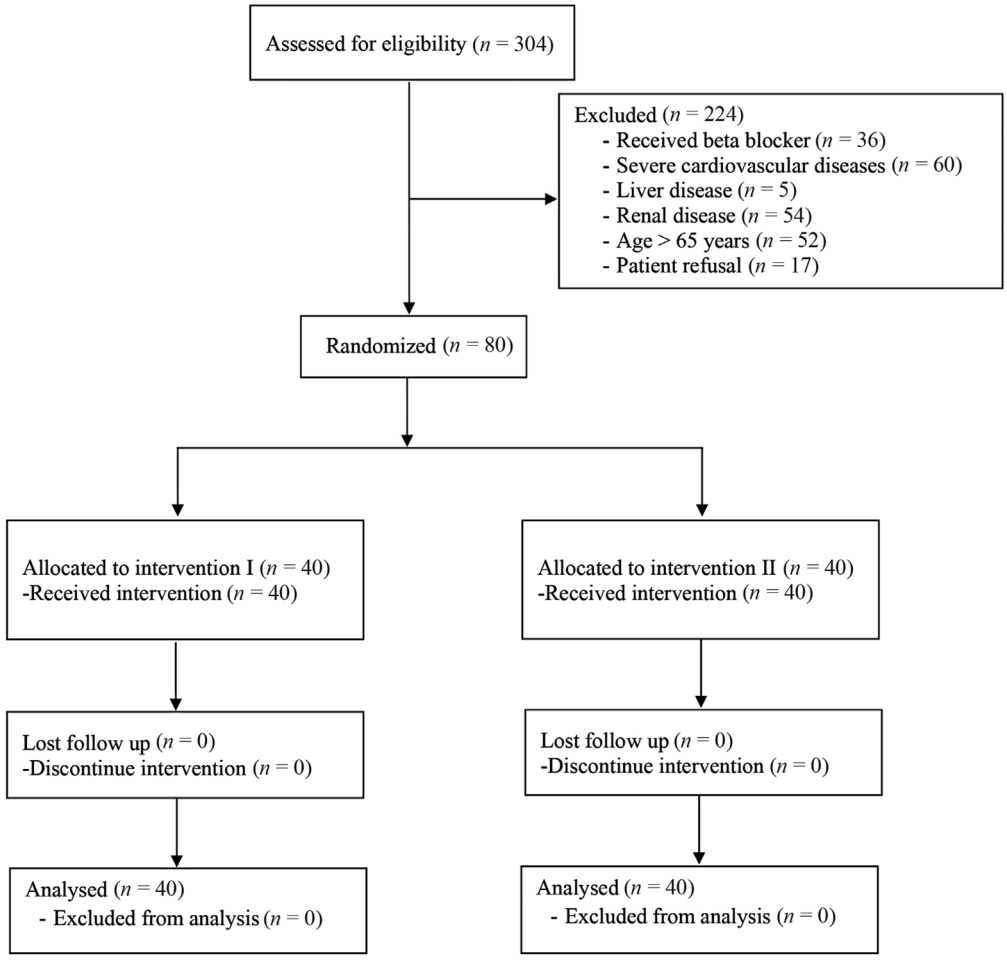

Fig. 2 Consort diagram of the study.

Table 1 Demographic data

	Group I ($n = 40$) (dex = 0.2 mcg/kg/h)	Group II ($n = 40$) (dex = 0.5 mcg/kg/h)	*p*-Value[a]
Age (y)	43.6 ± 12.9	47.9 ± 11.8	0.123
Weight (kg)	66.9 ± 11.9	63.8 ± 11.9	0.251
Male:female (*n*)	14:26	19:21	0.161
ASA physical status I:II	19:21	15:25	0.178
Pituitary tumor			0.099
Nonfunctioning	25 (62.5%)	25 (62.5%)	
Functioning	8 (20%)	2 (5.0%)	
Prolactin	2	2	
Growth hormone	5	0	
Adrenocorticotrophic hormone	1	0	
Hypofunction[b]	7 (17.5%)	13 (32.5%)	
Underlying diseases			
Diabetes mellitus	4 (10.0%)	6 (15.0%)	0.499
Hypertension	14 (35.0%)	15 (37.5%)	0.816
Others	3 (7.5%)	4 (10.0%)	0.614

Abbreviations: ASA, American Society of Anesthesiologists; dex, dexmedetomidine; SD, standard deviation.
Note: Data presented as mean ± SD or number (%) as appropriate.
[a]$p < 0.05$, statistically significant.
[b]Hypofunction, secondary hypothyroid or secondary adrenal insufficiency or hypopituitarism.

Table 2 Intra- and postoperative data

	Group I ($n = 40$) (dex = 0.2 mcg/kg/h)	Group II ($n = 40$) (dex = 0.5 mcg/kg/h)	*p*-Value
Tumor volume (cm^3)	8.3 (4.0–21.8)	10.0 (3.7–23.4)	0.827
Operative time (min)	179 ± 74	142 ± 58	0.018[a]
Estimated blood loss (mL)	320 (220–525)	250 (100–487)	0.070
Fluid intake (mL)	1,983 ± 1,084	1,530 ± 824	0.039[a]
Urine output (mL)	620 (300–957)	457 (310–750)	0.310
Total fentanyl (mcg)	178 ± 70	157 ± 67	0.174
Fentanyl maintenance (mcg)	78 ± 63	62 ± 63	0.262
Fentanyl maintenance (mcg/kr/operative hour)	0.43 ± 0.36	0.43 ± 0.44	0.720
Average bispectral index (0–100)	43 ± 4	44 ± 4	0.297
Average desflurane (%)	4.6 ± 0.58	4.2 ± 0.89	0.031[a]
Hypotension episodes 1 ≥ 2	 15 (37.5%) 7 (17.5%)	 7 (17.5%) 15 (37.5%)	0.034[a]
Riker sedation score (0–7)	4.1 ± 1.0	4.1 ± 0.7	0.979
Extubation time (min)	15.3 ± 7.6	12.7 ± 6.6	0.108
Postoperative 24-h morphine consumption (mg)	7.29 ± 5.72	7.93 ± 4.16	0.575
Postoperative nausea and vomiting	4 (10%)	4 (10%)	1.000
Length of stay (d)	12.2 ± 6.4	10.9 ± 4.5	0.307

Abbreviations: dex, dexmedetomidine; SD, standard deviation.
Note: The Riker sedation score was used for evaluation after extubation, with scores ranging from 1 (unarousable) to 7 (dangerous agitation) and a score of 4 indicating calm and cooperation. Data are presented as mean ± SD, median (range), or *n* (%), as appropriate. The comparisons used Student's *t*-test or Mann–Whitney *U* test, as appropriate.
[a]$p < 0.05$, statistically significant.

than group I (179 ± 74 vs. 142 ± 58 minutes, $p = 0.018$). For the same anesthetic depth, patients in group II required a lower percentage of end-tidal desflurane concentration than those in group I ($4.6 \pm 0.58\%$ vs. $4.2 \pm 0.89\%$, $p = 0.031$). However, there were no significant differences in extubation time and Riker sedation score after extubation between the two groups. Moreover, no differences were found in the 24-hour morphine consumption, postoperative nausea and vomiting, or length of hospital stay between the groups (►**Table 2**).

Two patients (one in each group) remained intubated due to delayed emergence (the reason for the delayed emergence in patient in group I was not noted) and severe unstable hemodynamics (need for vasopressor infusion). The patients were later extubated in the neurointensive care unit. One patient in group II experienced severe hypotension and needed norepinephrine infusion, and one patient in group I experienced severe hypertension and needed nicardipine infusion.

Discussion

Many studies[2–5,10,14] have supported the use of dexmedetomidine intravenous infusion for a transsphenoidal approach in patients undergoing pituitary tumor removal. The beneficial effects of dexmedetomidine intravenous infusion include improved hemodynamics, reduced blood loss, decreased anesthetics, and decreased extubation time. However, no previous studies have examined the different dosages of dexmedetomidine administration for maintenance or the lower loading dose (0.5 mcg/kg) in this type of surgery. Most trials[2–5,10,14] used dexmedetomidine infusion of 1 µg/kg over 10 minutes as a loading dose, followed by 0.5 mcg/kg/h continuously without any comparison with other regimens.

We compared the effects of low (0.2 mcg/kg/h, group I) and intermediate doses (0.5 mcg/kg/h, group II) of dexmedetomidine during maintenance of anesthesia. We found comparable blood loss and overall hemodynamics in both groups, but more brief episodes of hypotension and decreased surgical time were observed in group II.

The average amount of fluid administered to patients in group I was higher because of a slightly higher blood loss. Although optimal volume ratios to compensate for lost blood are estimated to be 1.5 to 2.0:1.0 for crystalloid, many anesthesiologists give crystalloid volume that is 3 to 4 times the amount of lost blood (liberal regimen) or even higher. Fluid management varied according to the blinded in-charge anesthesiologist. Considering the low surgical risk and low-risk patients in this study, the goal of 1 to 2 L positive fluid balance is recommended for preventing acute kidney injury.[15]

In our study, the protocol allowed for the use of vasoactive drugs and adjusted the anesthetic depth to maintain hemodynamics. Despite this, with an intermediate dose of dexmedetomidine infusion, these patients experienced more episodes of transient hypotension than patients with a low dose of dexmedetomidine infusion. After hypotension occurred, it was immediately treated; therefore, BP recording showed comparable results between both groups. Clinicians should be aware of the potential harmful effects of intraoperative bradycardia and hypotension.[14,16] In contrast to our results, other studies[3,5,17] showed that dexmedetomidine achieved better control of hemodynamics than placebo or oral clonidine.

With the same anesthetic depth (BIS 40–60) in our study, dexmedetomidine at 0.5 mcg/kg/h during anesthetic maintenance showed less desflurane consumption. Dexmedetomidine decreases the use of inhalation anesthetics.[5,9,10,14,16,18]

According to two recent meta-analyses[10,18] comparing dexmedetomidine with placebo, supplementation with dexmedetomidine for transsphenoidal resection of pituitary adenoma[10] and nasal surgeries[18] significantly reduced blood loss and doses of inhaled anesthetic gas and fentanyl.

In this study, dexmedetomidine at a dose of 0.5 mcg/kg/h during anesthetic maintenance significantly decreased operative time compared with 0.2 mcg/kg/h of dexmedetomidine. This result was in concordance with a recent meta-analysis (of nasal surgeries)[18] that showed that the systemic administration of dexmedetomidine decreased surgical time, intraoperative blood loss, and doses of intraoperative inhaled anesthetic gas and fentanyl compared with placebo. The decreased operative time might be related to the vasoconstrictive effect of dexmedetomidine,[5] which is a decrease in the need for multiple intraoperative pauses for suctioning and packing.

Emergence agitation (EA) is a common surgical complication in the nasal cavity. In nasal surgeries,[19] dexmedetomidine provides better postoperative pain scores and less EA. However, in our study, most patients woke up calm and cooperative in both groups because they all received dexmedetomidine. The low dexmedetomidine dose for anesthetic maintenance had the same emergence effect as the intermediate dose. EA can be better controlled with remifentanil than with dexmedetomidine.[20,21]

In previous studies,[21,22] dexmedetomidine infusion was associated with a reduced incidence of EA but delayed extubation due to residual sedation and prolonged postanesthetic care unit stay. In contrast, some studies[2,5] showed faster recovery. Delayed or faster recovery was not observed in the present study, possibly because of a lower loading dose and low-to-intermediate dexmedetomidine infusion.

There are some limitations to this study. This study was performed in patients with ASA physical statuses I and II. The result might not be applicable to sicker patients or patients with cardiovascular disease who may negatively react to dexmedetomidine. We did not investigate surgeons' viewpoints on operative field visualization and their corresponding satisfaction; therefore, we were unable to draw a definite conclusion on whether faster operative time in group II was related to the dose of dexmedetomidine infusion.

Conclusion

In patients undergoing transsphenoidal pituitary tumor removal, an intermediate dose of dexmedetomidine (0.5 mcg/kg/h) as an anesthetic adjuvant may be associated with a shorter operating time and more episodes of transient

hypotension than a low dose of dexmedetomidine (0.2 mcg/kg/h), however, the blood losses were comparable.

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Conflict of Interest
None declared.

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