Int J Clin Exp Med 2020;13(3):2086-2094
www.ijcem.com /ISSN:1940-5901/IJCEM0103045

Original Article

The effects of dexmedetomidine in general anesthesia on the perioperative hemodynamics and postoperative cognitive functions of patients with sleep apnea syndrome in the perioperative period of uvulopalatopharyngoplasty

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Received October 1, 2019; Accepted November 7, 2019; Epub March 15, 2020; Published March 30, 2020

Abstract: Objective: This study aimed to investigate the effects of dexmedetomidine hydrochloride on the postoperative cognitive dysfunction (POCD) of patients with sleep apnea syndrome (SAS) in the perioperative period of uvulopalatopharyngoplasty (UPPP). Methods: Sixty patients diagnosed with sleep apnea syndrome in our hospital between August 2016 and 2018 were randomly divided into two groups: the control group (n=30) underwent anesthesia using propofol and remifentanil, and the observation group (n=30) which was anesthetized using dexmedetomidine combined with propofol and remifentanil. The hemodynamic indexes in the perioperative period were compared between the groups by recording the average heart rate (HR) and arterial pressure (MAP) before anesthesia (T1), at 3 min from the start of the operation (T2), at 20 min from the start of operation (T3), at 1 min before extubation (T4), and at 5 min after extubation (T5). Moreover, the dosages of propofol and remifentanil, operation time, anesthesia time, blink time and extubation time were also recorded. During the period from 1 day before the operation to the post-operative 3rd day, the visual analog scale (VAS) and the Ramsay score after extubation were used to measure the cognitive functions of the patients in the groups. Results: The bispectral index measurements (BIS) in the observation group at T2 and T4 were lower than they were in the control group ($P<0.05$). The HR and MAP values in the two groups at timepoint T1 showed no differences ($P>0.05$). However, the values of HR and MAP at timepoints T2 and T5 in the observation group were lower than they were in the control group ($P<0.05$). Furthermore, the MAP in the observation group at timepoints T2-5 was relatively stable compared with the MAP at timepoint T1, and the intraoperative and post-extubation changes were relatively small in the observation group. Compared with the control group, the dosages of remifentanil and propofol from the observation group were lower ($P<0.05$). The VAS pain score and the Ramsay sedation score of the observation group at T5 were better than they were in the control group ($P<0.05$). On the third day post-operation, the Simple Mental State Assessment Scale (MMSE) scores in the observation group were higher than those in the control group, and the incidence of POCD in the observation group was also decreased ($P<0.05$). Conclusion: The application of dexmedetomidine during general anesthesia for patients with SAS in the perioperative period of UPPP can stabilize the hemodynamics and decrease the incidence rate of POCD.

Keywords: Dexmedetomidine, general anesthesia, hemodynamics, postoperative cognitive dysfunction, sleep apnea syndrome

Introduction

The incidence of adults with sleep apnea syndrome (SAS) is 5.0-25.0%, and SAS is closely associated with obesity and posture [1]. Obstructive sleep apnea (OSAS) accounts for about 4/5 patients with SAS, and it is characterized by partial or complete upper airway obstruction during sleep, often accompanied by hypercapnia and hypoxemia, adult hypertension, or cardiovascular and cerebrovascular diseases [2, 3]. Due to chronic hypoxia, SAS patients often have potential cognitive impairments such as Alzheimer's disease by cerebrovascular injury [4, 5]. There are various surgical methods for SAS treatment, among which uvulopalatopharyngoplasty (UPPP) is characterized as the most mature method with the most stable efficacy [6]. During the surgery, tracheal intubation is carried out for general anesthesia using common anesthetics such as propofol and remifentanil and dexmedetomidine [7].

Maintenance of perioperative hemodynamic stability, postoperative cognitive function, proper sedation and awakening are major parts of anesthetic management. Dexmedetomidine is a newer, highly selective α2-adrenergic agonist, which provides analgesia, sedation, sympatholysis, anxiolysis, and hypnosis [8]. Various doses and routes of administration of dexmedetomidine have been tried successfully in anesthesia [9-11]. During UPPP surgeries, various pathophysiological changes may occur in the patients. These changes mainly include a rise in systemic and pulmonary vascular resistance, heart rate (HR), and arterial pressure (MAP). The perioperative anesthesia also adds up to these pathophysiological changes further compromising the hemodynamics [12]. Various drugs such as propofol and remifentanil and dexmedetomidine have been tried to attenuate such stress responses, and effectiveness of dexmedetomidine in various doses for the prevention of stress-induced hemodynamic changes [10, 13]. Dexmedetomidine helps reduce the significant postoperative pain and provide proper sedation after major surgical procedures, which can result in hemodynamic stability in surgery [9]. In addition, dexmedetomidine has been used in routine anesthesia practice, and studies have shown that there is a reduction in the requirement for induction agents and opioids during the perioperative period [13].

UPPP is currently an effective surgical treatment for SAS. However, SAS patients are prone to hemodynamic fluctuations, upper respiratory tract obstruction, postoperative hypoxemia, and other serious complications [14]. Therefore, it is necessary to develop a standard system of UPPP perioperative treatment to ensure safer surgeries. The surgical treatment of SAS patients should be well monitored during the perioperative period, including hemodynamics. Severe snoring can cause systemic hemodynamic changes due to tissue ischemia and hypoxia resulting in multiple system organ damage, such as cardiovascular diseases (coronary heart disease, high blood pressure, etc.), lung diseases (chronic obstructive pulmonary disease, bronchial asthma, etc.), and nervous system diseases (neurasthenia, cerebrovascular disease, epilepsy) [15].

Postoperative cognitive dysfunction (POCD) commonly occurs after anesthesia and surgery. Studies show that SAS is closely related to POCD [16]. The manifestations are disorder in memory, abstract thinking, and disorientation after anesthesia, also accompanied by decreased social activity (i.e., changes in personality, social skills, cognitive capabilities, and skills) [17]. More sever POCD conditions, such as senile dementia, can lead to a decline or loss of social activities, work, and self-care ability [18, 19].

Anesthesia and monitoring indexes are key to the rational regulation of anesthetic depth during the operation [20]. However, currently, no study on the perioperative hemodynamics and the postoperative cognitive function of patients with sleep apnea syndrome in the perioperative period of UPPP has been reported. In the present study, we carried out anesthesia using dexmedetomidine combined with propofol and remifentanil for patients with moderate or severe OSAS and measured the effects of the anesthetics on hemodynamics and POCD in the perioperative period for UPPP, which can serve as a reference for improving the anesthetic effect.

Materials and methods

Sample selection

We selected a total of 60 patients who were diagnosed with moderate or severe OSAS and received treatment for UPPP at this hospital between August 2016 and 2018. The patients were divided into a control group (n=30) and an observation group (n=30) according to the order that they were admitted to the hospital. The inclusion criteria were set as follows: I) The patients were diagnosed with SAS [20]. The patients were between 18-65 years old, had ASA levels I or II, and they had a preoperative Mini-Mental State Exam (MMSE) score >27 points, exhibiting poor efficacy after 3 months of conventional treatment and had indications of UPPP; II) patients with complete clinical data who showed better treatment compliance and gave their informed consent. The exclusion criteria were set as follows: I) patients who were complicated with diseases in the mouth, nose, pharynx, or larynx; II) patients with severe hypertension, hepatic or renal dysfunction, cardiovascular or cerebrovascular diseases; III) patients with severe anxiety and depression; IV) patients allergic to dexmedetomidine. We also excluded patients who were taking drugs for cognitive disorders and psychotropic diseases. The ethics committee approved this research. Signed written informed consents were obtained from all participants before the study started.

Methods

After the preoperative examination was fully completed, the surgeries were carried out using the same team of surgeons, anesthetists, and nurses according to UPPP's standard procedures. All the patients were generally anesthetized with tracheal intubation. The induction of anesthesia was carried out using 2-3 mg/kg propofol, 0.2-0.3 μg/kg sufentanil and 0.2 mg/kg cisatracurium bromide in the two groups. The patients were connected to the ventilator with the oxygen content and oxygen flow rate set as 60% and 2 L/min, respectively. The remifentanil was pumped at a rate of 5-10 μg/kg/h, and the propofol was as administered at a rate of 5-8 mg/kg/h using microinjection pumps in order to maintain the anesthetic state. After the anesthesia induction, dexmedetomidine was continuously pumped into the patients in the observation group at a loading dose of 0.8 μg/kg for 10 min, and then maintained at a speed of 0.2 μg/kg/h. Approximately 10 min before the end of the surgery, the dexmedetomidine pumping was suspended. The patients in the control group were treated with normal saline. During the surgery, the dosages of propofol and remifentanil were adjusted according to the bispectral index (BIS). A BIS between 85 and 100 was for the waking state, between 65 and 84 was for the sedative state, and between 40 and 64 was for the anesthetic state. At the end of surgery, the pumping of propofol and remifentanil was suspended. Extubation was performed when the tidal volume of the spontaneous breathing capacity of the patients was ≥5 ml/kg, the heart rate (HR) was ≥50 beat/min, the SpO2 was ≥95% and such a state could be sustained for over 10 min. Before extubation, any excretions in trachea, mouth, or pharynx were eliminated.

Outcome measures

Comparisons on the hemodynamic indexes such as the average HR, MAP, PET CO_2, and BIS were carried out at different time points including before anesthesia (T1), at 5 min from the start of the operation (T2), at 20 min from the start of operation (T3), at 1 min before the extubation (T4), and at 5 min after the extubation (T5).

The comparisons of the dosages of propofol and remifentanil in the anesthesia maintenance stage between the two groups were observed.

On the third day after surgery, an assessment of the cognitive functions was conducted using The Mini-Mental State Exam (MMSE) and included time orientation, location orientation, memory and calculation, and language understanding to measure cognitive function, with a total score of 30. The MMSE test was used to assess cognitive functions before surgery and at 3 and 24 hours postoperatively, and POCD was defined as a drop by one standard deviation (more than 2 scores) in the MMSE tests from before to after surgery [21].

Statistical analysis

The statistical analysis in this study was performed using SPSS 17.0 software (Chicago, IL, USA). The measurement data were expressed as the means ± standard deviations. Independent sample t-tests were performed for the intergroup comparisons. Variance analyses of the repeated measurement data with post hoc Bonferroni tests were carried out for the comparisons at the different time points. Countable data were presented as cases or percentages, and an χ^2 test was conducted for the intergroup comparisons. $P<0.05$ indicated a significant statistical difference.

Results

Comparison of the basic information between the two groups

In the control group, there were 26 males and 4 females with an average age of 40.6±9.4 years, an average body mass index (BMI) of 28.7±3.8

Table 1. Comparison of the general information between the two groups

Category	Observation	Control
Males/Females (cases)	25/5	26/4
Age (years)	43.4±8.9	40.6±9.4
BMI (kg/m^2)	29.5±4.7	28.7±3.8
AHI (time/h)	38.2±10.3	36.8±9.2
Course of disease (years)	5.2±1.4	5.7±1.6
Hypertension (cases)	14	12
Diabetes (cases)	12	13
Hyperlipemia (cases)	16	15
Smoke (cases)	7	9
LVEF (%)	56.4±16.1	57.2±14.6

Note: LVEF, Left Ventricular Ejection Fraction. BMI, body mass index.

Table 2. Comparisons of the intraoperative data between the two groups

Group	Time of operation (min)	Extubated time (min)	Anesthesia time (min)	Bleeding volume (min)
Observation	44.6±9.2	13.5±3.4	63.8±15.4	70.2±21.7
Control	45.8±8.6	16.7±2.9	65.6±12.3	75.1±26.2

Table 3. Comparisons of $PETCO_2$ at the different time points between the two groups

Group	T2	T3	T4
Observation	39.0±2.2	38.9±2.1	38.9±2.1
Control	38.6±2.5	39.1±2.5	39.3±2.3

Note: T2, at 3 min from the start of operation; T3, at 20 min from the start of operation; T4, at 1 min before extubation.

kg/m^2, and an average apnea-hypopnea index (AHI) of 36.8±9.2 time/h, as measured using a monitor (Leibake Technology Company, Beijing, China). In the observation group, there were 25 males and 5 females with an average age of 43.4±8.9 years, an average BMI of 29.5±4.7 kg/m^2, and an average AHI of 38.2±10.3 time/h. The basic information and intraoperative data between two groups was comparable, and there were no statistical differences, as seen in **Tables 1** and **2**.

Comparison of the hemodynamic indexes at different time-points

There were no differences found in the comparisons of $PETCO_2$ at the different time points (T2 to T4) between the two groups ($P>0.05$), as shown in **Table 3**. The means of the average heart rate (HR) and arterial pressure (MAP) from T2-T5 in the observation group were lower than they were in the control group, with statistically significant differences ($P<0.05$), as shown in **Tables 4** and **5**.

Comparison of BIS values at different time points

The BIS values from T2-T5 in the observation group were lower than they were in the control group, with statistically significant differences ($P<0.05$), as shown in **Table 6**.

Comparison of the dosages of remifentanil and propofol between the two groups

The dosages of remifentanil and propofol in the observation group were significantly lower than they were in the control group ($P<0.05$), as shown in **Figure 1**.

Comparison of the MMSE scores and the POCD incidence rate between the groups

On the third day post-surgery, the MMSE scores and the incidence rate of POCD in the observation group were, respectively, higher and lower than they were in the control group, with statistically significant differences ($P<0.05$, **Table 7** and **Figure 2**).

Discussion

OSAS patients are prone to serious complications such as hemodynamic instability and upper airway obstruction during the perioperative period. Therefore, the selection of appropriate sedative drugs during the perioperative period can achieve sufficient anesthesia depth, maintain hemodynamic stability, and reduce the occurrence of POCD, which has become the focus of clinical anesthesia for such operations. Dexmedetomidine is a novel, highly effective and highly selective alpha 2 adrenergic receptor agonist with a central antisympathetic effect, which can induce and maintain natural non-eye movement sleep with hypnotic anesthetic effects on the locus coeruleus [22]. Yildiz et al. found that dexmedetomidine can maintain the stability of intraoperative hemodynamics and significantly reduce restlessness and cough during the waking period, which enables

Table 4. Data showing the heart rates between the control group and the observation group at different time points

Group	T1	T2	T3	T4	T5
Observation	74.9±8.8	67.3±8.2*	66.6±7.5*	74.7±8.7*	75.0±7.5*
Control	73.9±9.2	76.8±8.9	72.3±8.6	80.4±8.0	78.9±7.1

Note: Compared with those in control group, *indicated P<0.05. T1, the time before anesthesia; T2, at 3 min from the start of operation; T3, at 20 min from the start of operation; T4, at 1 min before extubation; T5, at 5 min after extubation.

Table 5. Comparisons of the arterial pressure at different time points between the two groups

Group	T1	T2	T3	T4	T5
Observation	97.3±7.3	93.9±5.8*	92.2±5.4*	95.7±5.9*	94.3±5.1*
Control	97.2±8.5	100.5±7.1	95.8±6.3	104.9±6.1	98.6±7.5

Note: Compared with those in the control group, *indicated P<0.05; T1, the time before anesthesia; T2, at 3 min from the start of operation; T3, at 20 min from the start of operation; T4, at 1 min before extubation; T5, at 5 min after extubation.

Table 6. Comparison of the BIS values at the different time points

Group	T1	T2	T3	T4	T5
Observation	97.7±2.5	56.7±2.4*	52.3±2.3*	70.2±2.9*	86.6±5.3*
Control	98.4±2.4	61.5±2.2	58.2±2.4	75.4±3.2	87.9±5.5

Note: Compared with those in the control group, *indicated P<0.05; BIS, bispectral index; T1, the time before anesthesia; T2, at 3 min from the start of operation; T3, at 20 min from the start of operation; T4, at 1 min before extubation; T5, at 5 min after extubation.

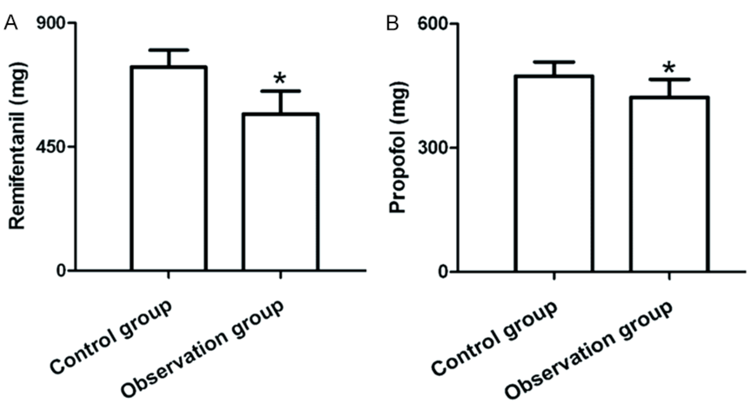

Figure 1. Comparison of the dosages of anesthetic drugs between the two groups. Compared with those in the control group, *indicated P<0.05. A: The dosage of remifentanil. B: The dosage of propofol.

extubation at lucid intervals may also lead to a strong stress response, which can excessively activate the sympathetic nerves, resulting in an acute increase of corticosteroid hormone by the hypothalamic-pituitary-adrenal axis, which mediates the inflammatory reaction and the glandular secretions to further destabilize local hemodynamics [24]. Dexmedetomidine can effectively suppress the above stress responses and maintain hemodynamic stability [25]. With a capability to reduce the tension of the sympathetic nervous system and decrease the release of catecholamines, not only can dexmedetomidine maintain low blood pressure during surgery, it also can suppress an increase in blood pressure during the lucid interval. Thus, dexmedetomidine is characterized by a biphasic effective regulation of the cardiovascular system [26]. In addition, it is reported that respiratory irritation, hypoxia, and carbon dioxide retention can be relieved by dexmedetomidine, so POCD is improved in patients [13]. Furthermore, remifentanil is characterized by a strong analgesic effect, a short half-life, and a fast onset, and dexmedetomidine can enhance the sedative effects of remifentanil. Thus, the dosage of remifentanil can be reduced, as it is more conducive to the stability of hemodynamics [27].

anesthesiologists to manage the perioperative safety of patients more effectively [23].

Operations on OSAS patients, including anesthesia, intubation, surgery and stimulation, can lead to stress responses such as accelerated HR and increased hypertension. Particularly,

Our results showed no significant differences in the levels of PET CO_2 between the groups, but the HR and MAP values from timepoints T2-5 in the observation group were lower than the corresponding values in the control group, and hemodynamic fluctuations were observed in both groups. Moreover, the MAP values of the

Table 7. Comparison of the MMSE scores and the incidence rate of postoperative cognitive dysfunction (POCD) between the two groups

Group	Cases	MMSE scores		Rate of POCD
		Pre-operation	At day 3 post-surgery	Case (n, %)
Observation	30	28.2±1.2	28.0±1.5*	1 (3.3%)*
Control	30	28.1±1.3	27.1±2.0	3 (10%)

Note: Compared with those in the control group, *indicated P<0.05. POCD, postoperative cognitive dysfunction; MMSE, Simple Mental State Assessment Scale.

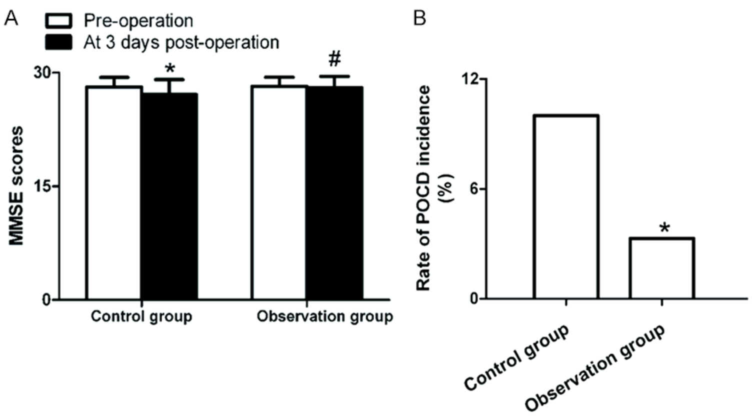

Figure 2. Comparison of the MMSE scores and the POCD incidence rates between the two groups. A: MMSE score, compared with the score before the operation, *indicated P<0.05. Compared with the score in the control group at day 3 post-surgery, #indicated P<0.05; B: The rate of POCD incidence, compared with that in control group, *indicated P<0.05. POCD, postoperative cognitive dysfunction; MMSE, Simple Mental State Assessment Scale.

observation group at timepoints T2-5 were slightly different at timepoint T1, and the intraoperative and extubation blood pressure values were relatively stable, and no drastic blood pressure fluctuations were observed at timepoints T4 and T5, suggesting that dexmedetomidine can provide more stable hemodynamic indexes. BIS was mainly used to reflect the sedative depth. We found that the patients could not be woken if their BIS was below 55, and until BIS was over 65, the patients were apt to be woken up with a favorable, cooperative willingness [28]. The BIS values at timepoints T2-4 in the observation group were lower than they were in the control group, and at timepoint T5, it was not significantly different from its level in the control group. These results suggested that the patients' BIS values would be more easily increased with the anesthetics being eliminated, and the patients would wake up after a shorter time period without any decrease in memory or delayed recalls from the time point of extubation [29]. Furthermore, no differences were found in the comparisons of the durations of surgery and anesthesia between the groups, and the dosages of propofol and remifentanil in the observation group were lower than they were in the control group under BIS monitoring. This finding is consistent with the research results of Turgut et al., which indicated that when the anesthetic dosages of propofol and remifentanil were reduced according to the bis value, the dexmedetomidine was not delivered a suitable anesthetic depth, nor did it maintain a relatively stable arterial pressure [30].

In the awake interval after surgery, the incidence of postoperative cognitive dysfunction (POCD) is 0.5-10.5%, which is correlated with age, the degree of hypoxia before surgery, anesthesia depth, and the stress response to the extubation of patients [31, 32]. Although the specific pathogenesis of POCD remains unclear, it is of great significance for the occurrence of POCD that various stimuli induced by anesthesia and operations can decrease the circulatory perfusion and lead to a disorder in immuno-inflammatory responses [33]. In the circulation, inflammatory factors such as TNF-α and IL-6, which are expressed in the circulatory system, result in hyperalgesia in the central nervous system. It may also participate in the occurrence of POCD [34]. Dexmedetomidine, as a specific α2 receptor agonist of epinephrine, can ameliorate the injuries mediated by acetylcholine, such as feelings, emotions, learning, awakening and judgement [35, 36]. Animal experiments conducted by Hofer et al. showed that pretreatment with dexmedetomidine significantly reduced the levels of TNF-α, IL-1, and IL-6 in serum inflammatory cytokines [37]. In addition, Chan et al. demonstrated that dexmedetomidine injection after anesthesia could significantly reduce the incidence of patients' postoperative psychosis and POCD [29]. An et al. found that anesthesia depth was closely related to the occurrence of POCD, and a deeper anesthesia depth reduced the incidence of postoperative POCD [38]. Our results showed the BIS values at timepoints T2-4 in the observation group were lower than they were in the control group, and the MMSE scores in the observation group were higher than they were in the control group. More interestingly, the incidence rate of POCD was significantly decreased on the 3rd day after surgery in observation group. This indicated that dexmedetomidine can maintain a deep anesthesia depth and reduce the incidence of POCD. To sum up, the present study was designed to investigate the effect of the application of dexmedetomidine on the hemodynamics and postoperative cognitive functions of patients with sleep apnea syndrome in the perioperative period of UPPP. However, several limitations still exist in this study, for example, a small sample size, the lack of a long-term follow-up supporting the results, and the failure to analyze the dose-dependent effects of dexmedetomidine on the patients and dexmedetomidine's mechanism of action for improving postoperative cognitive function. Additional studies with a larger sample size are required to substantiate the effects of dexmedetomidine. Further studies will also be performed to explore the association between the inflammatory factors and the postoperative cognitive functions mediated by dexmedetomidine.

In conclusion, the application of dexmedetomidine, combined with propofol and remifentanil, for patients with OSAS in the perioperative period of UPPP can stabilize the hemodynamics and decrease the incidence rate of POCD. Thus, dynamic monitoring of BIS shows a great application value for reasonably adjusting the dosages of propofol and remifentanil and evaluating the incidence of POCD.

Disclosure of conflict of interest

None.

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