SPANDIDOS PUBLICATIONS EXPERIMENTAL AND THERAPEUTIC MEDICINE 16: 4685-4689, 2018

Effects of dexmedetomidine on postoperative cognitive function in patients undergoing coronary artery bypass grafting

ZHENG GONG*, JUN LI*, YULING ZHONG, XUEHAI GUAN, AILAN HUANG and LI MA

Department of Anesthesiology, The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, Guangxi 530021, P.R. China

Received November 27, 2017; Accepted September 4, 2018

DOI: 10.3892/etm.2018.6778

Abstract. Effects of dexmedetomidine on postoperative cognitive function in patients undergoing coronary artery bypass grafting were investigated. Eighty patients undergoing systemic anesthesia with extracorporeal coronary artery bypass grafting in The People's Hospital of Guangxi Zhuang Autonomous Region from January 2015 to August 2017 were selected and randomly divided into the observation group (n=40) and control group (n=40). The two groups were treated with dexmedetomidine and equal volume of normal saline, respectively. Moreover, safety indexes including EEG bispectral index (BIS) at 30 min before induction of anesthesia (T0), immediately after intubation (T1), when incision was made (T2), when chest was closed (T3), when operation was completed (T4) and at 6 h after operation (T5), intraoperative circulatory system-related complications, cortisol, epinephrine and norepinephrine levels at the end of surgery as well as anesthesia recovery time and postoperative mechanical ventilation time were recorded and compared. All the patients were followed up for 1 week. Mini-mental state examination (MMSE) and Montreal cognitive assessment (MoCA) were administered at 1, 3 and 7 days after operation, and the incidence of intraoperative awareness and postoperative cognitive dysfunction was recorded. BIS value in the observation group was lower than that in the control group (P<0.05) at T1-T4 time points, and the BIS value in the observation group was higher than that in the control group (P<0.05) at T5. Incidence rates of intraoperative arrhythmia, hypertension and hypotension in the observation group was significantly lower than those in the control group (P<0.05). At the end of operation, levels of cortisol, epinephrine and norepinephrine in the observation group were significantly lower than those in the control group (P<0.05). Anesthesia recovery time and postoperative mechanical ventilation time in the observation group was significantly shorter than the time in the control group (P<0.05). MMSE and MoCA scores of the observation group were better than those of the control group (P<0.05). The incidence of cognitive impairment and postoperative cognitive impairment in the observation group was significantly lower than those in the control group (P<0.05). Therefore, it is concluded that dexmedetomidine can effectively reduce the incidence of postoperative cognitive impairment in patients undergoing coronary artery bypass grafting, and it is of high safety for circulatory function.

Correspondence to: Dr Li Ma, Department of Anesthesiology, The People's Hospital of Guangxi Zhuang Autonomous Region, 6 Taoyuan Road, Nanning, Guangxi 530021, P.R. China
E-mail: im56ap@163.com

*Contributed equally

Key words: dexmedetomidine, cardiopulmonary bypass, coronary artery bypass, postoperative cognitive function

Introduction

Postoperative cognitive dysfunction is defined as postoperative consciousness, cognitive function, memory and orientation disorders, complicated with mental and sleep disorders in patients without mental illness before operation. Postoperative cognitive dysfunction is caused by postoperative neurological disorders due to various factors including brain disorders (1). Strong surgical stimulation caused by cardiac surgery may lead to significant body stress response, leading to increased level of catecholamines secreted by sympathetic nervous system (2). In particular, bypass coronary artery bypass grafting is considered to be one of the most common predisposing factors for postoperative cognitive impairment during cardiopulmonary bypass (3).

In recent years, with the development of anesthesia and cardiopulmonary bypass technology, incidence of postoperative cognitive dysfunction was significantly decreased, but still cannot be eradicated (4). Dexmedetomidine, as a new and efficient adrenergic receptor agonist α2, can induce physiological sleep (5). Dexmedetomidine can also effectively inhibit the body's inflammatory response and thus improve the protection of the nervous system (6). This study mainly explores the impact of dexmedetomidine on postoperative cognitive function in patients with coronary artery bypass grafting.

Patients and methods

General information. A total of 80 patients undergoing systemic anesthesia and extracorporeal coronary artery

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

Groups	Sex (male/ female)	Age (years)	Body mass index (kg/m^2)	Left ventricular ejection fraction (%)	Intraoperative cardiopulmonary bypass time (min)	Total operation time (min)	MMSE	MoCA
Observation (n=40)	28/12	42.3±1.6	23.5±1.1	53.1±2.1	113.0±5.1	206.5±15.3	28.5±0.2	28.1±0.5
Control (n=40)	27/13	42.4±1.5	23.6±1.0	53.0±2.0	113.1±5.0	206.4±15.2	28.6±0.3	28.2±0.6
t or χ^2 value	0.001	0.288	0.425	0.218	0.089	0.029	1.754	0.810
p-value	0.999	0.774	0.672	0.828	0.930	0.977	0.083	0.421

bypass surgery in the People's Hospital of Guangxi Zhuang Autonomous Region (Nanning, China) from January 2015 to August 2017 were selected. Patients were diagnosed by preoperative imaging, clinical manifestations, and direct observations during surgery. Patients with cognitive impairment, mental and psychological illness and chronic alcoholics, drug addicts, abuse of psychotropic substances, illiterate education, intraoperative use of epinephrine and norepinephrine, or allergy to drugs used in this study were excluded. This study was approved by the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region, and all patients signed informed consent. Patients were randomly divided into two groups, 40 cases in each group. No significant differences in sex, average age, body mass index (BMI), left ventricular ejection fraction, intraoperative cardiopulmonary bypass time and total operation time were found between the groups (P>0.05). Preoperative mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MoCA, Beijing version) were performed and no significant differences in MMSE and MoCA scores were found between the groups (Table I).

Method. All patients underwent surgical treatment under general anesthesia with endotracheal intubation. Patients were fasted and not allowed to drink water before operation. Peripheral vein was opened and connected to the monitor, and patient's noninvasive blood pressure, electrocardiogram, heart rate and oxygen saturation were monitored continuously. Anesthesia machine was used to detect the changes of respiratory function in patients. Anesthesia was induced by intravenous infusion of midazolam, fentanyl, cisatracurium and etomidate. Tracheal intubation was performed under slow induction of anesthesia, and was connected to anesthesia machine for mechanical ventilation, oxygen flow rate was set to 50%, respiratory rate was set to 14 times/min, and tidal volume was set according to patient weight (10 ml/kg). Peripheral arterial puncture, central venous catheterization and pressure measurement were performed. Intraoperative anesthesia was performed by using propofol, remifentanil and cisatracurium. Cardiopulmonary bypass technology was used. Dexmedetomidine (SFDA approval number: H20130027, CISEN), solution (4 μg/ml) was prepared and pumped into patients in the observation group through a vein with a dose of 1 μg/kg during the first 10 min, followed by the dose of 0.2 μg/kg until the end of surgery. Equal volume of 0.9% saline was used at the same speed for patients in the control group, and 1 mg of midazolam was intravenously administered every 30 min. Based on patient circulatory function, vasoactive drug was given through extracorporeal circulation machine during surgery, and vasoactive drugs were intravenously administered after cardiopulmonary bypass. All patients had the same indications for the use of vasoactive drugs, and drugs used here included: popamine, metaxylamine, epinephrine, phenylephrine and norepinephrine.

Observation indexes. Circulatory function-related complications, such as arrhythmia, hypertension, and hypotension were compared between the two groups. BIS was recorded at 30 min before induction of anesthesia (T0), immediately after intubation (T1), when incision was made (T2), when chest was closed (T3), when operation was completed (T4) and at 6 h after operation (T5). The levels of cortisol, epinephrine and norepinephrine at the end of operation were recorded, and recovery time and mechanical ventilation time of the two groups were compared. MMSE and MoCA were performed at 1, 3 and 7 days after operation. The incidence rates of intraoperative awareness and postoperative cognitive dysfunction in the two groups were compared.

Assessment criteria. BIS value was measured by using A-3000 BIS monitor (Aspect Medical System, Covidien, MA, USA) and its ancillary equipment. BIS value fluctuated between 1 and 100. The higher the BIS value is, the higher the sober level is. BIS higher than 95% indicated completely awaken state, and BIS lower than 70% indicated disorder of consciousness. Stress factors, including cortisol (80-550 nmol/l), epinephrine (<480 pmol/l) and norepinephrine (615-3240 pmol/l), were measured by Bio-Rad 450 automatic biochemical analyzer (Bio-Rad Laboratories, Inc., Hercules, CA, USA). MMSE contains seven aspects and 30 questions with a score of 0 to 30, and 27 points was the threshold for cognitive impairment. Lower MMSE score indicated more severe cognitive impairment. MoCA: Test was completed within 10 min, and the highest score was 30 points, and the lowest score was 0. A score over 26 points indicated normal conditions. Lower MoCA score indicated more severe cognitive impairment. MoCA was not performed within 60 min after MMSE, and MMSE was not performed within 24 h after MoCA. Arrhythmias are indicated by electrocardiogram. Hypertension in anesthesia means: blood pressure is greater than 140/95 mmHg or elevated blood pressure is greater than 20%. Hypotension in anesthesia was defined as: blood pressure is less than 90/60 mmHg or decreased blood pressure is greater than 30%.

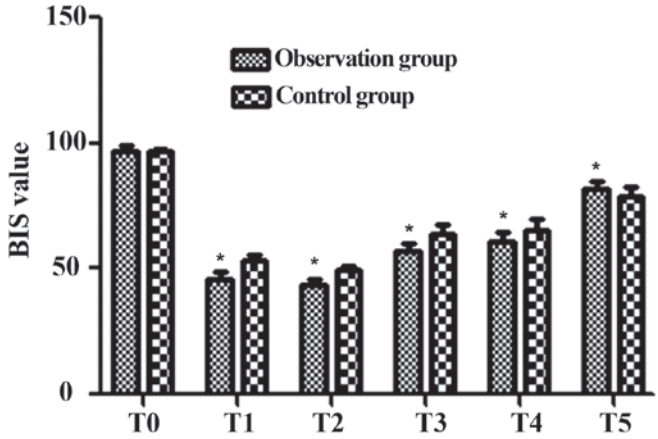

Figure 1. Comparison of BIS values between the two groups at different time-points. BIS values in the observation group were lower than those in the control group at T1 to T4, while BIS value in the observation group was higher than that in the control group at T5. *P<0.05 compared with the control group.

Table II. Comparison of intraoperative circulatory function-related complications between the two groups.

Groups	Arrhythmia	Hypertension	Hypotension	Total incidence
Observation (n=40)	1	1	1	3 (7.5%)
Control (n=40)	3	4	4	11 (27.5%)
χ^2 value		-		4.242
P-value		-		0.039

Statistical analysis. SPSS13.0 (SPSS, Inc., Chicago, IL, USA) was used. Measurement data are expressed as mean ± standard deviation. Comparisons of mean values between the two groups were performed by using t-test, and intragroup comparisons were performed by χ^2 test. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of BIS values between the two groups at different time-points. BIS values in the observation group at T0-T5 were 96.8±2.0, 45.8±2.9, 43.3±2.3, 56.9±3.1, 60.9±3.5 and 81.9±3.3, respectively, and BIS values in the control group at T0-T5 were 96.9±1.0, 53.3±2.6, 49.6±1.8, 63.5±3.9, 65.3±4.6 and 78.9±3.6, respectively. BIS values in the observation group were significantly lower than those in the control group at T1 to T4 (t=8.931, 4.980, 8.379 and 4.814, P<0.05), while BIS value in the observation group was significantly higher than that in the control group at T5 (t=3.885, P<0.05) (Fig. 1).

Comparison of intraoperative circulatory function-related complications between the two groups. The incidence rates of intraoperative arrhythmia, hypertension and hypotension in the observation group were significantly lower than those in the control group (P<0.05) (Table II).

Table III. Comparison of levels of cortisol, epinephrine and norepinephrine at the end of operation between the two groups (mean ± SD).

Groups	Cortisol (nmol/l)	Epinephrine (pmol/l)	Norepinephrine (pmol/l)
Observation (n=40)	10.1±0.7	50.3±2.3	58.5±5.0
Control (n=40)	23.2±1.9	100.1±6.5	179.6±11.7
t value	40.918	45.680	60.196
P-value	<0.001	<0.001	<0.001

Table IV. Comparison of anesthesia recovery time and mechanical ventilation time between the two groups (h, mean ± SD).

Groups	Anesthesia recovery time	Mechanical ventilation time
Observation (n=40)	6.2±0.8	13.8±2.1
Control (n=40)	9.9±1.3	18.6±2.6
t value	15.330	9.083
P-value	<0.001	<0.001

Comparison of levels of cortisol, epinephrine and norepinephrine between the two groups at the end of operation. At the end of surgery, the levels of cortisol, epinephrine and norepinephrine in the observation group were significantly lower than those in the control group (P<0.05) (Table III).

Comparison of anesthesia recovery time and mechanical ventilation time between the two groups. Anesthesia recovery time in the observation group was significantly shorter than that in the control group (P<0.05), and postoperative mechanical ventilation time in the observation group was also significantly shorter than that in the control group (P<0.05) (Table IV).

Changes in MMSE during follow-up. MMSE scores in the observation group were 20.6±0.5 points, 25.1±0.7 points and 28.6±0.3 points at 1 day, 3 days and 7 days after operation, respectively. MMSE scores in the control group were 17.5±0.9 points, 21.3±1.1 points and 23.8±0.7 points at 1 day, 3 days and 7 days after operation, respectively. MMSE scores in the observation group were significantly higher than those in the control group at the three time points (t=19.043, 18.433 and 39.862, P<0.001) (Fig. 2).

Changes in MoCA during follow-up. MoCA scores were 18.6±1.5 points, 25.6±1.0 points and 27.4±0.6 points in the observation group at 1 day, 3 days and 7 days after operation, respectively, and MoCA scores in the control group were 16.3±1.3 points, 21.5±0.8 points and 24.3±0.8 points at 1 day, 3 days and 7 days after operation, respectively. MoCA scores in the observation group were significantly higher than those in the control group (t=7.328, 20.248 and 19.606, P<0.001 <0.05) (Fig. 3).

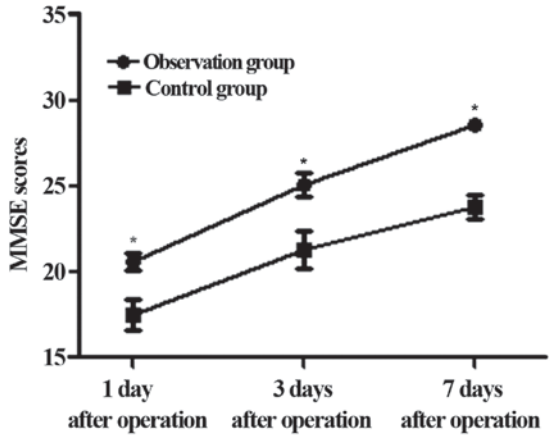

Figure 2. Changes in MMSE during follow-up. MMSE scores in the observation group were significantly higher than those in the control group at 1 day, 3 days and 7 days after operation (P<0.05). *P<0.05 compared with the control group.

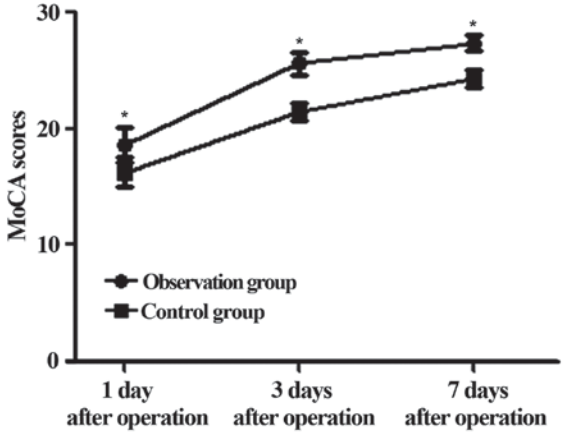

Figure 3. Changes in MoCA during follow-up. MoCA scores in the observation group were significantly higher than those in the control group at 1 day, 3 days and 7 days after operation. *P<0.05 compared with the control group.

Comparison of intraoperative awareness and postoperative cognitive impairment between the two groups. The incidence rates of intraoperative awareness and postoperative cognitive impairment in the observation group were significantly lower than those in the control group (Table V).

Table V. Comparison of intraoperative awareness and postoperative cognitive impairment between the two groups (cases, %).

Groups	Intraoperative awareness	Postoperative cognitive impairment
Observation (n=40)	1 (2.5)	1 (2.5)
Control (n=40)	9 (22.5)	10 (25)
χ^2 value	5.600	6.746
P-value	0.018	0.009

Discussion

Postoperative cognitive impairment is a relatively mild clinical cognitive disorder, but it may cause decreased social activities for a few weeks or months, leading to decreased self-care ability (7). Incidence of postoperative cognitive impairment in patients with coronary artery surgery was significantly higher than that in patients without the surgery (8). Studies have shown that >40% patients will develop cognitive dysfunction within 7 days after coronary artery-related surgery (9), and the incidence in elderly patients is even higher. Dexmedetomidine is currently the most widely used α2 adrenergic receptor agonist in the clinical treatment (10). Dexmedetomidine can induce physiological sleep, achieve certain synergistic analgesic and sympathetic inhibitory effects (11). Previous studies (12) have shown that dexmedetomidine can reduce body stress, inflammation, and inhibit oxidation reaction. Application of dexmedetomidine in anesthesia can maintain sedation, accelerate recovery and reduce the feeling of being drunk (13).

The patients in the observation group were treated with dexmedetomidine. It was found that BIS values in the observation group were lower than those in the control group at T1 to T4 (T1: immediately after intubation, T2: when incision was made, T3: when chest was closed, T4: when operation was completed), while BIS value in the observation group was higher than that in the control group at T5 (6 h after operation, t=3.885, P<0.05). The sedative effect was significantly better in the observation group than in the control group, suggesting that intraoperative sedation effect of dexmedetomidine can accelerate postoperative recovery. Comparison of cyclic function related complications showed that the incidence rates of arrhythmia, hypertension and hypotension were significantly lower in the observation group than in the control group, indicating that dexmedetomidine is safer than midazolam for circulatory function. The comparison of levels of cortisol, epinephrine and norepinephrine at the end of surgery showed that the levels of cortisol, epinephrine and norepinephrine in the observation group were significantly lower than those in the control group, indicating that dexmedetomidine can effectively inhibit the body's stress response and reduce catecholamine hormone secretion. The comparison of anesthesia recovery time and mechanical ventilation time showed that anesthesia recovery time and mechanical ventilation time were significantly shorter in the observation group than in the control group, indicating that dexmedetomidine can effectively shorten the postoperative mechanical ventilation, and promote postoperative recovery. The comparison of MMSE and MoCA scores showed that MMSE and MoCA scores in the observation group were significantly higher than those in the control group at 1 day, 3 days and 7 days after operation, and the incidence rates of intraoperative awareness and postoperative cognitive dysfunction were significantly lower in the observation group than in the control group, indicating that dexmedetomidine can effectively improve postoperative cognitive function and reduce the incidence of intraoperative awareness.

Continuous intravenous infusion of dexmedetomidine can alleviate the severity of the patient's stress response and reduce catecholamine hormone secretion (14), thereby reducing the activity of the sympathetic nervous system, effectively stabilizing patient's hemodynamics (15), alleviating the stress reaction, reducing the trauma to the body caused by operation

and anesthesia stimulation and ischemia-reperfusion injury caused by extracorporeal circulation, and improving the protection effects on the nervous system (16). Dexmedetomidine can also inhibit monocyte Toll-like receptor-1 and Toll-like receptor-2 expression (17), thereby reducing the body's inflammatory response (18) and reducing the incidence of postoperative cognitive dysfunction. In addition, the use of dexmedetomidine can reduce glutamate neurotoxicity (19) and apoptosis of neuronal cells (20). Therefore, it is of great significance to relieve postoperative cognitive dysfunction in patients.

In conclusion, dexmedetomidine can effectively reduce the incidence of postoperative cognitive dysfunction in patients undergoing cardiopulmonary bypass surgery and it is of high safety for circulatory function.

Acknowledgements

Not applicable.

Funding

This study was supported by the Self-financing research project of the Health and Family Planning Commission of Guangxi Zhuang Autonomous Region (nos. Z20180699, Z20170363 and Z2012259).

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ZG and LM conceived and designed the study. ZG, JL and YZ were responsible for the collection and analysis of the patient data. JL, XG and AH interpreted the data and drafted the manuscript. JL and LM revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region (Nanning, China). Signed informed consents were obtained from the patients or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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