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ORIGINAL RESEARCH

Effect of Intraoperative Dexmedetomidine Use on Postoperative Delirium in the Elderly After Laryngectomy: A Randomized Controlled Clinical Trial

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Purpose: To examine whether intraoperative dexmedetomidine reduces postoperative delirium (POD) in elderly patients who underwent a laryngectomy.

Methods: Patients were randomly assigned to receive dexmedetomidine or a saline placebo infused during surgery. The study period was July 2020 to January 2022. Participants were elderly individuals (≥65 years) who underwent a laryngectomy. Immediately after induction of anesthesia, a 0.5 $\mu g.kg^{-1}$ bolus of study solution was administered for 10 min, followed by a maintenance infusion of 0.2 $\mu g.kg^{-1}.hr^{-1}$ until the end of surgery. Patients were assessed daily for POD (primary outcome). Plasma inflammatory factors were measured at baseline, on the first postoperative day, and on the third postoperative day.

Results: In total, 304 male patients were randomized; 299 patients [median (interquartile range) age, 69.0 (67.0–73.0) years] completed in-hospital delirium assessments. There was no difference in the incidence of POD between the dexmedetomidine and control groups (21.3% [32 of 150] vs 24.2% [36 of 149], P=0.560). However, dexmedetomidine reduced POD in patients with laryngeal cancer and a higher tumor stage (21.6% vs 38.5%; OR, 0.441; 95% CI, 0.209–0.979; P=0.039). Dexmedetomidine reduced levels of C-reactive protein (CRP) (P=0.0056) and interleukin 6 (IL-6) (P<0.001) on the first and third postoperative days, respectively. More patients had intraoperative hypotension in the dexmedetomidine group (29.3% [44 of 150] vs 17.4% [26 of 149], P=0.015).

Conclusion: Intraoperative dexmedetomidine administration did not prevent POD in patients with laryngeal cancer. Dexmedetomidine reduced serum CRP and IL-6 levels postoperatively but caused a higher occurrence of intraoperative hypotension in elderly patients after a laryngectomy.

Keywords: dexmedetomidine, laryngectomy, postoperative delirium, inflammatory factors, surgery complication

Introduction

Populations are aging rapidly across the world,[1] and the number of older adults undergoing surgery is increasing.[2] Notably, postoperative delirium (POD) is a common postoperative complication, with an incidence of up to 54.4% especially in older patients after a major surgery.[3] POD is an independent predictor for postoperative mortality associated with adverse outcomes, such as a loss of independence, failure to return to work, substantial increase in healthcare costs, and death.[4–6] Delirium is also linked with cognitive decline[7,8] and an increased risk of dementia.[9] Patients with head and neck tumors are a high-risk group for POD due to impairment, disfigurement, and psychosocial problems during surgery treatment.[10,11] It is essential to develop effective strategies, both pharmacologic and nonpharmacologic interventions, to reduce POD.[12–14]

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Several studies have shown that dexmedetomidine, an α_2-adrenergic agonist, may be a promising pharmacologic option for preventing POD,[15–18] as the neuroprotective effect of dexmedetomidine relates to its anti-inflammatory effect.[19,20] Conversely, some studies do not support its neuroprotective effect in reducing POD.[21] In our previous observational study,[22] we found that intraoperative dexmedetomidine use had a preventive effect on POD in patients who underwent a laryngectomy. Due to limitations of our previous study and inconsistent findings of other studies, we conducted a prospective, single-center, randomized controlled trial to investigate whether intraoperative dexmedetomidine use prevents POD. We also aimed to evaluate perioperative changes in serum inflammatory factors, since inflammation contributes to the pathogenesis of delirium.[23,24]

Methods

Participants

This trial was approved by the Eye and ENT Hospital, Fudan University Review Board and registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2000032062). Written informed consent was obtained from all patients. This study was conducted in the accordance with the Declaration of Helsinki. During the period of July 2020 to January 2022, patients aged ≥65 years scheduled for a laryngectomy were recruited and randomly allocated (1:1 ratio) to receive dexmedetomidine or normal saline (NS).

Exclusion criteria consisted of patients who were unable to complete baseline cognitive assessments; factors that might affect cognitive assessment, such as language, visual, and auditory dysfunction; an unstable mental health or mental illness; sick sinus syndrome; second-degree or third-degree heart block or clinically significant sinus bradycardia; contraindication for use of an α_2-adrenergic agonist; female sex; preoperative delirium or pre-existing cognitive impairment; and patients who declined to participate.

Anesthesia Protocol

Dexmedetomidine or NS was unknown to participants, investigators, and clinicians. The anesthesiologist was not blinded to the study. The concentration of dexmedetomidine (Jiangsu Enhua Medicine Co., Ltd., Jiangsu, China) was 2 $\mu g.mL^{-1}$. Immediately after induction of anesthesia, a 0.5 $\mu g.kg^{-1}$ bolus of study solution was administered for 10 min followed by a maintenance infusion of 0.2 $\mu g.kg^{-1}.hr^{-1}$ until the end of surgery. In case malignant arrhythmia or severe bradycardia during dexmedetomidine pumping occurs, dexmedetomidine use discontinues. All patients underwent standard intraoperative monitoring. In general, anesthetic management comprised propofol for induction, sevoflurane for maintenance (minimal alveolar concentration, MAC 0.8–1.0), remifentanil and sufentanil for intraoperative use, and nondepolarizing muscle relaxant use. Hydromorphone was administered at the end of surgery for pain control. The depth of anesthesia was maintained at bi-spectral indices of 40–60 as long as possible. Body temperature was maintained at ≥36 °C. Antiemetics were administered to prevent nausea and vomiting. Postoperatively, patients typically received patient-controlled analgesia (sufentanil), one intravenous bolus containing 0.025 $\mu g.kg^{-1}$ sufentanil, and 2 mg of flurbiprofen axetil, with a lockout of 10 min and a background hourly infusion of 0.025 $\mu g.kg^{-1}$ sufentanil and 2 mg of flurbiprofen axetil.

POD Assessment

Investigators with psychological training in POD assessments were blinded. The once-daily POD assessment was conducted on the first 5 postoperative days because evidence suggests that over 90% of delirium occurs within this period.[25] Patients were interviewed once daily between 4:00 pm and 6:00 pm. The presence of delirium was assessed using the confusion assessment method diagnostic algorithm.[26] Once the patients are diagnosed with POD, they will be evaluated continuously and be treated if necessary until patients' cognitive functioning return to normal.

Inflammatory Factor Measurements

Blood samples were collected at three time points: shortly after anesthesia induction, and in the morning on postoperative day 1 and postoperative day 3. Samples were collected in tubes containing ethylenediaminetetraacetic acid and processed within 3 h of collection. Samples were centrifuged at 3000 × g for 10 min, and plasma was removed and stored at −80 °C until the assay. Plasma concentrations of C-reactive protein (CRP) and interleukin 6 (IL-6) were measured using enzyme-linked immunosorbent

assay (ELISA) according to the manufacturer's instructions (Human ELISA Kits, Biotech Well, Shanghai, China). All experiments were repeated three times. All coefficients of intra-assay and inter-assay variation for quantitative detection were less than 5%.

Other Data

Participants were interviewed prior to surgery to obtain baseline information, including level of education, as well as Mini-Mental State Examination (MMSE) and Cumulative Illness Rating Scale (CIRS) results. Additional perioperative information was obtained through a review of medical records. The earliest stage of laryngeal cancer is stage 0, also known as carcinoma in situ; the other main stages range from stage I to IV. We defined tumor stages 3 and 4 as higher tumor stages. Intraoperative hypotension was defined as a blood pressure 70% of baseline and lasting at least 30 min.[27,28] Self-reported sleep quality was assessed using five dichotomous questions: (1) "Did you sleep well?" (2) "Did you sleep better than expected?" (3) "Did you sleep better than at home?" (4) "Were you awake for a long time before falling asleep?" and (5) "Do you feel sufficiently rested?" If the patient answered yes, they scored 1 point for these questions. The score for question 4 was reversed. A score <2 was categorized as poor sleep.[29] An unauthorized version of the Chinese MMSE was used by the study team without permission. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

Statistical Analysis

Based on our previous study,[22] we found that in patients aged ≥65 years, the overall incidence of POD was 15.0%, with 8.6% in patients who received dexmedetomidine and 20.3% in patients who did not receive dexmedetomidine. A sample size of 284 participants (142 per group) was calculated to have 80% power to detect differences at a statistical threshold of <0.05. We anticipated a 5% withdrawal and recruited 304 participants.

Continuous variables were compared using Student's unpaired *t*-test or the Mann–Whitney *U*-test, as appropriate. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test. Changes in the serum inflammatory factors of CRP and IL-6 were analyzed using generalized linear mixed modeling. We reported two-sided P-values and considered a value of $p<0.05$ to be statistically significant.

Results

Participant Characteristics

During the study period, 350 patients were included. Thirteen patients declined to participate preoperatively. Thirty-three patients switched to laser treatment after re-assessment by surgeons in the operating room. Therefore, 304 participants were included and categorized as follows: 152 to the dexmedetomidine group and 152 to the saline placebo group. Five patients dropped out during POD assessment, with two patients dropping out after receiving dexmedetomidine and three patients dropping out after receiving saline (Figure 1).

At baseline, the median (interquartile range) age of patients was 69.0 (67.0–73.0) years. Characteristics of patients in the dexmedetomidine and placebo groups are shown in Table 1. There were more patients with a higher tumor stage in the dexmedetomidine group (74 vs 52, P=0.012). Intraoperative sufentanil use was less in the dexmedetomidine group (27.1 μg vs 30.6 μg, P<0.001).

Outcome of POD

A total of 299 patients completed the in-hospital POD assessments. Among these patients, 68 (22.7%) developed POD, including 32 in the dexmedetomidine group (21.3%) and 36 (24.2%) in the control group; the incidence of POD was comparable between the two groups (OR, 0.851; 95% CI, 0.493–1.45; P=0.560) (Table 2).

Participants were stratified by tumor stage into two strata (lower tumor stage and higher tumor stage). We found that in patients with laryngeal cancer and a lower tumor stage, the incidence of POD was similar between the control group (21.1%) and the dexmedetomidine group (16.5%) (OR, 1.35; 95% CI, 0.61–2.99; P=0.444). However, dexmedetomidine reduced POD in patients with laryngeal cancer and a higher tumor stage (21.6% vs 38.5%; OR, 0.441; 95% CI, 0.209–0.979; P=0.039) (Table 2).

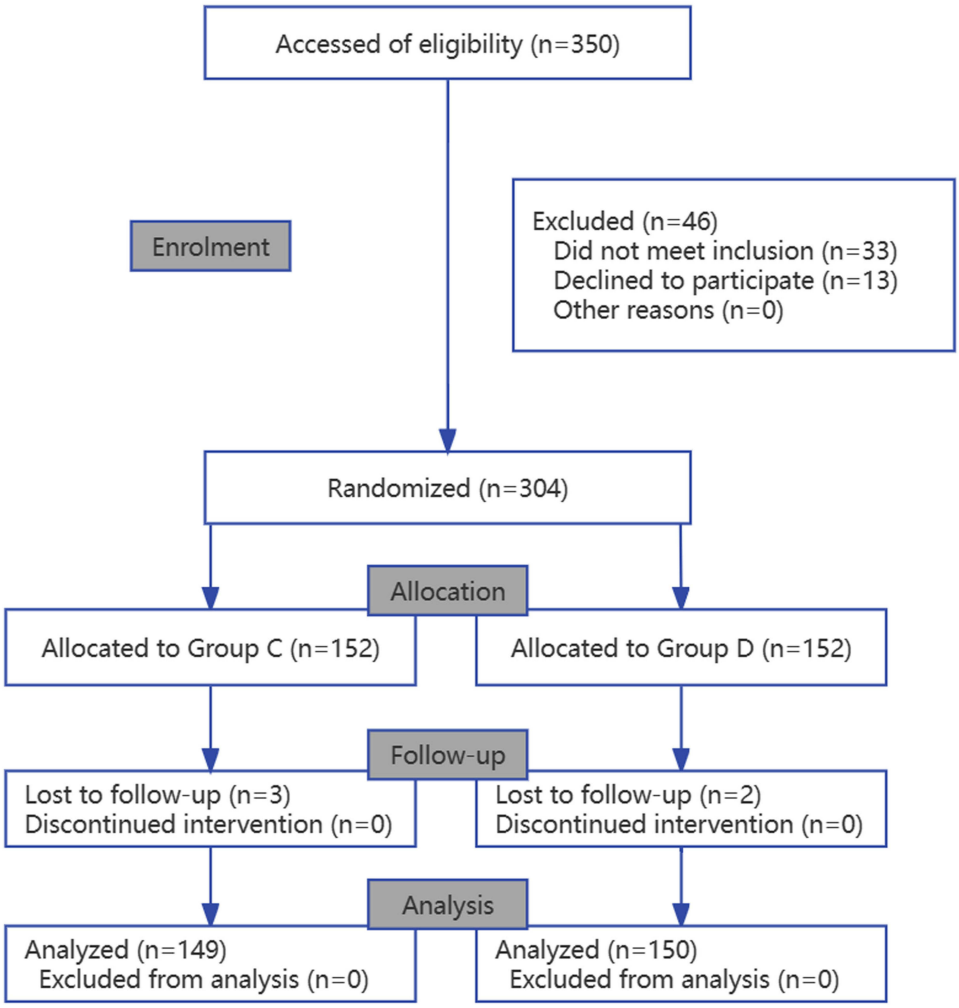

Figure 1 Consolidated Standards of Reporting Trials diagram. A patient flow diagram is shown. Group C, Control group; Group D, Dexmedetomidine group.

Changes in Inflammatory Factors

In total, 160 patients underwent a full course of blood sampling. Patient characteristics are presented in Table 3. Results of the mixed effect model showed that there were significant differences in CRP and IL-6 levels between the dexmedetomidine and control groups (P=0.0056 for CRP and P<0.001 for IL-6) (Figure 2). Figure 2A illustrates that CRP levels in the control group show an upward trend, while those in the dexmedetomidine group are stable Figure 2B illustrates that IL-6 levels in the control group show an upward trend, whereas those in the dexmedetomidine group show a downward trend.

Other Outcomes

More patients in the dexmedetomidine group had intraoperative hypotension (42 vs 26, P=0.015). Hospital stay length (median:13 days vs 13 days, P=0.785) were comparable between the two groups. No patients experienced malignant arrhythmia or severe bradycardia during dexmedetomidine pumping.

Discussion

In the current study, we found that intraoperative dexmedetomidine did not reduce POD in elderly patients after a laryngectomy. Intraoperative dexmedetomidine use prevented the inflammatory factors of CRP and IL-6 from increasing postoperatively but was related to a higher occurrence of intraoperative hypotension.

Table 1 Patient Characteristics Between the Two Groups

Factors	Control (N=149)	Dexmedetomidine (N=150)	P
Age (year) Mean±SD	70.1 ± 4.2	70.4 ± 5.0	0.622
Tumor stage			0.012
Lower tumor stage (I&II)	97 (65.1)	76 (50.7)	
Higher tumor stage (III&IV)	52 (34.9)	74 (49.3)	
Educational level			0.321
High (greater than high school degree), no. (%)	38 (25.5)	46 (30.7)	
Low (middle school and elementary school), no. (%)	111 (74.5)	104 (69.3)	
MMSE, Mean ± SD	23.9 ± 4.9	24.3 ± 4.8	0.389
CIRs, Mean ± SD	5.1 ± 2.3	5.0 ± 2.2	0.676
Previous cerebral stroke			0.093
Yes, no. (%)	21 (14.1)	12 (8.0)	
No, no. (%)	128 (85.9)	138 (92.0)	
Poor sleep quality			0.770
Yes, no. (%)	44 (29.5)	42 (28.0)	
No, no. (%)	105 (70.5)	108 (72.0)	
Hypertension			0.272
Yes, no. (%)	77 (51.7)	68 (45.3)	
No, no. (%)	72 (48.3)	82 (54.7)	
Diabetes mellitus			0.899
Yes, no. (%)	25 (16.8)	26 (17.3)	
No, no. (%)	124 (83.2)	124 (82.7)	
Alcohol abuse			0.657
Yes, no. (%)	99 (66.4)	96 (64.0)	
No, no. (%)	50 (33.6)	54 (36.0)	
Current Smoker			0.491
Yes, no. (%)	133 (89.3)	130 (86.7)	
No, no. (%)	16 (10.7)	20 (13.3)	
Family history of dementia			0.723†
Yes, no. (%)	4 (2.7)	3 (2.0)	
No, no. (%)	145 (97.3)	147 (9.0)	
Intraoperative hypotension			0.015
Yes, no. (%)	26 (17.4)	44 (29.3)	
No, no. (%)	123 (82.6)	106 (70.7)	
Use of sufentanil (μg), Mean ± SD	30.6 ± 8.7	27.1 ± 8.3	<0.001
Surgery duration (min), Median (IQR)	175 (112, 283)	194 (123, 296)	0.350
Anesthesia duration (min), Median (IQR)	223 (130, 298)	233 (124, 286)	0.498
Recovery time (min), Median (IQR)	38 (32, 45)	39 (30, 43)	0.168
Hospital stay (day), Median (IQR)	13 (10, 15)	13 (9, 15)	0.785

Notes: †, Fisher's exact test.
Abbreviations: MMSE, Mini-Mental State Examination; CIRs, Cumulative Illness Rating Scale; SD, standard deviation; IQR, interquartile range.

Table 2 Incidence of POD Between Two Groups

Factors	Control	Dexmedetomidine	OR (95% CI)	P
Over-all POD	N=149	N=150	0.851 (0.493–1.453)	0.560
Yes, no. (%)	36 (24.2)	32 (21.3)		
No, no. (%)	113 (32.1)	118 (78.7)		

(*Continued*)

Table 2 (Continued).

Factors	Control	Dexmedetomidine	OR (95% CI)	P
POD in patients with lower tumor stage (I& II) Yes, no. (%) No, no. (%)	N=97 16 (16.5) 81 (83.5)	N=76 16 (21.1) 60 (78.9)	1.350 (0.610–2.987)	0.444
POD in patients with higher tumor stage (III& IV) Yes, no. (%) No, no. (%)	N=52 20 (38.5) 32 (61.5)	N=74 16 (21.6) 58 (78.4)	0.441 (0.209–0.979)	0.039

Abbreviations: POD, postoperative delirium; OR, odd ratio.

Table 3 Patient Characteristics Between the Two Groups of Blood Sampling

Factors	Control (N=80)	Dexmedetomidine (N=80)	P value
Age (year), Mean±SD	67.4 ± 5.5	67.7 ± 5.7	0.685
Higher tumor stage, n(%)	25 (31.3%)	35 (43.8%)	0.103
Low educational level, n(%)	56 (70%)	55 (68.8%)	>0.999
MMSE, median (IQR)	26 (21, 28)	25 (22, 28)	0.941
CIRs, median (IQR)	4 (4,7)	4 (4,6)	0.392
Presence of previous cerebral stroke, n(%)	12 (15.0)	7 (8.8%)	0.329
Presence of hypertension, n(%)	36 (45)	35 (43.8)	>0.999
Presence of diabetes mellitus, n(%)	17 (21.3)	15 (18.8)	0.844
Presence of alcohol abuse, n(%)	19 (23.8)	26 (32.5)	0.291
Presence of current smoker	10 (12.5)	11 (13.8)	>0.999
Intraoperative hypotension, n(%)	11 (13.8)	25 (31.3)	0.013
Use of sufentanil (μg), Mean ± SD	30.6 ± 9.7	26.0 ± 7.4	0.001
Surgery duration(min), median (IQR)	191 (107.3, 317.0)	197 (122.2, 298.5)	0.968
Anesthesia duration (min), Median (IQR)	224 (120, 311)	228 (138, 295)	0.850
Recovery time (min), Median (IQR)	37 (30, 43)	39 (31, 44)	0.293
POD, n(%)	16 (20%)	18 (22.5)	0.847

Abbreviations: MMSE, Mini-Mental State Examination; CIRs, Cumulative Illness Rating Scale; POD, postoperative delirium; SD, standard deviation; IQR, interquartile range.

The incidence of POD was 21.3% in patients who received dexmedetomidine. This is higher than a previously reported rate that was used to calculate the sample size (8.6%).[22] Possible reasons for this are as follows. First, the study design was different (a prospective, randomized study vs an observational study). Second, the sample size of patients aged ≥65 years in the current study was larger (150 vs 58 patients).

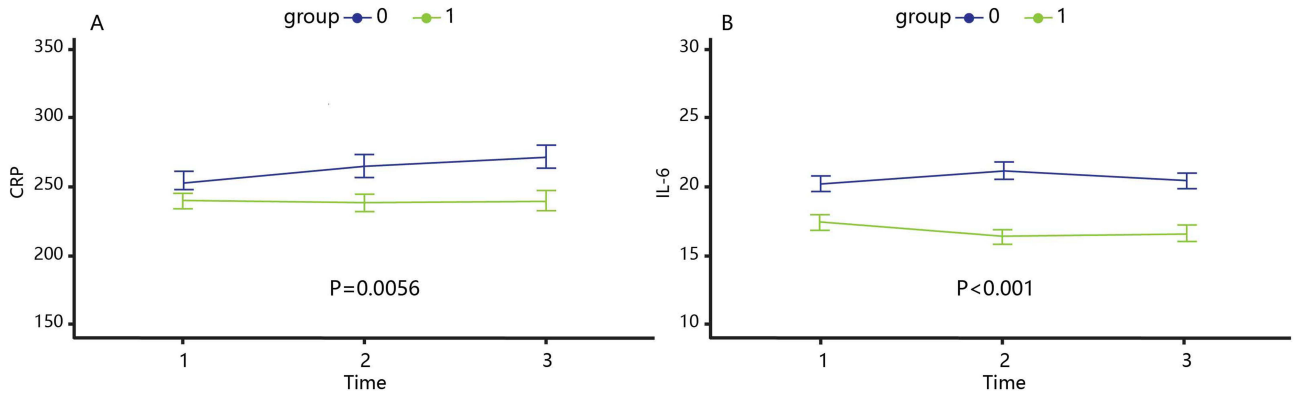

Figure 2 The change in serum inflammation factors CRP (**A**) and IL-6 (**B**) at three timepoints. Group 0=Control group, Group 1=Dexmedetomidine group; Time 1=baseline, Time 2=postoperative day 1, Time 3=postoperative day 3.

The findings of our study add to those of several studies that tested whether intraoperative dexmedetomidine use can reduce POD. Previous research involving patients under general anesthesia suggests that perioperative dexmedetomidine use can reduce POD after a major surgery.[15–19,30] Though, consistent with a previous study,[21] we did not find a difference in delirium in patients randomized to perioperative dexmedetomidine use. However, subgroup analyses show that intraoperative dexmedetomidine use decreased the incidence of POD in patients with a higher tumor stage.

Previous studies concerning POD were usually carried out for severe traumatic surgery such as cardiac surgery[16] and major non-cardiac surgery such as abdominal and thoracic surgery.[15] The surgical procedure for a laryngectomy is relatively less traumatic, especially for laryngeal tumors of stage I and II. However, the higher the stage, the more advanced the cancer, indicating more tissue trauma and a more severe inflammatory response caused by a laryngectomy. In addition, research on the association between inflammation and cancer pathogenesis reveals that inflammation can facilitate cancer angiogenesis, invasion, and metastasis.[31] Furthermore, CRP was significantly correlated with tumor size and stage in a previous study.[32] This may explain why one of our observations was that dexmedetomidine use reduced the incidence of POD in patients with a higher tumor stage.

Surgery elicits a systemic inflammatory response[33] that involves the pathophysiology of delirium.[34] Dexmedetomidine has been reported to exert its neuroprotective effect by inhibiting the expression and release of inflammatory factors.[19,20] CRP is associated with an increased risk for POD[35] and IL-6 has a clear association with severe postoperative complications in thoracic surgery.[36] In our study, we found that, compared to NS, dexmedetomidine reduced CRP and IL-6 postoperatively. This finding may provide evidence for the anti-inflammatory effects of dexmedetomidine.

We found that more patients in the dexmedetomidine group experienced intraoperative hypotension. Hypotension is one of the most common adverse reactions associated with dexmedetomidine.[37] As a result of temporarily insufficient cerebral perfusion, delirium may be a more sensitive manifestation of postoperative cerebral dysfunction. In terms of the negative result that dexmedetomidine use did not reduce the incidence of POD, an explanation may be that intraoperative hypotension outweighs the anti-inflammatory effect of dexmedetomidine. Our findings also support the optimization of intraoperative hemodynamics to lower the incidence of POD.

Limitations and Strengths

This study had several limitations. First, as this was a single-center study, only patients scheduled for a laryngectomy were enrolled. Therefore, the generalizability of our results may be limited. Second, we assessed POD only once daily and its incidence may have been underestimated. The single assessment was performed each day between 4:00 pm and 6:00 pm by investigators experienced in assessing POD, which means that POD may have been well detected only in the evening. In addition, we only included male patients, since there were few female patients with a laryngeal tumor and they tended to decline to participate in the study. Third, we did not collect data regarding the number of POD episodes, duration of POD, severity of POD, or potential consequences of POD, such as those affecting mortality and cognitive function at certain time points (eg, 6 months and 1 year). Finally, for pragmatic reasons, anesthesiologists were not blinded to group assignments. Furthermore, investigators who performed postoperative follow-ups and blood tests did not participate in perioperative care and had no knowledge of treatment assignments.

Strengths of this study include the following. We conducted our research in a homogeneous group for which we can make conclusive statements, and the observed changes in plasma levels of inflammatory factors over several days after surgery may improve our understanding of the correlation between postoperative inflammation and POD.

Conclusions

Based on these findings, we conclude that intraoperative dexmedetomidine use did not reduce POD in elderly patients after a laryngectomy. Dexmedetomidine use was associated with decreased postoperative CRP and IL-6 levels. The use of intraoperative dexmedetomidine resulted in a higher occurrence of intraoperative hypotension.

Data Sharing Statement

All data generated or analyzed during this study were included in the published article. Further inquiries about the datasets can be directed to the corresponding author on reasonable request. Any information we share will be deidentified.

Ethical Statement

Ethics Approval: This trial was approved by the Eye and ENT Hospital, Fudan University Review Board and registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2000032062). Written informed consent was obtained from all patients.

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Disclosure

The authors report no conflicts of interest in this work.

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