Abstract. This study investigated the effects of dexmedetomidine on heart-type fatty acid binding protein (H-FABP), creatine kinase isoenzymes (CK-MB), and troponin I (cTnI) levels, neurological function and near-term prognosis in patients undergoing heart valve replacement. Patients undergoing heart valve replacement were randomly allocated to remifentanil anesthesia (control group, n=48) or dexmedetomidine anesthesia (observation group, n=48). Hemodynamic parameters were measured before anesthesia induction (T1), 1 min after intubation (T2), 10 min after start of surgery (T3), and on completion of surgery (T4). Levels of plasma H-FABP, CK-MB and cTnI were measured 10 min before anesthesia induction (C1), 10 min after start of surgery (C2), on completion of surgery (C3), 6 h after surgery (C4), and 24 h after surgery (C5). S100β protein and serum neuron-specific enolase (NSE) were detected 10 min before anesthesia induction (C1), and 24 h after surgery (C5). Neurological and cardiac function was evaluated 24 h after surgery. Incidence of cardiovascular adverse events was recorded for 1 year of follow-up. There were no significant differences in the average heart rate between the two groups during the perioperative period. The mean arterial pressure in the observation group was significantly lower than control group (P<0.05). Levels of H-FABP, CK-MB and cTnI at C2, C3, C4 and C5, were significantly higher than C1, but significantly lower in the observation versus control group (P<0.05). Twenty-four hours after surgery, levels of S100β and NSE in both groups were higher than those before induction (P<0.05), but significantly lower in the observation versus control group (P<0.05). Twenty-four hours after surgery, neurological function scores were better, and myocardial contractility and arrhythmia scores significantly lower in the observation versus control group (P<0.05 for all). After follow-up for 1 year, incidence of cardiovascular adverse events was significantly lower in the observation versus control group (P<0.05). Dexmedetomidine anesthesia can effectively maintain hemodynamic stability, reduce myocardial injury and the occurrence of cognitive dysfunction, and improve prognosis in patients undergoing heart valve replacement.

Introduction

Heart valve disease is a common clinical heart disease, which involves the aortic valve, mitral valve, tricuspid valve and pulmonary valve; the main clinical manifestations are valve stenosis and insufficiency (1). Traditional cardiopulmonary bypass (CPB) is the main method of treating valvular heart disease. CPB represents a stress on the body, and intubation and sternotomy during surgery further enhances the stress response, resulting in hemodynamic fluctuations in patients, making them prone to myocardial ischemia and ischemia-reperfusion injury. This may lead to systemic inflammatory response syndrome, and multiple organ dysfunction, affecting the prognosis. Brain damage is one of the most serious potential complications after heart valve replacement surgery (2).

In the 1990s, non-CPB coronary artery bypass grafting, that is, heart off pump bypass surgery began to be applied clinically. This technique can help avoid damage caused by CPB, and is more conducive to the protection of heart and brain function and reducing postoperative complications (3). Heart-type fatty acid binding protein (H-FABP), creatine kinase myocardial isoenzyme (CK-MB), troponin I (cTnI) are markers that can reflect the degree of myocardial injury (4). S100β protein and serum neuron-specific enolase (NSE) are markers that can reflect the degree of brain injury and neurological impairment (5).

Anesthesia can also induce a stress response and inhibit immune function, while postoperative pain will prolong the hospital stay, increasing the economic burden. Dexmedetomidine (Dex) is a highly selective α2 adrenergic receptor agonist with analgesic, sedative and anti-sympathetic tonic effects (6). In this study, we examined the effects of performing Dex anesthesia on patients undergoing cardiac valve replacement on H-FABP, CK-MB, cTnI and neurological function of patients.
Materials and methods

Subjects. Ninety-six patients admitted to Shanxi Provincial People's Hospital from January 2015 to December 2015 for heart valve replacement surgery were selected. Inclusion criteria were New York Heart Society heart function grade II-III; non-CPB heart off-pump coronary artery bypass surgery opted for, with a certain degree of preoperative myocardial injury, and complete patient medical records; informed consent signed. Exclusion criteria were severe renal insufficiency, heart failure history and coagulation abnormalities; allergy to dextromethorphan. Patients were divided into observation group and control group according to random number table (both n=48). The study was approved by the Ethics Committee of Shanxi Provincial People's Hospital and informed consents were signed by the patients and/or guardians.

Surgical treatment. Patients were fasted for 8 h before surgery, with blood pressure, heart rate (HR), oxygen saturation (SpO2) and Bipolar Spectrum Index (BIS) monitoring. All patients underwent non-CPB off-pump coronary artery bypass surgery. The control group was treated with remifentanil anesthesia, using propofol (3 mg/kg) (Sichuan Guorui Pharmaceutical Co., Ltd., approval no.H20040079), remifentanil (0.3 µg/kg; Yichang Humanwell Pharmaceutical Co., Ltd., approval no. H20054171) and vecuronium bromide (0.1 mg/kg) (Beijing Mengjin Medical Technology Development Co., Ltd., approval no. H20063122) to induce anesthesia; tracheal intubation was performed when BIS was less than 55, then the patient was connected to the ventilator (respiratory rate: 12-15 times/min, suction ratio: 1:2, tidal volume: 8-9 ml/kg), and remifentanil was intermittently added to maintain the BIS value at 40-45, with remifentanil dosage adjusted according to BIS value, the floating range was ±30%.

The observation group were treated with Dex anesthesia, and the anesthesia induction was the same as that of the control group. Dex (0.5 µg/kg/h) was pumped after tracheal intubation. Intravenous injection of remifentanil (0.3 µg/kg) was performed every 3-5 min during surgery to maintain anesthesia, the pumping of Dex was stopped 30 min before the end of surgery, and tracheal extubation was performed when the patient’s spontaneous breathing tidal volume reached 5 ml/kg, heartrate 20 beats/min, oxygen SpO2 ≥95% and maintained for more than 5 min.

Detection of related indicators. Immediately before induction (C1), 10 min after the start of surgery (C2), at the end of surgery (C3), 6 h after the end of surgery (C4), and 24 h after surgery (C5), 4 ml of central venous blood was taken, centrifuged and the supernatant isolated and stored in liquid nitrogen (-70˚C). The levels of H-FABP, CK-MB and cTnI were measured by enzyme-linked immunosorbent assay (ELISA) before the induction of anesthesia (C1), after 10 min of surgery (C2), immediately at the end of surgery (C3), 6 h after surgery (C4), and 24 h after surgery (C5). The levels of S100β and NSE were measured by ELISA before and 24 h after anesthesia induction.

One day before and 24 h after surgery, the cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA) scale and the Simple Mental State Examination Scale (MMSE). The MoCA scale was evaluated from the eight areas including space and the ability of implementation, memory, attention, naming, language, delayed memories, abstract thinking and orientation, with a total score of 30 points. A total of <26 points was judged as impaired cognitive function. MMSE criteria scored the orientation force, language, memory, attention and computing power. Scores were judged as mild cognitive dysfunction: 21-24 points, moderate cognitive dysfunction 11-20 points, severe cognitive dysfunction 0-10 points.

Myocardial contractility score formula 24 h after operation was (dopamine + dobutamine) x 1 + milrinone x 15 + (adrenaline + norepinephrine + isoproterenol) x 100 µg/kg/min; ventricular arrhythmia criteria was judged as 0 points: no arrhythmia occurred, 1 point: atrial arrhythmia or <10 pre-ventricular contractions, 2 points: ≥10 times ventricular contraction, 3 points: ventricular tachycardia attack 1-2 times, 4 points: ventricular tachycardia or ventricular tachycardia attack ≥3 times. Patients were followed up for 1 year, and the incidence of adverse cardiovascular events was observed, including cardiac arrest, arrhythmia, and heart functional failure.

Statistical analysis. Data were processed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA), measurement data were expressed as mean ± standard deviation, using t-test; enumeration data were expressed as a percentage, using χ² test, and P<0.05 indicated statistical significance.

Results

Comparison of hemodynamics. There was no significant difference between the two groups in terms of baseline characteristics (P>0.05) (Table I). There was no significant difference in perioperative HR between the two groups (P>0.05). The MAP of the observation group was lower than that of the control group after anesthesia (P<0.05) (Table II).

Concentration changes of H-FABP, CK-MB, cTnI. At the time points C1, C2, C3, C4, and C5, the levels of H-FABP were 0.26±0.06, 0.48±0.13, 1.36±0.27, 1.94±0.23,
1.42±0.37 µg/ml in the observation group, and were 0.25±0.04, 0.65±0.14, 1.89±0.26, 2.34±0.25, 1.71±0.45 µg/ml in the control group (Fig. 1A). The levels of CK-MB in the observation group were 22.78±1.56, 60.68±2.53, 110.36±2.47, 130.64±2.13, 89.52±2.37 U/ml, and in the control group were 22.44±1.34, 69.63±2.74, 141.75±3.26, 156.64±3.25, 112.73±3.45 U/ml (Fig. 1B). The levels of cTnI in the observation group were 0.38±0.06, 0.63±0.13, 1.34±0.13, 1.12±0.27 ng/ml, and in the control group 0.39±0.08, 0.79±0.14, 1.25±0.26, 1.78±0.25, 1.48±0.25 ng/ml (Fig. 1C). The levels of H-FABP,
CK-MB and cTnI at C2, C3, C4 and C5 were significantly higher than at C1 in both groups (P<0.05), however, the levels in the observation group at C2, C3, C4 and C5 were significantly lower than those in the control group (P<0.05). The levels of S100β and NSE in the two groups.

The levels of S100β and NSE in the two groups. The levels of S100β and NSE after surgery were significantly higher than those before surgery (P<0.05). The levels of S100β and NSE in the observation group were significantly lower than those in the control group (P<0.05) (Table III).

The MoCA and MMSE scores of the two groups. The MoCA and MMSE scored in the two groups after surgery were lower than those before surgery, and the decrease in scores in the observation group was lower than that of the control group, P<0.05 (Table IV).

Cardiac parameters. The myocardial contractility and cardiac arrhythmias scores in the observation group were significantly lower than those of the control group 24 h after surgery (P<0.05); after 1-year follow-up, the incidence of adverse events observed in the observation group was significantly lower than in the control group (P<0.05) (Table V).

Discussion

The incidence of neurological complications of heart valve replacement surgery is higher than other surgeries, and the degree of postoperative neurological impairment of patients is more severe than other heart surgeries. Possible reasons for this are the formation of brain micro-thrombi during surgery, the strong stimulation of the operation, hypoxia due to low perfusion, ischemia and systemic inflammatory responses (7). Related studies have shown that the incidence of postoperative cognitive dysfunction (POCD) after heart valve replacement can be as high as 69% (8). Heart valve replacement surgery can cause damage to the myocardium, and different methods of anesthesia can lead to certain stress responses during the
perioperative period, which may have some influence on the surgical outcomes. It has recently become a clinical focus to define strategies to reduce the neurological impairment and myocardial damage after heart valve replacement, and how to preserve heart and brain function and improve the success rates of surgery and prognosis (9).

Both tracheal intubation and the surgical procedure in the perioperative period of heart valve replacement can result in stress responses that cause HR acceleration and elevated blood pressure (10). Studies have shown that Dex activates the α2 receptor in the medullary dorsal motor neuron complex, thereby reducing blood pressure (11). The results of this study showed that there was no significant difference in perioperative HR between the two groups (P>0.05). MAP in the observation group was lower than that in the control group (P<0.05) after anesthesia, which was consistent with the results of related studies. Various anesthetic methods can bring varying degrees of stress response, resulting in the increased release of glucagon, catecholamines and norepinephrine and other secretions, therefore exciting the sympathetic nervous system, causing neuroendocrine system changes and hemodynamic instability (12). Dex can inhibit a variety of stress responses, maintaining hemodynamic stability. Dex has both analgesic and sedative effects, inhibits the release of norepinephrine, reduces the tension of the sympathetic nervous system, reduces the increased blood pressure response during surgery, and regulates blood pressure in the recovery period (13).

H-FABP is a low molecular weight cytosolic protein present in cardiomyocytes, which is commonly used as an early indicator of myocardial injury. Usually in early myocardial injury H-FABP quickly leaks from the cardiomyocytes, and is released into the peripheral blood, entering into the energy metabolism system by binding with long-chain fatty acid, and providing energy for the myocardium; its release is positively correlated with the level of myocardial injury (14). CK-MB is composed of the four isomers of creatine kinase, which is related to muscle contraction and intracellular energy transport. It is clinically used as an indicator of myocardial injury, and its concentration level is positively correlated with the degree of myocardial injury (15).

cTnI is an inhibitory protein in the troponin-protocelin-modulating complex that regulates the interaction between myofibrin and myosin and can inhibit muscle contractions, and is rapidly released into the peripheral blood during myocardial ischemia and reaches a peak in a few hours (16). The results of this study showed that H-FABP, CK-MB and cTnI were significantly increased in the two groups at the beginning of surgery for 10 min, at the end of surgery, 6 and 24 h after surgery, however, the increases occurring in the observation group were significantly lower than those in the control group (P<0.05). After one year of follow-up, the incidence of cardiovascular adverse event in the observation group was significantly lower than in the control group (P<0.05), and this may be due to patient discomfort after surgery, excessive tension of the sympathetic nervous system, and inflammatory reactions leading to POCD in the control group. Dex has anti-inflammatory effects, which can inhibit the production of inflammatory factors, thereby reducing the damage to the nervous system, improving the level of acetylcholine, reducing cognitive impairment and protecting the brain (20). Dex can also reduce the surgical stress response, inhibit apoptosis, reduce myocardial ischemia and reperfusion injury, therefore reducing intraoperative and postoperative ventricular arrhythmia (21).

In conclusion, Dex can maintain perioperative hemodynamic stability of patients undergoing heart valve replacement surgery and reduce myocardial and brain damage, playing a protective role on the heart and the brain, which is conducive to a better prognosis.

References

1. Cavero I and Guillon JM: Safety Pharmacology assessment of drugs with biased 5-HT2B receptor agonism mediating cardiac valvulopathy. J Pharmacol Toxicol Methods 69: 150-161, 2014.
2. Nombela-Franco L, Elchaninoff H, Zahn R, Testa L, Leon MB, Trillo-Noche R, D’Onofrio A, Smith CR, Webb J, Bleiziffer S et al: Clinical impact and evolution of mitral regurgitation following transcatheter aortic valve replacement: A meta-analysis. Heart 101: 1395-1405, 2015.
3. Gurbuz O, Kumtepe G, Yolgoosteren A, Ozkan H, Karal IH, Ercan A and Ener S: A comparison of off- and on-pump beating heart coronary artery bypass surgery on long-term cardiovascular events. Cardiovasc J Afr 27: 1, 2016.
4. Willemsen RT, Buntinx F, Winkens B, Glatz JF and Dinant GJ; ‘RAPIDA’-study team: The value of signs, symptoms and plasma heart-type fatty acid-binding protein (H-FABP) in evaluating patients presenting with symptoms possibly matching acute coronary syndrome: Background and methods of a diagnostic study in primary care. BMC Fam Pract 15: 203, 2014.
5. Patro N, Naik A and Patro IK: Differential temporal expression of S100β in developing rat brain. Front Cell Neurosci 9: 87-99, 2015.
6. Tomasi R and Dossow-Hanfstingl VV: Analgesie-, sedierungs- und delir- management auf der intensivstation. Intensiv- und Notfallbehandlung 39: 167-172, 2015 (In German).
7. Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, Paparella D, Sessler DI, Karthikeyan G, Villar JC, et al; SIRS Investigators: Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): A randomised, double-blind, placebo-controlled trial. Lancet 386: 1243-1253, 2015.
8. Sigaut S, Tremeau B, Ouattara A, Couturier R, Taberlet C, Grassin-Delyle S, Dreyfus JF, Schlumberger S and Fischler M: Comparison of two doses of tranexamic acid in adults undergoing cardiac surgery with cardiopulmonary bypass. Anesthesiology 120: 590-600, 2014.
9. Howard BT, Iles TL, Coles JA, and Iaizzo PA: Reversible and irreversible damage of the myocardium: Ischemia/reperfusion injury and cardioprotection. In: Handbook of Cardiac Anatomy, Physiology, and Devices. 3rd edition. Springer International Publishing, pp279-293, 2015.
10. Green JS and Tsui BC: Impact of anesthesia for cancer surgery: Continuing Professional Development. Can J Anaesth 60: 1248-1269, 2013.
11. Kiliç K, Hanci V, Selek S, Sizmen M, Kiliç N, Citi M, Yurtlu DA and Yurtlu BS: The effects of dexmedetomidine on mesenteric arterial occlusion-associated gut ischemia and reperfusion-induced gut and kidney injury in rabbits. J Surg Res 178: 223-232, 2012.
12. Jung SM and Cho CK: The effects of deep and light propofol anesthesia on stress response in patients undergoing open lung surgery: A randomized controlled trial. Korean J Anesthesiol 68: 224-231, 2015.
13. Bell MT, Agoston VA, Freeman KA, Puskas F, Herson PS, Mares J, Fullerton DA and Reece TB: Interruption of spinal cord microglial signaling by alpha-2 agonist dexmedetomidine in a murine model of delayed paraplegia. J Vasc Surg 59: 1090-1097, 2014.
14. Glatz JF and Renneberg R: Added value of H-FABP as plasma biomarker for the early evaluation of suspected acute coronary syndrome. Clin Lipidol 9: 205-220, 2014.
15. Banning A, Musuamec F, Penny W and Tovey JA: Reference intervals for cardiac troponin T, creatine kinase and creatine kinase-MB isoenzyme following coronary bypass graft surgery. Ann Clin Biochem 33: 561-562, 1996.
16. Sandoválov Y, Smith SW, Schulz KM, Murakami MM, Love SA, Nicholson J and Apple FS: Diagnosis of type 1 and type 2 myocardial infarction using a high-sensitivity cardiac troponin I assay with sex-specific 99th percentiles based on the third universal definition of myocardial infarction classification system. Clin Chem 61: 657-663, 2015.
17. Funai Y, Pickering AE, Uta D, Nishikawa K, Mori T, Asada A, Imoto K and Furue H: Systemic dexmedetomidine augments inhibitory synaptic transmission in the superficial dorsal horn through activation of descending noradrenergic control: An in vivo patch-clamp analysis of analgesic mechanisms. Pain 155: 617-628, 2014.
18. Pfeifer R, Franz M and Figulla HR: Hypothermia after cardiac arrest does not affect serum levels of neuron-specific enolase and protein S-100b. Acta Anaesthesiol Scand 58: 1093-1100, 2014.
19. Benedict C, Cedernaes J, Giedraitis V, Nilsson EK, Hogenkamp PS, Vägesjö E, Massena S, Pettersson U, Christoffersson G, Phillipson M, et al: Acute sleep deprivation increases serum levels of neuron-specific enolase (NSE) and S100 calcium binding protein B (S-100B) in healthy young men. Sleep 37: 195-198, 2014.
20. Sun L, Guo R and Sun L: Dexmedetomidine for preventing sevoflurane-related emergence agitation in children: A meta-analysis of randomized controlled trials. Acta Anaesthesiol Scand 58: 642-650, 2014.
21. Chen S, Hua F, Lu J, Jiang Y, Tang Y, Tao L, Zou B and Wu Q: Effect of dexmedetomidine on myocardial ischemia-reperfusion injury. Int J Clin Exp Med 8: 21166-21172, 2015.