Effect of dexmedetomidine for sedation and cognitive function in patients with preoperative anxiety undergoing carotid artery stenting

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Abstract

Objective: This study was performed to examine the effect of dexmedetomidine for intra-operative sedation and postoperative cognitive function in patients with preoperative anxiety undergoing carotid artery stenting.

Methods: Eighty patients were randomly divided into two groups: the dexmedetomidine group and the control group. Cognitive function was assessed using the Mini-Mental State Examination (MMSE). Anxiety was evaluated using the Amsterdam Preoperative Anxiety and Information Scale. Routine monitoring indices were recorded during surgery, and cognitive function indices were recorded before drug infusion (T_0), 10 minutes after drug infusion (T_1), at the end of surgery (T_2), and 6 hours after surgery (T_3).

Results: The anxiety scores were not significantly different between the two groups at T0, but they became significantly different at $T_{1–3}$. The MMSE scores in both groups increased at 1 and 7 days postoperatively; although the increase in the dexmedetomidine group was sharper, there was no significant difference. In both groups, the MMSE scores at 1 and 7 days after surgery were not significantly different from those at 1 day before surgery.

Conclusion: Dexmedetomidine can improve patients' anxiety and achieve a sufficient sedation effect without causing postoperative cognitive dysfunction.

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Introduction

Stroke occurs in approximately 1.5 million people in China every year, and 20% to 30% of strokes are caused by carotid stenosis or occlusion. Carotid artery stenting (CAS) is an effective, widely adopted treatment for carotid stenosis because it involves relatively minor trauma and permits rapid recovery after surgery.[1] However, the procedure is generally performed under local anesthesia, which often inadequately blocks nerve transmission and subjects patients to negative emotions and feelings such as fear, pain, and discomfort during the operation. In severe cases, the guidewire used in CAS may pierce the blood vessel and cause life-threatening cerebral hemorrhage. In addition, surgery is a source of intense psychological stress in some patients and can lead to a series of preoperative psychological and emotional reactions, among which anxiety is one of the most common. Indeed, one study showed that 60% to 80% of patients experience some degree of anxiety before surgery.[2] Remifentanil, a commonly used opioid analgesic, is an essential component of balanced anesthesia; however, it can cause apoptosis of nerve cells and cognitive impairment in parts of the brain. Propofol, a sedative drug, is associated with cognitive impairment by altering the expression of certain proteins in brain cells. Therefore, a main focus in the field of anesthesia is to identify reliable sedative and analgesic drugs that can reduce the amount of traditional anesthetics, reduce patients' stress response due to pain, and reduce postoperative complications. The present study enrolled patients with preoperative anxiety who underwent CAS. Sedation was performed with dexmedetomidine (Dex), a highly selective $\alpha2$ adrenergic receptor agonist, to keep the patients asleep but arousable at any time. The purpose of this study was to further explore the effect of Dex on postoperative cognitive function, sedation, and the alleviation of anxiety and observe and evaluate its safety and feasibility.

Patients and methods

Design

This study followed the principles of randomized controlled trials and the CONSORT guidelines. All patients or their families provided written informed consent (if a patient became delirious, informed consent was provided by the family). The study was approved by the Ethics Committee of Shanghai Dongfang Hospital Affiliated to Tongji University (17 December 2017) (Trial registration: ChiCTR1800014370).

Inclusion and exclusion criteria

We included patients with carotid stenosis confirmed by global cerebral angiography at Dongfang Hospital, Shanghai, China from January to December 2018. There were no missing data. The inclusion criteria were an American Society of Anesthesiologists physical status of II or

III, patient age of 40 to 75 years, severe carotid stenosis (>70%) as confirmed by digital subtraction angiography, and a score of >11 points on the Amsterdam Preoperative Anxiety and Information Scale (APAIS).[3] The exclusion criteria were cognitive dysfunction, a history of large extensive cerebral infarction or intracranial hemorrhage, mental disorders, and a history of carotid endarterectomy.

Sample size and randomization

According to previous studies, if the mean-$\pm$ standard deviation score on the Mini-Mental State Examination (MMSE) in the experimental group and control group was 28.2 ± 1.5 and 25.5 ± 2.1, respectively, inclusion of seven or more patients in each group would provide a 90% probability of achieving a statistically significant result at a two-sided 5% level. As a result, 80 patients were enrolled in the study. After they had provided informed consent, the patients were randomly allocated to the Dex group (n = 40) or control group (n = 40). The randomization process was carried out with a series of sealed envelopes in which the group assignment was allocated using random number tables and block randomization in a fixed box on each layer.

Intervention and control groups

After the patient entered the operating room, his or her blood pressure, heart rate (HR), respiratory rate (RR), and blood oxygen saturation (SpO_2) were routinely monitored, and an intravenous route was established. The patients in the Dex group were given $1 \mu g/kg$ of Dex (lot number 181111BP; Jiangsu Hengrui Pharmaceutical Co., Ltd., Jiangsu, China), and they were then given a loading dose of $0.5 \mu g/kg$ through an infusion pump 15 minutes before the operation. The patients in the control group were given normal saline (lot number S181102E53; Zhejiang Jimin Pharmaceutical Co., Ltd., Zhejiang, China). Both solutions were infused at a rate of 0.6 µg/kg per hour until the end of the surgery. CAS was performed by two to three experienced neurologists with a flat-panel detector digital subtraction angiography system (GIGALIX 125/30/40/90-G; Siemens, Erlangen, Germany). Local anesthesia with lidocaine (lot number C1810122; Hebei Tiancheng Co., Ltd., Hebei, Cangzhou, China) was administered at the thigh in both groups of patients. A 6F/8F sheath was placed after the femoral artery was punctured, cerebral angiography was performed to determine the position of the carotid stent, and the appropriate balloon and stent were selected. If the stenosis was severe, the vessel was first dilated with the balloon and the stent was then implanted. All patients received oral clopidogrel at 75 mg/day and aspirin enteric-coated tablets at 100 mg/day for 3 days prior to surgery. The medication was continued for 3 to 6 months after the stent was implanted.

Observational indicators

The patients' general clinical data were evaluated, including their demographic data (age and sex), level of education, cerebrovascular risk factors (hypertension, diabetes, and coronary heart disease), and smoking and drinking history. Cognitive function assessment was performed using the MMSE 1 day before surgery, 1 day after surgery, and 7 days after surgery. The MMSE can comprehensively, accurately, and rapidly indicate a patient's mental state and degree of cognitive dysfunction. The mean arterial pressure (MAP), HR, RR, SpO_2, Ramsay sedation scale scores, and anxiety scores were recorded before drug infusion (T_0), 10 minutes after drug infusion (T_1), at the end of surgery (T_2), and 6 hours after surgery (T_3). The degree

Table 1. Comparison of general clinical data of the two groups of patients.

	Group C (n = 40)	Group D (n = 40)	$F/\chi^2/Z$	P
Age, years	67.68 ± 8.75	68.20 ± 8.61	0.421	0.674
Years of education	10.17 ± 1.07	10.39 ± 1.09	1.441	0.151
Male	22 (55.0)	20 (50.0)	0.377	0.539
Smoking	24 (60.0)	24 (60.0)	0.032	0.858
Alcohol drinking	24 (60.0)	24 (60.0)	0.032	0.858
Hypertension	17 (42.5)	13 (32.5)	0.854	0.355
Diabetes	36 (90.0)	34 (85.0)	0.790	0.374
CHD	21 (52.5)	20 (50.0)	0.069	0.793

Data are presented as mean ± standard deviation or n (%).
C, control; D, dexmedetomidine; CHD, coronary heart disease.

of intraoperative sedation was assessed using the Ramsay sedation scale score. The Ramsay score is the most widely used and reliable sedation score in clinical practice. It is divided into six grades. Anxiety was evaluated using the APAIS, which consists of six items and provides a total score of 6 to 30 points. The APAIS is a simple and easy-to-understand scoring method for preoperative anxiety.

Statistical analysis

SPSS24.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Measurement data are expressed as mean-± standard deviation. The t-test was used for comparisons between the two groups. Classification data are expressed as frequency or percentage, and the χ^2 test was used for comparisons between the two groups. Differences were considered statistically significant at $P < 0.05$.

Results

Comparison of general clinical data

Comparison of the general clinical data between the two groups revealed no statistically significant differences in age, years of schooling, sex, smoking history, drinking history, history of hypertension, history of diabetes, or history of coronary heart disease between the two groups (Table 1).

Comparison of HR, RR, MAP, SpO_2, and Ramsay score between the two groups at different time points

In the Dex group, the HR and RR decreased significantly from T_0 to T_{1-2} ($P < 0.001$ for both), and the Ramsay score increased significantly from T_0 to T_{1-2} ($P < 0.001$ for both). In the control group, the HR increased significantly from T_0 to T_{1-3} ($P = 0.005$, $P < 0.001$, and $P < 0.001$, respectively), and the SpO_2 decreased significantly from T_0 to T_{1-2} ($P < 0.001$ for both). Compared with the control group, the HR in Dex group was significantly lower at T_1 ($P < 0.001$), the RR was significantly lower at T_{1-3} ($P < 0.001$ for all), the MAP was higher at T_{1-3} ($P = 0.009$, $P < 0.001$, and $P < 0.001$, respectively), the SpO_2 was significantly higher at T_{2-3} ($P < 0.001$ for both), and the Ramsay score was significantly higher at T_{1-2} ($P < 0.001$ for both) (Table 2).

Comparison of anxiety scores between the two groups

Compared with T_0, the anxiety scores increased at T_{1-2} ($P < 0.001$ for both) and decreased at T_3 in the control group; they decreased at T_{1-3} in the Dex group

Table 2. Comparison of HR, RR, MAP, SpO$_2$, and Ramsay score between the two groups.

Item	Grouping	T$_0$	T$_1$	T$_2$	T$_3$
HR, beats/minute	Group D	87.86 ± 7.83	71.86 ± 7.84[ab]	74.86 ± 7.84[a]	75.86 ± 7.84
	Group C	88.60 ± 10.16	92.60 ± 10.16[a]	96.60 ± 10.16[a]	93.60 ± 10.16[a]
RR, breaths/minute	Group D	17.44 ± 1.83	16.30 ± 1.77[ab]	16.24 ± 1.73[ab]	16.14 ± 1.63[b]
	Group C	17.81 ± 1.32	17.94 ± 1.40	17.99 ± 1.38	17.93 ± 1.32
MAP, mmHg	Group D	94.57 ± 2.13	94.30 ± 1.99[b]	94.17 ± 1.90[b]	94.08 ± 1.85[b]
	Group C	94.82 ± 2.09	95.04 ± 1.98	95.17 ± 2.05	95.11 ± 2.10
SpO$_2$, %	Group D	99.44 ± 0.72	99.52 ± 0.72	99.55 ± 0.21[b]	99.53 ± 0.72[b]
	Group C	99.38 ± 0.77	98.38 ± 0.77[a]	98.58 ± 0.76[a]	99.11 ± 0.86
Ramsay score	Group D	1.47 ± 0.70	3.47 ± 0.70[ab]	3.41 ± 0.66[ab]	1.53 ± 0.70
	Group C	1.49 ± 0.70	1.47 ± 0.70	1.53 ± 0.70	1.54 ± 0.70

Data are presented as mean ± standard deviation.
HR, heart rate; RR, respiratory rate; MAP, mean arterial pressure; SpO$_2$, blood oxygen saturation; D, dexmedetomidine; C, control.
[a]Intra-group comparison, $P < 0.05$; [b]Group D vs. Group C, $P < 0.05$.
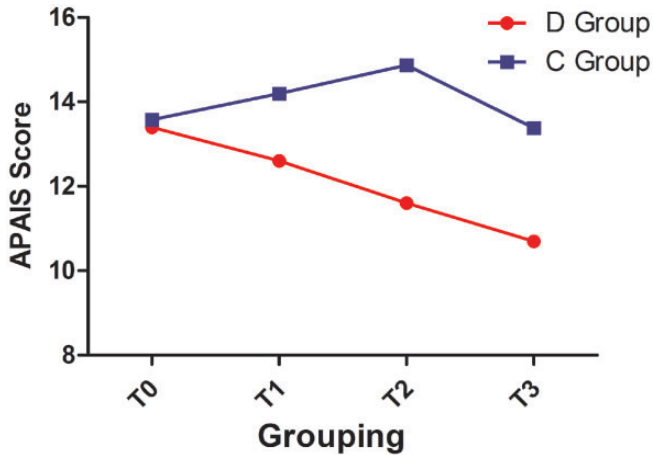
Figure 1. Comparison of APAIS scores between the two groups at different time points. APAIS, Amsterdam Preoperative Anxiety and Information Scale; D, dexmedetomidine; C, control.

($P = 0.031$, $P < 0.001$, and $P < 0.001$, respectively). The difference between the two groups was not statistically significant at T$_0$ but became statistically significant at T$_{1–3}$ ($P < 0.001$ for all) (Figure 1).

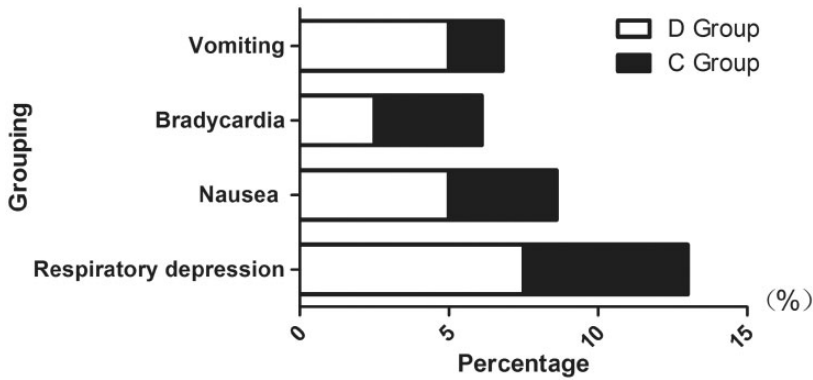## Comparison of postoperative complications between the two groups

There was no statistically significant difference in the proportion of postoperative respiratory depression, nausea, vomiting, or bradycardia between the two groups (Figure 2).

Comparison of cognitive function between the two groups

The MMSE scores of the two groups increased 1 and 7 days after the operation; although the increase in the Dex group was sharper, there was no significant difference

Figure 2. Comparison of postoperative complications between the two groups. D, dexmedetomidine; C, control.
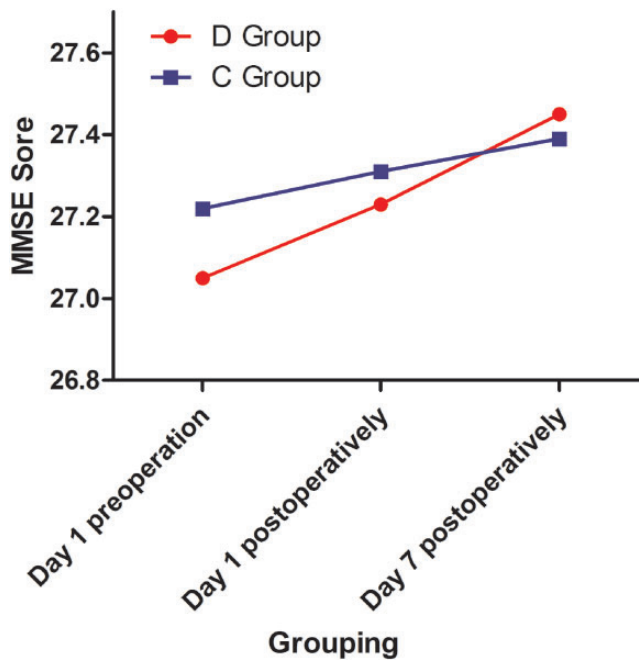
Figure 3. Comparison of MMSE scores between the two groups at different time points. MMSE, Mini-Mental State Examination; D, dexmedetomidine; C, control.

in the MMSE scores between the two groups at the three time points (Figure 3). The MMSE scores in both groups at 1 and 7 days after the surgery were not significantly different from those at 1 day before the surgery (Figure 3).

Discussion

Anxiety is a subjective psychological feeling characterized by fear, tension, worry, and irritability. Severe preoperative anxiety can reduce patient compliance during anesthetic

induction, increase the required dosage of anesthetic drugs,[4] and increase the incidence of perioperative cardiovascular adverse events. Therefore, it is necessary to quickly and effectively identify patients with severe preoperative anxiety and perform targeted treatment. The APAIS is a scoring method for preoperative anxiety that is used worldwide because of its simple content, which eases understanding and completion.[3,5]

Dex is a novel adrenergic receptor agonist that, in addition to inhibiting sympathetic responses, exerts sedative, analgesic, and anxiolytic effects. The present study confirmed that Dex can effectively inhibit sympathetic responses. Although there was no significant difference in alleviation of anxiety between the Dex and control groups at T_0, the difference was statistically significant at T_{1-3} (P < 0.001), suggesting that Dex can improve patients' anxiety. Preoperative anxiety also induces an increase in catecholamine secretion, causing changes in hemodynamics such as an elevated blood pressure, increased HR, and even arrhythmia. For patients with preoperative anxiety, adequate sedation requires an increase in the dosage of sedatives. Although midazolam acts quickly, it inhibits the duration of rapid eye movement and can cause drowsiness, memory loss, and cognitive impairment. Compared with midazolam, Dex is a more selective alpha-adrenergic receptor agonist that can counteract the response caused by elevated catecholamines in the body and features good sedative, analgesic, and anxiolytic effects. This is consistent with the study results reported by Urban et al.,[6] Chhangani and Papadakos,[7] and Sturaitis et al.[8]

The MMSE scores in both groups increased after surgery. There was no significant difference in the MMSE scores between the two groups or within the same groups at different time points, indicating that Dex did not cause postoperative cognitive dysfunction (POCD). Some animal experiments[9–11] have shown that Dex can increase the number of nerve cells, alleviate brain injury, and play a role in brain protection after transient local or global cerebral ischemia injury. POCD is a decline in cognitive function after surgery and often manifests as impairment of memory, attention, language understanding, abstract thinking, and social skills. Its diagnosis requires the performance of a series of neuropsychological tests before and after surgery.[12,13] Surgical stress reportedly induces neuroinflammation and thereby impairs the blood–brain barrier, which leads to migration of macrophages into the brain, damaging neurons and ultimately causing POCD.[14] A study conducted by Evered et al.[15] showed that the incidence of POCD ranged from 17% to 43% at 7 days after surgery and was approximately 17% at 3 months after surgery. Dex is reportedly associated with increased levels of circulating blood and extracellular catecholamines in brain tissue, and decreased sympathetic nervous system activity may improve nervous system function.[16,17] This may be one of the mechanisms underlying the neuroprotective effect of Dex.

Dex belongs to the class of imidazole derivatives and is a specific, highly selective alpha receptor agonist. Its receptor selectivity is eight times that of clonidine, and its titer is three times that of clonidine. Previous studies have suggested that the mechanism underlying the Dex-mediated improvement in POCD is related to inhibition of the inflammatory and stress responses.[18,19] Ge et al.[20] administered Dex to patients undergoing carotid endarterectomy and found that Dex could significantly reduce the level of S100B protein (a marker of cerebral ischemic injury) and malondialdehyde (a marker of oxidative stress) relative to a control, indicating that Dex can promote cognitive function recovery after carotid endarterectomy by

alleviating brain injury and inhibiting oxidative stress. An animal experiment performed by Zhu et al.[21] showed that Dex pretreatment could alleviate neuroinflammation caused by tibial fracture in rats by vagus nerve-dependent and $\alpha 7$ nicotinic acetylcholine receptor-dependent mechanisms. Gao et al.[22] observed that Dex could improve learning and memory in rats with depression caused by electroconvulsive therapy by inhibiting overactivation of the 2B subunit of the N-methyl-D-aspartate receptor in the hippocampus and enhancing phosphorylation of extracellular signal-regulated protein kinases. Xiong et al.[23] demonstrated that Dex could inhibit neuronal overexcitation and improve cognitive function in aged rats by inhibiting the expression of relaxin-3 and c-fos.

In conclusion, the present study revealed that Dex can improve patients' anxiety and achieve a sufficient sedation effect without causing POCD; however, whether Dex improves postoperative cognitive function remains to be further studied. This study also showed that the use of Dex in patients undergoing CAS does not increase the incidence of postoperative complications. Therefore, strong sedation is necessary in high-risk patients undergoing CAS. The application of Dex can attenuate sympathetic activity, effectively inhibit patients' stress responses, and stabilize patients' hemodynamics while maintaining arousable sedation; Dex thus improves patient compliance and surgical safety. Hence, this study provides support for the safety and feasibility of using Dex for intraoperative sedation in patients undergoing CAS with local anesthesia.

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