ORIGINAL RESEARCH

Effect of Perioperative Dexmedetomidine Infusion on Postoperative Delirium in Elderly Patients Undergoing Oral and Maxillofacial Surgery: A Randomized Controlled Clinical Trial

Tianlin Liu [ID], Jingtang Tuo, Qianjie Wei, Xiuwei Sun, Haochen Zhao, Xiaochen Zhao, Min Qu

Department of Anesthesiology, Cangzhou Central Hospital, Cangzhou, People's Republic of China

Correspondence: Tianlin Liu, Department of Anesthesiology, Cangzhou Central Hospital, Cangzhou, 061000, People's Republic of China,
Tel +86 18003370383, Email 1377689587@qq.com

Purpose: The aim of the study was to determine whether perioperative dexmedetomidine administration can improve postoperative delirium in elderly patients undergoing oral and maxillofacial surgery.

Patients and Methods: This was a prospective double-blind randomized controlled clinical trial conducted in Cangzhou Central Hospital from December 2021 to March 2022. Patients aged 65 and older underwent oral and maxillofacial surgery under general anesthesia. Eligible patients were randomly assigned to dexmedetomidine or control group. Dexmedetomidine was injected intravenously from 10 min before induction of anesthesia to 30 min before the end of surgery in dexmedetomidine group, while patients in the control group were given normal saline at the same rate during the same time period. The primary measurement indicators were the incidence and duration of delirium in the first five days after surgery. The secondary measurement indicators were Visual Analogue Score (VAS) for the first 24 hours following surgery, subjective sleep quality score within 24 hours postoperatively and intraoperative adverse reactions.

Results: One hundred and twenty patients were randomly assigned. Baseline characteristics were similar between two groups. The incidence and duration of postoperative delirium did not differ statistically between two groups (all P > 0.05). Compared with control group, VAS scores in dexmedetomidine group were significantly lower at 6, 12, and 24 hours after surgery (all P < 0.05); moreover, Richards-Campbell Sleep Questionnaire (RCSQ) results were significantly improved 1 day after surgery in dexmedetomidine group (P < 0.05). Dexmedetomidine-related adverse reactions were similar in both groups (P > 0.05).

Conclusion: Intravenous infusion of dexmedetomidine 10 min before induction of anesthesia to half an hour before the end of surgery did not improve postoperative delirium in elderly patients undergoing oral and maxillofacial surgery; however, dexmedetomidine may be associated with decreased postoperative pain and improved postoperative sleep quality.

Keywords: postoperative delirium, dexmedetomidine, elderly, oral and maxillofacial surgery

Introduction

Postoperative delirium (POD) refers to brain dysfunction with acute onset and short course that occurs within 1 week after surgery.[1] It is characterized by attention disorder, consciousness level disorder (such as excitement, restlessness, gibberish, etc.), orientation disorders and sleep disorders (sleep-wake cycle disorder) and cognitive function change with obvious fluctuation and occurrence with obvious time characteristics.[2] It mainly occurred within 24h-72h after operation.[3,4] Postoperative delirium has adverse effects on early and long-term prognosis. Studies have shown that patients with delirium have an increased risk of postoperative complications, an increased risk of perioperative death, and a longer hospital stay and increased medical costs during hospitalization.[5,6] Long-term follow-up studies showed an increased incidence of long-term cognitive dysfunction, decreased quality of life, and increased long-term mortality after delirium.[7–9] There are many factors leading to postoperative delirium, including advanced age (≥65 years), dementia or cognitive impairment, a history of

neurological or psychiatric disorders, hearing or visual impairment, postoperative pain and disturbed sleep cycle.[10,11] The incidence of postoperative delirium has been reported to be ranging from 5% to 40%.[12]

In recent years, with the continuous development and improvement of surgical technology and anesthesia level, more and more patients suffering from oral and maxillofacial diseases have received surgical treatment. Patients undergoing oral and maxillofacial surgery were considered to be at high risk of postoperative delirium.[13] Furuya[14] showed that the incidence of delirium after oral and maxillofacial was higher than that of plastic surgery and ear, nose and throat surgery, and similar to that of neurosurgery. Advanced age, postoperative incision swelling and pain, and disturbed sleep cycle were risk factors for delirium.

Dexmedetomidine, a highly selective α_2 adrenergic receptor agonist, has analgesic effects and can produce sedative effects similar to natural sleep.[15,16] Dexmedetomidine can inhibit sympathetic excitation, reduce the release of catecholamine hormone, and play the roles of anti-inflammatory and anti-stress. However, the effect of dexmedetomidine on postoperative delirium remains controversial. A randomized controlled trial of perioperative infusion of dexmedetomidine showed that dexmedetomidine reduced the incidence of postoperative delirium.[17] However, in another randomized controlled trial, dexmedetomidine did not reduce the risk of postoperative delirium.[18] We hypothesized that perioperative administration of dexmedetomidine could improve postoperative delirium in patients undergoing oral and maxillofacial surgery.

Materials and Methods
Trial Design and Oversight
This was a prospective, double-blind, parallel randomized clinical trial conducted in Cangzhou Central Hospital. The study began on December 2nd, 2021 and ended on February 28th, 2022. This study was approved by the Ethics Committee of Cangzhou Central Hospital (2020–028-02) and was in compliance with the Helsinki Declaration. The project was registered in China Clinical Trial Center (ChiCTR2100053891). The informed consent was signed during the patient's visit the day before surgery.

Study Population
Inclusion criteria: Patients undergoing elective oral and maxillofacial surgery, regardless of gender, age ≥65 years, ASA I–II, preoperative MMSE score >24. Exclusion criteria: dementia, combined neuropsychiatric system diseases, emergency surgery, bradycardia (HR <50 beats/min), pathological sinus syndrome, heart block, serious cardiovascular and cerebrovascular diseases (Heart failure, myocardial infarction, cerebral infarction, cerebral hemorrhage), liver and kidney insufficiency, coagulation dysfunction and other systemic diseases, preoperative lesions with infection, drug allergy and patients transferred to ICU postoperatively.

Randomization and Masking
Patients were recruited and randomized by designated investigators. One day before surgery, patients who were cognitively normal and met the inclusion criteria were randomly assigned to dexmedetomidine group (group D) or the control group (group C) in a 1:1 ratio using a computer-generated random number table opaque envelopes containing sequential numbered and group assignments were used to ensure blindness prior to randomization. The patient and all researchers, including the anesthesiologist, post-anesthetic resuscitation unit (PACU) medical staff and postoperative follow-up staff, were blinded to the treatment being administered.

Trial Procedures
Venous access was opened for all patients after admission to the operating room. Electrocardiography (ECG), pulse oximetry (SpO_2), PCO_2 at END-Tidal (Pet CO_2), and invasive blood pressure were routinely monitored. Preoxygenation was given before induction of anesthesia. In group D, dexmedetomidine was injected intravenously at a dosage of 0.5 μg/kg for 10 min before anesthesia induction, followed by continuous infusion at a rate of 0.4μg/kg/h until half an hour before the end of surgery.[19] Group C was given the same amount of normal saline intravenously at the same time. Anesthesia induction was followed by intravenous propofol 1.5 mg/kg, cis-atracurium 0.2 mg/kg, and sufentanil 0.3 μg/kg. Three minutes later, endotracheal intubation was

performed. About 0.1μg/kg sufentanil was added intravenously before slicing. Propofol $2.0 \sim 4.0$ mg/(kg·h) and remifentanil $0.1 \sim 0.25$ μg/(kg·h) were used to maintain anesthesia. The dosage of propofol and remifentanil was adjusted according to the surgical stimulation to maintain the mean arterial pressure (MAP) within 20% of the base value, the heart rate (HR) was maintained at more than 50 beats/min, and noradrenaline and atropine were used when necessary. The Pet CO_2 remains in the range of 35 and 45 mmHg. Bispectral index (BIS) remained in the 40–60 range. Flurbiprofen axetil 50mg was injected intravenously 20 min before the end of surgery. At the end of the procedure, the infusion of all anesthetic drugs was stopped. When the patient returned to consciousness, cough and swallowing reflexes returned, and tidal volume reached pre-anesthesia level, the endotracheal tube was removed and the patient was transferred to the PACU.

Postoperative delirium was assessed from the first postoperative day by the investigators who were trained prior to the study and did not know the grouping using the 3-Minute Diagnostic Interview for CAM (3D-CAM) once every night until the fifth postoperative day.[20,21] 3D-CAM, a new 3-minute diagnostic assessment of delirium using CAM algorithms. It contains the following characteristics: ①acute change or fluctuating in consciousness, attention or speech, ②inattention, ③disorganized thinking, ④altered level of consciousness, ⑤an acute change in mental status from baseline. Delirium could be diagnosed when the patient's clinical symptoms meet the ①+ ②+③, ①+ ②+④ or ②+⑤ criteria.[21]

Postoperative Analgesia

The patient controlled intravenous analgesia pump was connected during skin suturing (1.5 μg/kg sufentanil in 100 mL saline for all patients). Parameter Settings were as follows: Flow rate, 2 mL/h; Bolus, 0.5 mL; lockout time, 15 min. Visual Analogue Scores (VAS) were used to assess postoperative pain within 24 hours after surgery.[22] When VAS score ≥4, 50 mg flurbiprofen axetil was administered intravenously as rescue analgesia. VAS scores (rest/moving) at 6, 12, and 24 hours postoperatively, numbers of postoperative analgesic pump compression and flurbiprofen axetil consumption within 24 hours following surgery were recorded.

Postoperative Sleep Quality

Richards Campbell Sleep Questionnaire (RCSQ) was adopted to assess sleep quality the first day following surgery, which was one of the few valid assessments for measuring sleep at night and has been used in another study related to delirium.[23]

Adverse Reactions

The incidence of bradycardia, hypotension and hypoxemia in two groups were recorded during surgery. The above three adverse reactions were defined as bradycardia (heart rate <50 beats/min), hypotension (systolic blood pressure <90 mm Hg or a decrease of more than 20% from baseline), hypoxemia (pulse oxygen saturation <90%).

Statistical Analysis

Based on previous clinical studies, the incidence of postoperative delirium was assumed to be 30% in older patients undergoing oral and maxillofacial surgery.[13] A total of 118 randomized patients (1:1, 54 in each group) completed the primary outcome assessment to achieve 80% efficacy with alpha error at 5%. A total of 125 patients were screened for this study, taking 5% drop rate into account.

SPSS (version 21.0 for Windows; IBM Corporation, Armonk, NY, USA) was used to analyze and process all data. The measurement data of normal distribution were expressed as mean ± standard deviation. Independent sample t-test was used for inter-group comparison, and ANOVA of repeated measurement data was used for intra-group comparison. Enumeration data were represented by example (%), chi-square test or Fisher exact test (as appropriate) was used for the ratio between groups. $P < 0.05$ was considered statistically significant.

Result

A total of 125 patients were screened. Of these patients, 1 patient refused to participate, 2 patients had a history of atrioventricular block, 1 patient had a history of mental illness, and 1 patient inability to cooperate due to aural disorders. Finally, 120 patients met the inclusion criteria and were randomly assigned to dexmedetomidine or control group (Figure 1). The basic data of patients in the two groups are shown in Table 1. There were no significant differences in
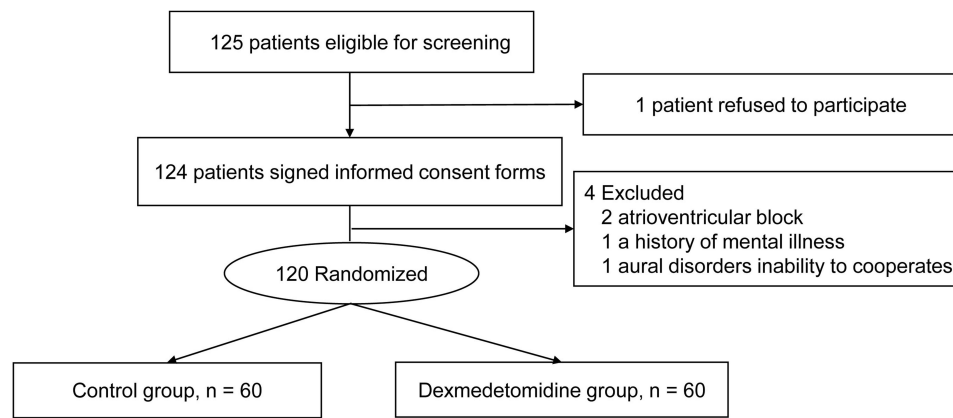
Figure 1 Flow diagram of the study.

gender, age, body mass index (BMI), American society of Anesthesiologists (ASA), education level, incidence of hypertension, diabetes, coronary heart disease, smoking and drinking history between the two groups.

Incidence and Duration of Delirium

A total of 13 patients developed postoperative delirium after surgery, including 5 patients in dexmedetomidine group (8.3%) and 8 patients in control group (13.3%) (P = 0.378).

In this study, all 13 patients with postoperative delirium presented symptoms on the first postoperative day, and the longest duration was 4 days. The mean duration of postoperative delirium in the control group and dexmedetomidine group were 2.25 ± 1.035 and 2.0 ± 1.225 days, respectively, the duration of delirium was not statistically different between the two groups (P = 0.700).

VAS Scores, the Numbers of Analgesic Pump Compression and Flurbiprofen Axetil Consumption

Compared to control group, dexmedetomidine group had lower VAS scores both at rest and with movement at 6, 12, and 24 hours following surgery (all P < 0.05, Table 2).

Table 1 Clinical Characteristics of Patients

Characteristics	Group C (n=60)	Group D (n=60)	P
Age [years, mean (SD)]	72.07±5.880	71.30±6.680	0.506
Gender [Male (%)]	29 (48.3)	31 (51.7)	0.855
Weight [kg, mean (SD)]	68.33±9.038	69.07±12.260	0.710
BMI [kg/m2, mean (SD)]	24.98±2.69	24.85±3.49	0.828
ASA (I, %)	34 (56.7)	28 (46.7)	0.361
Education ≥ 9 years [n (%)]	10 (16.7)	14 (23.3)	0.494
Hypertension [n (%)]	23 (38.3)	19 (31.7)	0.566
Diabetes mellitus [n (%)]	10 (16.7)	7 (11.7)	0.602
Coronary heart disease [n (%)]	13 (21.7)	9 (15)	0.480
Smoker [n (%)]	12 (20)	16 (26.7)	0.518
Heavy drinking [n (%)]	10 (16.7)	12 (20)	0.814

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; C, control; D, dexmedetomidine.

Table 2 VAS Scores, the Numbers of Analgesic Pump Compression, Flurbiprofen Axetil Consumption and RCSQ Between Two Groups

		Group D (n=60)	Group C (n=60)	P value
VAS rest	6 hrs	2.0±0.6	2.5±0.7	<0.001
	12 hrs	1.5±0.5	1.8±0.6	0.001
	24 hrs	1.2±0.4	1.5±0.5	0.001
VAS moving	6 hrs	2.5±0.5	2.8±0.4	0.002
	12 hrs	1.9±0.5	2.1±0.5	0.039
	24 hrs	1.3±0.5	1.6±0.5	0.013
Numbers of compression		30.6±9.1	33.9±10.9	0.074
Flurbiprofen axetil consumption		52.5±39.5	110.8±47.9	<0.001
RCSQ		61.8±6.1	54.3±6.9	<0.001

Abbreviations: C, control; D, dexmedetomidine; VAS, Visual Analogue Scores; RCSQ, Richards-Campbell Sleep Questionnaire; hrs, hours.

Compared to control group, although the numbers of postoperative analgesic pump compression in the dexmedetomidine group showed a trend of fewer, there was no significant statistical difference between the two groups ($P > 0.05$, Table 2).

Compared to control group, the consumption of flurbiprofen axetil in dexmedetomidine group was significantly reduced ($P < 0.05$, Table 2).

Postoperative Sleep Quality

RCSQ scores of dexmedetomidine group were significantly higher than that of control group in the first day following surgery ($P < 0.05$, Table 2).

Intraoperative and Postoperative Measures

There was no significant difference in infusion volume, blood loss, urine volume, operating time, anesthesia time, BIS and hospital stay between the two groups (Table 3).

Table 3 Intraoperative and Postoperative Variables

Variables	Group D (n=60)	Group C (n=60)	P value
Infusion volume [mL, mean (SD)]	1018.33±425.26	981.67±353.43	0.608
Blood loss [mL, mean (SD)]	99.50±50.07	101.67±43.15	0.800
Urine volume [mL, mean (SD)]	228.33±125.00	217.50±92.89	0.591
Operating time [minutes, mean (SD)]	155.92±77.50	153.50±60.78	0.850
Anesthesia time [minutes, mean (SD)]	190.08±85.69	186.67±71.14	0.813
BIS	51.9±1.16	52.02±0.77	0.518
Length of stay (days)	9.03±2.80	9.02±2.45	0.972

Abbreviations: C, control; D, dexmedetomidine; BIS, bispectral index.

Table 4 Intraoperative Adverse Reactions of Two Groups

	Group D (n=60)	Group C (n=60)	P value
Bradycardia [no. (%)]	8 (13)	4 (7)	0.362
Hypotension [no. (%)]	3 (5)	1 (2)	0.619
Hypoxemia [no. (%)]	0	0	

Abbreviations: C, control; D, dexmedetomidine, no, number.

Adverse Reactions

Intraoperative adverse reactions including bradycardia and hypotension showed no statistical difference between the two groups (all P > 0.05, Table 4). There was no hypoxemia in both two groups during surgery.

Discussion

In this single-center, randomized, double-blind, placebo-controlled trial, we found no significant difference in the incidence and duration of delirium between the dexmedetomidine group and the placebo group, however, we found that dexmedetomidine may be associated with decreased postoperative pain score and improved postoperative sleep quality in elderly patients undergoing oral and maxillofacial surgery.

In this study, the incidence of postoperative delirium in elderly patients undergoing oral and maxillofacial surgery was 10.8%, much lower than 33% in a previous retrospective clinical study.[24] The reasons are as follows. First of all, when selecting subjects, we excluded patients with preoperative mental disorders, including dementia, which was reported to be a risk factor for postoperative delirium,[25] and the exclusion of patients with mental disorders was one of the reasons for the low incidence in this study. Secondly, we excluded patients admitted to ICU after surgery. It has been reported that the noisy ICU environment and lack of comfort from relatives may contribute to higher rates of delirium,[26] however, the comfort and care of family members and the relatively quiet environment in the ward may reduce the incidence of delirium to a certain extent. Thirdly, in our study, propofol was selected to induce and maintain anesthesia. In oral surgery, the incidence of delirium after inhalation anesthesia with sevoflurane was reported to be higher than that of total intravenous anesthesia with propofol.[27] Therefore, propofol use may potentially reduce the incidence of delirium. Lastly, anesthesia induction was not performed with midazolam. Midazolam is a short-acting benzodiazepine, often used to induce anesthesia, which has been reported to increase the risk of delirium.[28]

The incidence and duration of postoperative delirium are two ways to evaluate the efficacy of delirium treatment.[29,30] Previous reports have shown that dexmedetomidine reduces the incidence of postoperative delirium in ICU patients and in patients undergoing major surgery such as cardiac surgery or major non-cardiac surgery.[17,31] However, the results of our study suggest that dexmedetomidine has a neutral effect on postoperative delirium after oral and maxillofacial surgery. There are probably several reasons. In that cardiac surgery, dexmedetomidine was injected from entry into the operating room to admission to ICU after the end of surgery,[17] while in this study, the infusion time was from 10 minutes before anesthesia induction to half an hour before the end of surgery, the infusion duration of dexmedetomidine was significantly shortened. In that major non-cardiac surgery, the loading dose and maintenance dose of dexmedetomidine were 0.6 μg/kg within 10 min and 0.5 μg/kg·h, respectively,[31] which were higher than the dose in this study. A randomized controlled trial conducted by Turan A also showed that dexmedetomidine did not reduce the incidence of delirium,[18] which was similar to our results.

Dexmedetomidine, a selective alpha$_2$ agonist, exerts analgesic effects and its analgesic mechanism was different from opioids.[16] The results in our study suggested that dexmedetomidine can reduce postoperative pain scores, which was consistent with previous study.[32] Continuous infusion of dexmedetomidine from 10 min before induction of anesthesia to half an hour before the end of surgery, combined with opioids during surgery, may play a multi-mode analgesic effect, thereby reducing postoperative pain score.[33] There was no significant difference in the number of postoperative analgesic

pump presses between the two groups, which may be because surgeons tend to use salvage analgesia of flurbiprofen axetil after surgery, thus reducing the number of patients pressing analgesic pump.

Dexmedetomidine is widely used as a sedative. In 2021, Huang et al published a systematic review showing that dexmedetomidine had advantages in improving postoperative sleep quality,[34] which was consistent with our results that dexmedetomidine improved the RCSQ scores in elderly patients undergoing oral and maxillofacial surgery. Sleep deprivation was reported to be closely related to delirium,[35] however, in this study, dexmedetomidine improved sleep quality but did not improve delirium symptoms. The reason may be that dexmedetomidine improves sleep quality but does not alter sleep cycles, and normalizing sleep cycles was more effective in reducing delirium.[36]

In this study, we found that dexmedetomidine did not increase the incidence of adverse events, which was consistent with a previously published review,[37] but monitoring and management still should be taken to ensure clinical safety.

It must be admitted that there are still some limitations in our research. First, the incidence of delirium in this study was lower than that selected for sample size calculation, so the sample size of this study may not be enough to detect differences in delirium, and a larger randomized controlled trial could be conducted in the future. Second, the dose of dexmedetomidine used in this study was relatively small, which could not rule out the improvement effect of larger dose of dexmedetomidine on delirium. Third, we only followed up the occurrence of postoperative delirium during the night period of each day. Although delirium was characterized by nocturnal exacerbation and a higher chance of delirium was found during the night follow-up, the loss of follow-up of delirium during the day cannot be ruled out.

Conclusion

In elderly patients undergoing oral and maxillofacial surgery, intravenous infusion of dexmedetomidine 10 minutes before induction of anesthesia to half an hour before the end of surgery did not reduce the incidence and duration of postoperative delirium; however, it may be associated with reduced postoperative pain and improved sleep quality.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study will be available upon reasonable request from Cangzhou Central Hospital. Email: 1377689587@qq.com; Telephone: +86 18003370383.

Ethical Approval

The study was approved by Cangzhou Central Hospital Ethics Committee (ethical register number: 2020-028-02) and was in compliance with the Helsinki Declaration. The project was registered in China Clinical Trial Center (ChiCTR2100053891).

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

References

1. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth*. 2020;125:492–504. doi:10.1016/j.bja.2020.06.063
2. Curtis MS, Forman NA, Donovan AL, et al. Postoperative delirium: why, what, and how to confront it at your institution. *Curr Opin Anaesthesiol*. 2020;33:668–673. doi:10.1097/ACO.0000000000000907
3. Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br J Anaesth*. 2018;121:1005–1012. doi:10.1016/j.bja.2017.11.087
4. Glumac S, Kardum G, Karanovic N. Postoperative cognitive decline after cardiac surgery: a narrative review of current knowledge in 2019. *Med Sci Monit*. 2019;25:3262–3270. doi:10.12659/MSM.914435
5. Duning T, Ilting-Reuke K, Beckhuis M, et al. Postoperative delirium - treatment and prevention. *Curr Opin Anaesthesiol*. 2021;34:27–32. doi:10.1097/ACO.0000000000000939

6. Hughes CG, Boncyk CS, Culley DJ, et al. American society for enhanced recovery and perioperative quality initiative joint consensus statement on postoperative delirium prevention. *Anesth Analg*. 2020;130:1572–1590. doi:10.1213/ANE.0000000000004641

7. Goldberg TE, Chen C, Wang Y, et al. Association of delirium with long-term cognitive decline: a meta-analysis. *JAMA Neurol*. 2020;77:1373–1381. doi:10.1001/jamaneurol.2020.2273

8. Shi Z, Mei X, Li C, et al. Postoperative delirium is associated with long-term decline in activities of daily living. *Anesthesiology*. 2019;131:492–500. doi:10.1097/ALN.0000000000002849

9. Janssen TL, Steyerberg EW, van Hoof-de Lepper C, et al. Long-term outcomes of major abdominal surgery and postoperative delirium after multimodal prehabilitation of older patients. *Surg Today*. 2020;50:1461–1470. doi:10.1007/s00595-020-02044-0

10. Wu J, Yin Y, Jin M, et al. The risk factors for postoperative delirium in adult patients after Hip fracture surgery: a systematic review and meta-analysis. *Int J Geriatr Psychiatry*. 2021;36:3–14. doi:10.1002/gps.5408

11. Enomoto R, Lee-Hiraiwa E. Elimination of the causes of poor sleep underlying delirium is a basic strategy to prevent delirium. *Curr Mol Pharmacol*. 2021;14:132–137. doi:10.2174/1874467213666200424150709

12. Swarbrick CJ, Partridge JSL. Evidence-based strategies to reduce the incidence of postoperative delirium: a narrative review. *Anaesthesia*. 2022;77 (Suppl 1):92–101. doi:10.1111/anae.15607

13. Ortner F, Eberl M, Otto S, et al. Patient-related and anesthesia-dependent determinants for postoperative delirium after oral and maxillofacial surgery. Results from a register-based case-control study. *J Stomatol Oral Maxillofac Surg*. 2021;122:62–69. doi:10.1016/j.jormas.2020.04.002

14. Furuya H, Nakahashi K, Hirai K, et al. Masui-go kurinikku de no chokusetsu mensetsu o shiyō shita masui manzoku-do no hyōka [Assessment of anesthesia satisfaction using direct interviews at post-anesthesia clinic]. *Masui*. 2001;50:240–245. Japanese.

15. Qin C, Jiang Y, Lin C, et al. Perioperative dexmedetomidine administration to prevent delirium in adults after non-cardiac surgery: a systematic review and meta-analysis. *J Clin Anesth*. 2021;73:110308. doi:10.1016/j.jclinane.2021.110308

16. Kaye AD, Chernobylsky DJ, Thakur P, et al. Dexmedetomidine in Enhanced Recovery After Surgery (ERAS) protocols for postoperative pain. *Curr Pain Headache Rep*. 2020;24:21. doi:10.1007/s11916-020-00853-z

17. Likhvantsev VV, Landoni G, Grebenchikov OA, et al. Perioperative dexmedetomidine supplement decreases delirium incidence after adult cardiac surgery: a randomized, double-blind, controlled study. *J Cardiothorac Vasc Anesth*. 2021;35:449–457. doi:10.1053/j.jvca.2020.02.035

18. Turan A, Duncan A, Leung S, et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. *Lancet*. 2020;396:177–185. doi:10.1016/S0140-6736(20)30631-0

19. Xin X, Chen J, Hua W, et al. Intraoperative dexmedetomidine for prevention of postoperative delirium in elderly patients with mild cognitive impairment. *Int J Geriatr Psychiatry*. 2021;36:143–151. doi:10.1002/gps.5406

20. Ji M, Wang J, Yang X, et al. Validation of the 3-minute diagnostic interview for CAM-defined Delirium in Chinese older adults. *Geriatr Nurs*. 2021;42:21–26. doi:10.1016/j.gerinurse.2020.10.021

21. Marcantonio ER, Ngo LH, O'Connor M, et al. 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. *Ann Intern Med*. 2014;161:554–561. doi:10.7326/M14-0865

22. Shafshak TS, Elnemr R. The visual analogue scale versus numerical rating scale in measuring pain severity and predicting disability in low back pain. *J Clin Rheumatol*. 2021;27:282–285. doi:10.1097/RHU.0000000000001320

23. Sun Y, Jiang M, Ji Y, et al. Impact of postoperative dexmedetomidine infusion on incidence of delirium in elderly patients undergoing major elective noncardiac surgery: a randomized clinical trial. *Drug Des Devel Ther*. 2019;13:2911–2922. doi:10.2147/DDDT.S208703

24. Ishibashi-Kanno N, Takaoka S, Nagai H, et al. Postoperative delirium after reconstructive surgery for oral tumor: a retrospective clinical study. *Int J Oral Maxillofac Surg*. 2020;49:1143–1148. doi:10.1016/j.ijom.2020.01.018

25. Ding G, Hua S, Chen J, et al. Does cognitive decline/dementia increase Delirium risk after stroke? *Psychogeriatrics*. 2021;21:605–611. doi:10.1111/psyg.12720

26. Boehm LM, Jones AC, Selim AA, et al. Delirium-related distress in the ICU: a qualitative meta-synthesis of patient and family perspectives and experiences. *Int J Nurs Stud*. 2021;122:104030. doi:10.1016/j.ijnurstu.2021.104030

27. Kocaturk O, Keles S. Recovery characteristics of total intravenous anesthesia with propofol versus sevoflurane anesthesia: a prospective randomized clinical trial. *J Pain Res*. 2018;11:1289–1295. doi:10.2147/JPR.S164106

28. Bastos AS, Beccaria LM, Silva DCD, et al. Prevalence of delirium in intensive care patients and association with sedoanalgesia, severity and mortality. *Rev Gaucha Enferm*. 2020;41:e20190068.

29. Janssen TL, Alberts AR, Hooft L, et al. Prevention of postoperative delirium in elderly patients planned for elective surgery: systematic review and meta-analysis. *Clin Interv Aging*. 2019;14:1095–1117. doi:10.2147/CIA.S201323

30. Shokri H, Ali I. A randomized control trial comparing prophylactic dexmedetomidine versus clonidine on rates and duration of delirium in older adult patients undergoing coronary artery bypass grafting. *J Clin Anesth*. 2020;61:109622. doi:10.1016/j.jclinane.2019.09.016

31. Li CJ, Wang BJ, Mu DL, et al. Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. *Br J Surg*. 2020;107:e123–e132. doi:10.1002/bjs.11354

32. Sane S, Shokouhi S, Golabi P, et al. The effect of dexmedetomidine in combination with bupivacaine on sensory and motor block time and pain score in supraclavicular block. *Pain Res Manag*. 2021;2021:8858312. doi:10.1155/2021/8858312

33. Maheshwer B, Knapik DM, Polce EM, et al. Contribution of multimodal analgesia to postoperative pain outcomes immediately after primary anterior cruciate ligament reconstruction: a systematic review and meta-analysis of level 1 randomized clinical trials. *Am J Sports Med*. 2021;49:3132–3144. doi:10.1177/0363546520980429

34. Huang X, Lin D, Sun Y, et al. Effect of dexmedetomidine on postoperative sleep quality: a systematic review. *Drug Des Devel Ther*. 2021;15:2161–2170. doi:10.2147/DDDT.S304162

35. Oh ES, Fong TG, Hshieh TT, et al. Delirium in older persons: advances in diagnosis and treatment. *JAMA*. 2017;318:1161–1174. doi:10.1001/jama.2017.12067

36. Hollinger A, von Felten S, Sutter R, et al. Study protocol for a prospective randomised double-blind placebo-controlled clinical trial investigating a better outcome with melatonin compared to placebo administered to normalize sleep-wake cycle and treat hypoactive ICU Delirium: the Basel BOMP-AID study. *BMJ Open*. 2020;10:e034873. doi:10.1136/bmjopen-2019-034873

37. Plambech MZ, Afshari A. Dexmedetomidine in the pediatric population: a review. *Minerva Anestesiol*. 2015;81:320–332.