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Original Article

Preventive effects of low-dose dexmedetomidine on postoperative cognitive function and recovery quality in elderly oral cancer patients

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Abstract: This study analyzed the preventive effects of low-dose dexmedetomidine on postoperative cognitive function and recovery quality in elderly oral cancer patients by observing the perioperative kinetics of inflammatory cytokines, cortisol and melatonin.A total of 149 elderly oral cancer patients who had undergone tumor resection surgery were selected and randomly divided into 2 groups, Group D and Group S. After surgery, Group D was assigned to take intravenous dexmedetomidine at a dose of 0.2 μg/kg/h for 12 h, while Group S was administered physiological saline in the same manner. On the day of surgery and for the first three postoperative days, the patients were assessed with the Mini-Mental State Examination (MMSE) and a 40-item quality of recovery score questionnaire (QoR40) at 7:00 am every morning. Venous blood was harvested at the same time. Then, IL-6, CRP, cortisol and melatonin levels were measured. There were no significant between-group differences in the baseline characteristics. After surgery, the MMSE and QoR40 scores in Group D were better than those in Group S. No between-group differences were observed in the incidences of severe hypotension and bradycardia. Moreover, respiratory depression was not observed in the 2 groups. The peaks of IL-6, CRP and cortisol concentrations in Group D were lower than those in Group S. However, the melatonin levels did not differ between the 2 groups. In elderly patients, intravenous dexmedetomidine administered postoperatively for 12 h at a dose of 0.2 ug/kg/h could improve postoperative cognitive function and recovery quality by decreasing excessive inflammation and stress levels.

Keywords: Elderly oral cancer patient, dexmedetomidine, postoperative cognitive function, postoperative recovery quality

Introduction

Postoperative cognitive dysfunction (POCD) is a common complication of the central nervous system (CNS) after surgery. It is characterized by impaired memory, orientation, perception, attention, verbal articulation and abstract thinking [1, 2]. The pathogenesis of POCD is complex. In addition, a recent study has found that infection, age, type and duration of surgery, type of and exposure time to narcotic drugs, preoperative cognitive impairment, sleep disorder and pain may be associated with POCD [3, 4]. Elderly oral cancer patients who undergo tumor resection surgery sometimes experience prolonged operation times, severe trauma, and long-term indwelling artificial airway; therefore, they are more inclined to experience POCD. POCD impairs patient quality of life, increases the burden of care, increases the in-hospitalization mortality rate, and causes long-term cognitive impairment [5]. The release of cytokines caused by the systemic stress evoked by surgery under anesthesia might lead to disturbances in brain function and, eventually, POCD [6].

Dexmedetomidine is a highly selective α2-adrenergic receptor agonist that can act as an analgesic, anxiolytic, sedative, and sympathetic blockade. However, it can also produce a dose-dependent decrease in blood pressure and heart rate, particularly in the elderly [7]. A past study reported that in bariatric surgery, combining the use of low-dose dexmedetomidine with general anesthesia could contribute to early postoperative recovery and minimize cardiovascular complications [8]; however, the efficacy and safety of using low-dose dexmedetomidine postoperatively in elderly oral cancer patients requires further practice and research.

This study analyzed the preventive effects of low-dose dexmedetomidine on postoperative cognitive function and recovery quality in elderly oral cancer patients by observing the perioperative kinetics of inflammatory cytokines, cortisol and melatonin.

Materials and methods

Patients and settings

A total of 149 elderly oral cancer patients who had undergone tumor resection surgery under general anesthesia and completed the observation period in the past several months were studied. The following inclusion criteria were applied: ASA (American Society of Anesthesiologists) physical status I~III, Age ≥65 years and ≤80 years, and postoperative stay in the SICU (Surgery Intensive Care Unit) ≥3 days. The following exclusion criteria were applied: an allergy to dexmedetomidine or another α2-adrenergic receptor agonist; the occurrence of severe hypotension (less than -30% of baseline values), and the requirement for continuous infusion of a vasoactive drug during the perioperative period to maintain blood pressure; a preoperative or intraoperative ECG (electrocardiogram) that prompted severe bradycardia (sinus rhythm, less than 50 beats/min) or a conduction block; a history of CNS, such as brain injury, stroke, neurosurgery, etc.; a history of mental illness; an MMSE (the Mini-Mental State Examination) score of <24 or dementia due to various etiologies; a history of endocrine and metabolic disorders; a history of inflammatory diseases; recent acceptance of glucocorticoid therapy; alcohol or drug dependence; secondary surgery or severe infectious complications (we used the presence of more than two SIRS criteria as a marker of inflammation) [9]; unwillingness to complete the experimental processes or language barriers; severe hearing or visual impairment; and illiteracy. This study was approved by the Ethics Committee at Shanghai Ninth People's Hospital Affiliated with Shanghai Jiao Tong University School of Medicine (Shanghai, China) and registered in the China Clinical Trial Registry (No.: ChiCTR-IPR-15006101). All patients provided written informed consent.

Anesthesia, surgery and postoperative treatment

None of the patients accepted premedication. SBP (systolic blood pressure), DBP (diastolic blood pressure), SPO2 (pulse oxygen saturation), ECG, SVV (stroke volume variation), BIS (bispectral index) and ETCO2 (end-tidal CO2) levels were continuously monitored during the perioperative period. Anesthesia was induced with intravenous midazolam, sufentanil, propofol and rocuronium, in turn. Anesthesia was maintained with sevoflurane inhalation, continuous intravenous infusion of propofol, intermittent intravenous sufentanil and vecuronium to maintain analgesia and muscle relaxant effects. During surgery, the respiratory parameters of the anesthesia machine were modulated to maintain ETCO2 between 30~40 mmHg, and the depth of anesthesia was adjusted to keep the BIS value at 40~60. The intraoperative Bp (blood pressure) fluctuations were maintained within ±30% of baseline values, and the HR (heart rate) was kept at 50~100 beats/min. All patients required an indwelling artificial airway postoperatively; then, they were transferred to the post anesthesia care unit (PACU). After a 2-h stay in the PACU, the patients woke up and were transported to the SICU. After entering the SICU, the patients were randomly divided into 2 groups: Group D and Group S. Group D was assigned to take intravenous dexmedetomidine at a dose of 0.2 μg/kg/h for 12 h, while Group S was administered physiological saline in the same manner. After surgery, the same treatments, such as continuous analgesic pump, anti-infection, eliminating phlegm and detumescence, were provided to all.

Assessment of postoperative cognitive function and recovery quality

On the day of surgery and for the first three postoperative days (i.e., T0, T1, T2 and T3), the patients were assessed with the Mini-Mental State Examination (MMSE) and a 40-item quality of recovery score questionnaire (QoR40) at 7:00 am every morning.

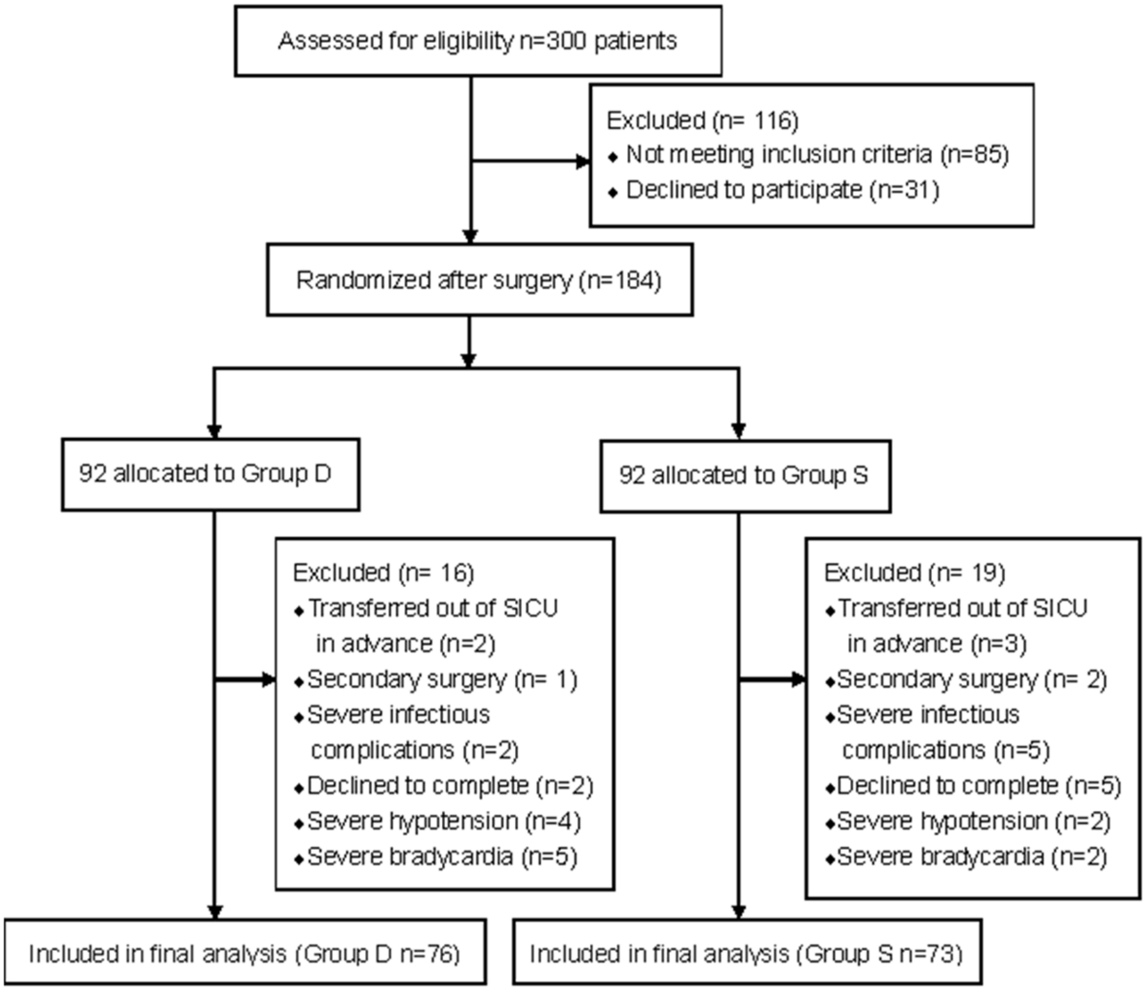

Figure 1. CONSORT diagram showing the flow of participants through each stage of our randomized trial.

The MMSE is a common, quick and convenient cognitive screening test that is composed of orientation, registration, attention, memory, calculation and language domains. The QoR40 was used to quantify the quality of recovery. Five aspects (dimensions) of recovery are commonly measured by these metrics: emotional state, physical comfort, psychological support, physical independence and pain [10].

Concurrently, sedation complications, such as postoperativebradycardia (sinus rhythm, less than 50 beats/min), hypotension (less than 30% of basal blood pressure) and respiratory depression, were recorded and treated. Intravenous dopamine or atropine was administered if postoperative hypotension or bradycardiaoccurred. Of course, the patients who suffered from sedation complications were recorded and excluded from the final analysis.

Blood sample collection and detection

Firstly, the general characteristics of all patients included in this study were recorded. On the day of surgery and for the first three postoperative days, venous blood was drawn at 7:00 am every morning (T0, T1, T2 and T3). Blood samples from 2 groups were stored in anticoagulant tubes and centrifuged at 4°C for 10 min (3000 rpm) as soon as possible. Then, the plasma was frozen at -80°C in a refrigerator (SANYO, Japan) for analysis. IL-6 (interleukin-6) levels were determined by enzyme-linked immunosorbent assay (R&D system, Minneapolis, MN, USA). CRP (C-reactive protein) and cortisol analyses were performed using a VITROS 5600 analyzer (Johnson and Johnson, Rochester, NY, USA). Melatonin levels were measured with an enzyme-linked immunosorbent assay (Beijing Yonghui Biological Technology Ltd.,

Table 1. Demographic characteristics of Group D and Group S

Characteristic	Group D (n=76)	Group S (n=73)	*P* value
Age (year)	70.7±5.2	71.3±5.1	0.478
Female	37	31	0.550
BMI	20.9±3.15	21.3±2.92	0.423
Education (year)	8.1±2.6	8.5±3.0	0.385
ASA (I/II/III)	17/48/11	20/43/10	0.778
Preoperative MMSE scores	28.23±1.61	27.98±1.59	0.342
Charlson Comorbidity Index at T0	1.5±0.7	1.6±0.8	0.418
Artificial airway			0.729
Tracheal intubation	49	50	
Tracheotomy	27	23	
Operation duration (min)	208±53	213±58	0.583
Anesthesia duration (min)	233±57	240±56	0.451

Table 2. Comparison of the MMSE scores between Group D and Group S

Time		T0	T1	T2	T3
MMSE score	Group D	28.23±1.61	22.53±2.85	24.61±2.67	27.11±2.01
	Group S	27.98±1.59	17.25±3.63	21.01±2.19	25.81±2.65
p value		0.342	<0.001	<0.001	0.001

Table 3. Comparison of the QoR40 scores between Group D and Group S

Time		T0	T1	T2	T3
QoR40 score	Group D	166.3±27.5	146.8±24.2	155.3±26.4	163.1±25.3
	Group S	163.9±25.6	129.5±22.5	136.9±21.1	145.6±28.6
p value		0.583	<0.001	<0.001	<0.001

Beijing, China), according to the manufacturer's instructions.

Statistical analysis

SPSS 16.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive results of continuous variables are expressed as the mean ± standard deviation. Categorical data are expressed as counts. The Kolmogorov-Smirnov test was used to test for normality. If continuous variables were not normally distributed, the Mann-Whitney U test was used. Otherwise, Student's t test was applied (eg, Age, Education, Operation duration, Anesthesia duration). Numerical data (eg, MAP, HR, IL-6, CRP, cortisol and melatonin) between groups were analyzed by the Student's t test and intragroup numerical data were analyzed by repeated measures ANOVA. Nominal data (eg, Female, ASA, Artificial airway and postoperative sedation complications) were analyzed by Chi-squared test. Statistical significance was accepted as P<0.05.

Results

Comparison of general characteristics between Group S and Group D

Originally, 300 eligible patients were scheduled to undergo oral cancer resectionsurgery, but ultimately 151 patients were excluded, and a total of 149 patients completed perioperative detection (**Figure 1**).

Demographic patient data are shown in **Table 1**. There were no significant between-group differences in terms of age, gender, BMI (body mass index), education level, ASA grade, preoperative MMSE scores, preoperative Charlson Comorbidity Index [11], etc. (*P*>0.05).

Between-group comparison of perioperative MMSE and QoR40 scores

As shown in **Tables 2** and **3**, there were no significant differences at T0 in the MMSE and QoR40 scores between the 2 groups (*P*>0.05). However, the MMSE and QoR40 scores declined after surgery. Meanwhile, the MMSE and QoR40 scores at T1, T2 and T3 were better in Group D compared with Group S (*P*<0.05).

Between-group comparison of postoperative sedation complications

As described in **Tables 4** and **5**, MAP and HR levels decreased after dexmedetomidine medication, but no differences were observed in the incidences of postoperative severe hypotension (less than 30% of basal blood pressure) and bradycardia (sinus rhythm, HR≤50 beats/min) between the 2 groups (*P*>0.05). Moreover,

Table 4. Between-group comparison of MAP and HR levels during the administration of dexmedetomidine

	Groups	n	Before medication	3 h after medication	6 h after medication	9 h after medication	12 h after medication
MAP	Group D	76	77.1±4.6	72.9±5.0[a,b]	70.1±4.9[a,b]	69.5±6.6[a,b]	68.8±5.9[a,b]
	Group S	73	77.5±5.3	75.0±6.3	75.2±4.8	75.5±5.6	76.1±6.2
	p value		0.623	0.025	<0.001	<0.001	<0.001
HR	Group D	76	87.3±12.1	82.6±7.3[a,b]	77.1±8.8[a,b]	74.3±11.6[a,b]	70.7±11.3[a,b]
	Group S	73	85.6±10.2	86.5±8.4	85.7±12.0	85.6±9.8	84.2±11.9
	p value		0.356	0.003	<0.001	<0.001	<0.001

[a]*P*<0.05 compared with the pre-medication levels, [b]*P*<0.05 compared with Group S.

Table 5. Between-group comparison of other postoperative sedation complications

	n	Hypotension	Bradycardia	Respiratory depression
Group D	76	4	5	0
Group S	73	2	2	0
p value		0.714	0.472	0.870

Table 6. Between-group comparison of postoperative IL-6, CRP, cortisol and melatonin concentrations

Time	Marker	Group D (n=76)	Group S (n=73)	*p* value
T0	IL-6 (pg/ml)	63±5	62±6	0.270
	CRP (mg/L)	10±6	11±5	0.272
	Cortisol (nmol/mL)	322±49	331±53	0.283
	Melatonin (ng/L)	17.3±2.0	17.1±3.1	0.639
T1	IL-6 (pg/ml)	109±12[a,b]	144±22[a]	<0.001
	CRP (mg/L)	98±19[a,b]	109±21[a]	0.001
	Cortisol (nmol/mL)	601±85[a,b]	821±105[a]	<0.001
	Melatonin (ng/L)	15.7±2.3[a]	15.1±4.4[a]	0.296
T2	IL-6 (pg/ml)	88±9[a,b]	106±13[a]	<0.001
	CRP (mg/L)	103±15[a,b]	111±18[a]	0.004
	Cortisol (nmol/mL)	508±80[a,b]	542±82[a]	0.011
	Melatonin (ng/L)	17.0±3.2	16.8±3.4	0.712
T3	IL-6 (pg/ml)	66±7[a]	68±7[a]	0.083
	CRP (mg/L)	82±15[a]	86±16[a]	0.117
	Cortisol (nmol/mL)	383±66[a]	400±65[a]	0.116
	Melatonin (ng/L)	17.6±4.4	17.5±3.7	0.881

[a]*P*<0.05 compared with T0, [b]*P*<0.05 compared with Group S.

no difference in respiratory depression was observed between the 2 groups.

Comparison of IL-6, CRP, cortisol and melatonin concentrations between the 2 groups

As shown in **Table 6**, no differences were observed for all tested markers at T0 (*P*>0.05). After surgery, IL-6, CRP and cortisol levels increased; in addition, the peaks of IL-6, CRP and cortisol concentrations were lower in Group D than in Group S (*P*<0.05). However, melatonin concentrations decreased at T1 (*P*<0.05), and no between-group differences were observed after surgery (*P*>0.05).

Discussion

Oral cancer patients who undergo tumor resection surgery can suffer from severe trauma, prolonged surgical times, long-term indwelling artificial airway, and postoperative SICU stays. Meanwhile, old age is an independent risk factor of POCD [12]. Under such stressful conditions, there is a higher incidence of POCD in elderly oral cancer patients. The extent of postoperative cognitive impairment following surgery has a significant influence on patient health and is substantially related to prolonged postoperative recovery, greater morbidity, and delayed functional restoration [13]. The prevention of POCD is of great importance to ensure patient safety.

Dexmedetomidineis a highly efficient and highly selective α2 agonist that can decrease the activity of norepinephrine cells in the locus coeruleus, reduce the release of norepinephrine, and depress sympathetic tone, as well as exert anti-anxiety and calming roles and lessen sleep cycle disorders [14-17]. It can also exert analgesic effects and reduce the consumption of opioids by exhibiting a synergistic effect with opioids through activation of the spinal α2 adrenergic receptor [18, 19]. Dexmedetomidine can also inhibit the hypothalamic-pituitary-adrenal axis and reduce cortisol secretion [18, 20]. However, it can induce a dose-dependent decrease in blood pressure and heart rate, particularly in elderly patients [7, 21], which has limited its use [22, 23]. Although a past study has reported that in bariatric surgery, combining the use of low-dose dexmedetomidine with general anesthesia could contribute to early postoperative recovery and minimize cardiovascular system complications [8], the efficacy and safety of using dexmedetomidine in elderly oral cancer patients after surgery requires further clinical study. Our results suggested that there were no significant between-group differences in the baseline characteristics. However, the postoperative MMSE and QoR40 scores in the dexmedetomidine group were better than those in the saline group. Furthermore, no between-group differences were observed in the incidences of severe hypotension or bradycardia. Moreover, no respiratory depression was observed in the 2 groups. Hence, we concluded that intravenous dexmedetomidine at a low-dose of 0.2 μg/kg/h for 12 h after surgery could ameliorate postoperative cognitive functionand recovery quality in elderly patients. Because our study excluded patients with severe hypotension or bradycardia prior to administering dexmedetomidine, low-dose dexmedetomidine did not result in severe cardiovascular complications.

Surgical trauma can activate the immune system and trigger hyperactivity of the hypothalamic-pituitary-adrenal axis [24]. The inflammation and endocrine responses are thought to cause a series of serious complications, such as postoperative fatigue, atrial fibrillation and cognitive dysfunction [25-27]. High cortisol levels are indisputably linked to POCD [28]. Peripheral inflammatory cytokines can enter into CNS through the blood brain barrier (BBB) or activate neuroendocrine cells in the BBB to synthesize and release inflammatory cytokines. Inflammatory cytokines can interfere with neural activity, thereby disturbing the connection and transmission functions of synapses. It is believed that CNS inflammation is involved in the occurrence of cognitive impairment and neurodegenerative disease [6, 29]. In vitro studies of human whole blood or in animal models have shown that dexmedetomidine can exert anti-inflammatory effects through the α2 receptor-mediated inhibition of HMGB1 (high mobility group box-1 protein), depressing TLR4 (Toll-like receptor 4)/MyD88 (myeloid differentiation factor 88) expression and NF-κB (nuclear factor-kappa B) activation [30, 31]. Our study found that continuous infusion of low-dose dexmedetomidine for 12 h in elderly oral cancer patients after surgery could improve their postoperative MMSE scores, while postoperative IL-6 and cortisol concentrations were lower than those in the saline group. We suggest that postoperative use of dexmedetomidine could still suppress excessive inflammation and the stress response, resulting in a lower incidence of postoperative neurological dysfunction in elderly oral cancer patients.

As an acute phase protein, CRP appears in the serum during the acute phase of infection, tissue injury, ischemia, tumor malignancy and other symptoms. McGrane S has reported that CRP levels could predict the duration of acute brain dysfunction in critically ill patients [32]. Dexmedetomidine could depress the production of cytokines from macrophages and monocytes during the stress reaction [33, 34]. Our study found that in elderly oral cancer patients, CRP levels significantly increased after surgery. The lower CRP levels in the dexmedetomidine group might have been triggered by decreases in the concentrations of pro-inflammatory cytokines, which could evoke the production of acute phase proteins, strengthen cell-mediated immune reactions, and enhance the chemotaxis of inflammatory cells [35].

Melatonin is a neurohormone that is secreted by the pineal gland. Its secretion declines during the day and increases at night to maintain the "sleep-wake cycle". A recent study found that the postoperative secretion rhythm of melatonin was disturbed; it was characterized by significantly decreased basal secretion of melatonin on the first postoperative night [36]. POCD was associated with deteriorative sleep quality and fluctuations in endogenous melatonin levels [37, 38]. In our study, although low-dose dexmedetomidine ameliorated postoperative cognitive function and improved patient recovery, at 7:00 am on the first three postoperative mornings, the melatonin concentrations were not affected. Due to time and labor constraints, the effects of dexmedetomidine on the nocturnal peak and total metabolites of melatonin secretion require further study.

In conclusion, in elderly oral cancer patients, the postoperative use of low-dose dexmedetomidine (0.2 μg/kg/h for 12 h) can improve postoperative cognitive function and recovery quality without severe hypotension, bradycardia, and respiratory depression, likely by reducing excessive inflammation and the stress response.

Disclosure of conflict of interest

None.

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