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Original Article

Study on cerebral protective effect of dexmedetomidine during anesthesia in cardiac valve replacement surgery

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Abstract: Objective: To evaluate the cerebral protection of Dexmedetomidine during anesthesia of cardiac valve replacement surgery. Methods: 60 patients who underwent elective cardiac valve replacement surgery under cardiopulmonary bypass (CPB) in our hospital were randomly divided into Dexmedetomidine group and control group (30 cases in each group); patients in Dexmedetomidine group were injected with Dexmedetomidine 1.0 μg/kg intravenously at 10 min before routine anesthesia induction, then injected with 0.5 μg/kg/h till surgery finished; the control group received equal volume of normal saline with the same infusion speed. Heart rate (HR) and blood pressure were recorded at T1 (establish of CPB), T2 (end of CPB) and T3 (end of surgery), in the meanwhile, the doses of vasoactive agents used during operation were also recorded. Jugular venous oxygen saturation ($SjvO_2$), Arterial venous oxygen content difference ($Da\text{-}jvO_2$) and cerebral extraction of oxygen ($CERO_2$) at T1-T3 were monitored analyzed. Central venous blood was drawn at time points of T1-T3 to detect the concentrations of plasma S-100β protein, TNF-α and serum neuronspecific enolase (NSE) by ELISA. Mini-Mental State Examination (MMSE) and Delirium Rating Scale (DRS) were used to assess postoperative cognitive function and postoperative delirium, respectively. Results: Compared with the control group, the amount of Phenylephrine, Dopamine, Adrenaline used in Dexmedetomidine group was significantly reduced (94 μg *vs.* 185 μg; 24 μg *vs.* 44 μg; 6.3% *vs.* 21%), while the volume of Atropine was significantly increased (18% *vs.* 6.1%), the differences were statistically significant (all $P < 0.05$); the $SjvO_2$ of two groups of patients at T2 was significantly higher than that at T1 while $Da\text{-}jvO_2$ and $CERO_2$ were significantly lower than those at T1. Moreover, by comparing with control group, the $SjvO_2$ of Dexmedetomidine group at T2 and T3 was significantly higher while $Da\text{-}jvO_2$ and $CERO_2$ were significantly lower (all $P < 0.05$). The postoperative delirium score of dexmedetomidine group (15.8±4.2) was significantly lower than that of control group (18.6±6.2), the difference was statistically significant ($P < 0.05$); there was a significant difference in MMSE score ($P < 0.05$) between two groups at postoperative 1 week; the concentrations of TNF-α, S-100β protein and NSE level of both groups at T2 and T3 were significantly increased ($P < 0.05$) by comparing with the values at T1, and the levels in dexmedetomidine group were significantly lower than those of control group ($P < 0.05$) at T2 and T3. Conclusion: Dexmedetomidine could improve brain oxygen metabolism and reduce intraoperative cerebral ischemia and hypoxia during cardiac valve replacement surgery under CPB; to a certain extent, Dexmedetomidine has cerebral protective effect.

Keywords: Cardiac valve replacement surgery, dexmedetomidine, cardiopulmonary bypass, cerebral protection

Introduction

Cardiac valve replacement surgery under CPB is the main method to treat rheumatic heart disease. With the continuous improvement in surgical techniques, there is a gradual reduce in postoperative fatality rate; however, there is no obvious improvement in postoperative complications of the central nervous system. Studies have shown that about 1.8-2.4% of patients had stroke during cardiac valve replacement surgery, and the elder patients had a higher incidence [1, 2]. During CPB, the brain is at different levels of hypoxia, cerebral ischemia is the main cause of brain damage. Cardiopulmonary blood bypass, different from physiological perfusion, may have embolism and inflammation that lead to local hypoxic and ischemic changes of brain tissues, which may worsen the postoperative cognitive impairment

and other symptoms of brain damage [3]. Therefore, select an anesthetic with cerebral protective effect is crucial for patients undergoing heart valve replacement surgery under CPB.

Dexmedetomidine is a highly selective α2-adrenoceptor agonist, which is commonly used in clinic as an adjuvant anesthesia that has effects of sedation, analgesia, and anti-anxiety [4, 5]. For coronary artery bypass surgery, dexmedetomidine could enhance hemodynamic stability and maintain cardiac oxygen supply balance [6]; for acute craniocerebral injury, the application of Dexmedetomidine could suppress perioperative inflammatory response and protect cerebral function at certain level [7, 8]; in animal models of cerebral ischemia injury, Dexmedetomidine was also confirmed to possess the ability of reduce the concentrations of brain damage markers, such as S100β protein. Currently, whether Dexmedetomidine could maintain stable hemodynamics and have cerebral protection effect during cardiac valve replacement surgery under CPB has not been clearly manifested yet. In this study, we investigated the effect of Dexmedetomidine on hemodynamic, brain injury markers and postoperative cognitive function in patients undergoing cerebral valve replacement surgery under CPB, in order to provide experimental evidence for clinical practice.

Materials and methods

General information

60 patients underwent elective cardiac valve replacement surgery under CPB at our hospital from January 2014 to March 2015 were selected for this study. The participants were consist of 34 males and 26 females, aged from 45-75 years old and weight from 51-75 kg, ASA classification was II or III, and NYHA heart function was at II-III level. Inclusion criteria: patients without atrioventricular block (AVB), cerebral infarction (CI) or atherosclerosis disease; patients without diabetes, or history of allergies and cardiac surgery, or liver pulmonary dysfunction; the study was approved by the hospital ethics committee, and the informed consent was obtained from the family members of patients. According to the random number table, patients were divided into Dexmedetomidine group and control group with 30 patients in each group. Dexmedetomidine in observation group was applied as: loading dose at 1.0 μg/kg, continuous infusion at a dose of 0.5 μg/kg/h; while the control group was infused with the same volume of normal saline.

Methods

All patients breathed with application of oxygen mask after entering the operation room; heart rate, blood pressure, bispectral index and saturation of pulse oximetry (SpO_2) as well as other indicators of the patient were closely monitored during the operation; left radial artery and the right internal jugular vein were punctured to place catheter under local anesthesia; in the meanwhile, the nasopharyngeal and the rectal temperature were monitored. Patients in Dexmedetomidine group were intravenously injected with Dexmedetomidine at 1.0 μg/kg in 10 min, followed with continuous transfusion of 0.5 μg/kg/h until the end of surgery. The patients in control group were transfused with same volume of normal saline in the same way as described. Intravenous injection of sufentanil 1 μg/kg, midazolam 0.05 mg/kg, rocuronium 0.6 mg/kg and etomidate 0.3 mg/kg for induction of anesthesia. After tracheal intubation, patients were mechanically ventilated to maintain end-tidal carbon dioxide at 35-45 mmHg. The crystal/colloid ratio of priming solution used in CPB was 3:1, non-pulsatile perfusion was applied with a flow of 2.0-2.5 L/m^2/min, and mean arterial pressure was maintained at 50-80 mmHg. Rewarming treatment was processed after intracardiac operation; protamine was used to neutralize heparin at a ratio of 1:1 after machine shutdown. Maintenance of anesthesia: inhalation of 1%-2% sevoflurane, continuous intravenous injection of 0.5-0.6 μg/kg/h sufentanil, intermittent injection of atracurium to maintain muscle relaxants, in the meanwhile, maintain the brain bispectral index value at 40-50.

The application method of cardiovascular drugs during the surgery

Before CPB, intravenous injection of atropine 0.05 mg/kg if heart rate was less than 45 beats/min, and esmolol 20 mg/kg if heart rate was greater than 100 beats/min; intravenous injection of phenylephrine 20-40 μg when systolic blood pressure was less than 80 mmHg, and nicardipine 0.4 mg/kg if blood pressure was higher than 160 mmHg. After

Table 1. The comparison of general information and in perioperative situation between two groups of patients

Group	Number (n)	Age (year)	Male/ Female (n)	BMI (kg/m^2)	LVEF (%)	Time of CPB (min)	Aortic Clamping Time (min)	Extubation Time (h)
Dexmedetomidine Group	30	47.7±8.7	18/12	22.3±1.7	55.3±5.7	71±11	56±8	21.8±9.2
Control Group	30	46.8±7.4	16/14	22.4±2.1	55.4±4.7	72±13	57±6	22.3±8.7

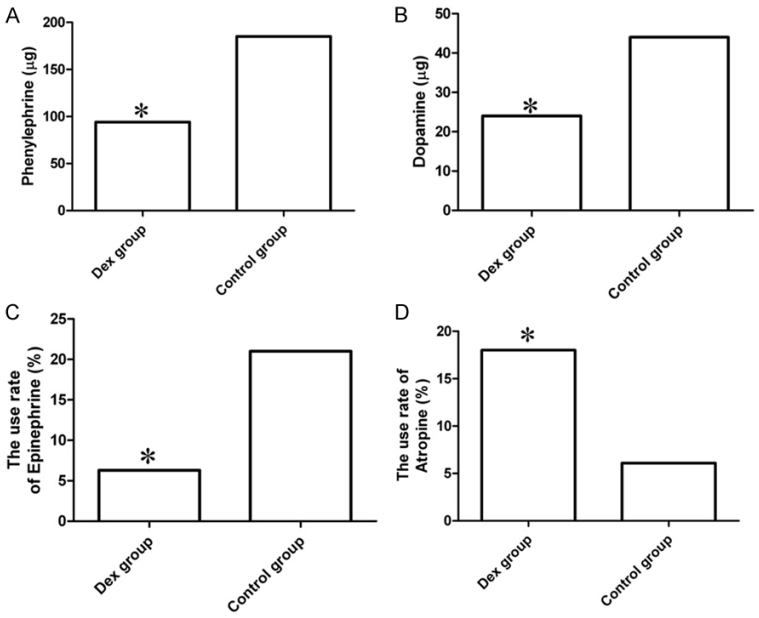

Figure 1. Comparison of vasoactive drugs consumed in two groups of patients, *P < 0.05. A: The amount of Phenylephrine; B: The amount of Dopamine; C: Adrenaline usage rate; D: Atropine usage rate.

aortic unclamping, dopamine was intravenously transfused at 4 μg/kg/min, if the mean arterial pressure was still less than 50 mmHg after shutdown, dopamine was increased at a rate of 1 μg/kg/min; if a dose of 10 μg/kg/min still could not maintain mean arterial pressure over 50 mmHg, intravenously inject adrenaline at 0.04-0.1 ug/kg/min.

Observation indices

The usage rate of atropine and epinephrine, and the amount of dopamine and phenylephrine used in the surgery was recorded; the heart rate (HR) and blood pressure at the time of establishing CPB (T1), end of CPB (T2) and the end of surgery (T3) were carefully recorded; radial artery and jugular vein blood samples were collected at T1-T3 and postoperative 6h (T4) for blood gas analysis, and the jugular venous oxygen saturation ($SjvO_2$), arterial venous oxygen content difference ($Da\text{-}jvO_2$) and cerebral extraction of oxygen ($CERO_2$) were calculated according to Fick formula; Venous blood (2 mL) was collected at postoperative 24 h (T5), and ELISA was used to detect the concentrations of plasma protein S100β, TNF-α and serum neuronspecific enolase (NSE) at T1, T2, T3 and T5. Mini-Mental State Examination (MMSE) was used to assess postoperative cognitive function: the total score was 30 points with 24 points as cut-off value, and patients with score under cut-off value were regarded as cognitive impairment; delirium rating scale (DRS) was used to assess postoperative delirium: the patients were evaluated without using any sedative drugs, the total score was 46 points, the score for the most severe condition was 39 points, delirium was defined as total score > 18 or the score of severity > 15.

The statistical analysis

SPSS 19.0 software was used for statistical data analysis; measurement data was expressed as mean ± standard deviations, the comparison between the two groups was examined by t-test; the comparison between different time points within group were analyzed by using ANOVA; count data was examined by χ^2 test. $P < 0.05$ was considered statistically significant.

Results

Comparison of the general data between two groups of patients

The age, sex ratio, BMI and preoperative LVEF value of two groups were comparable, without significant difference ($P > 0.05$). As for the conditions during perioperative period, there were no significant differences in the cardiopulmo-

Table 2. The Comparison of hemodynamic changes at different times between two groups of patients

Group	Heart rate (times/min)	Mean arterial pressure (mmHg)
Dexmedetomidine Group		
T1	77.4±8.7	74.5±8.1
T2	77.3±9.1	74.1±7.9
T3	79.7±8.5	75.0±8.2
Control Group		
T1	78.1±8.3	73.7±7.8
T2	77.9±8.4	74.3±8.2
T3	80.1±8.1	74.7±8.8

Table 3. The comparison of $SjvO_2$, Da-jvO_2 and $CERO_2$ at each time point betweentwo groups of patients

Group	$SjvO_2$ (%)	Da-jvO_2 (mmol/L)	$CERO_2$ (%)
Dexmedetomidine Group			
T1	63.1±8.1	51.2±8.8	35.7±9.2
T2	82.3±5.2*,#	24.3±9.1*,#	17.2±6.2*,#
T3	66.5±6.8#	45.1±8.3#	35.5±8.7#
Control Group			
T1	63.8±8.7	53.2±7.1	36.8±8.0
T2	71.7±9.4*	35.3±8.4*	27.5±7.1*
T3	58.9±9.1	52.4±7.8	41.6±6.3

Note: *P < 0.05, *vs.* T1; #P < 0.05, *vs.* control group at same time point.

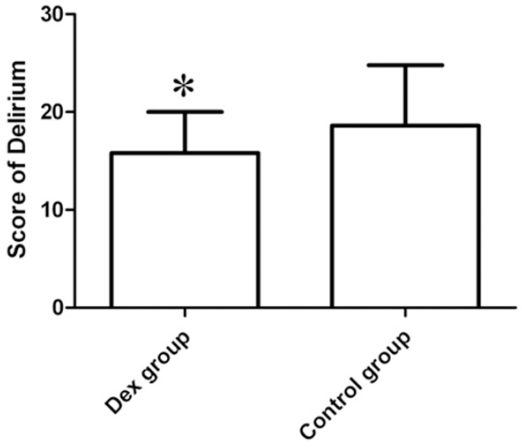

Figure 2. Comparison of the postoperative delirium score between two groups, *P < 0.05.

nary bypass time, aortic clamping time or tracheal extubation time between two groups (P > 0.05), see **Table 1**.

Comparison of the doses of vasoactive drugs

There was no statistical difference in the dose or application rate of esmolol and nicardipine between two groups of patients (P > 0.05). Compared with the control group, the doses of phenylephrine, dopamine and adrenaline in Dexmedetomidine group were significantly reduced (94 μg *vs.* 185 μg; 24 μg *vs.* 44 μg; 6.3% *vs.* 21%), while the doses of Atropine was significantly increased (18% *vs.* 6.1%), the differences was statistically significant (P < 0.05), see **Figure 1**.

Comparison of heart rate and blood pressure between two groups of patients

Heart rate (HR) and mean arterial pressure (MAP) of patients in two groups at each time point are shown in **Table 2**, and we can see that the differences were not statistically significant (P > 0.05).

Comparison of $SjvO_2$, Da-jvO_2 and $CERO_2$ between two groups of patients

$SjvO_2$ at T2 of both groups were significantly higher than that of T1, while Da-jvO_2 and $CERO_2$ were significantly lower than those of T1; moreover, the $SjvO_2$ at T2 and T3 of Dexmedetomidine group were significantly higher than those of the control group, while Da-jvO_2 and $CERO_2$ were significantly lower than those of the control group (P < 0.05), see **Table 3**.

Assessment of postoperative neurological function

Compared with the control group, the postoperative delirium score of Dexmedetomidine group was significantly decreased ((15.8±4.2) *vs.* (18.6±6.2)), the difference was statistically significant (P < 0.05), see **Figure 2**. In control group, 7 patients (23.3%) had delirium, while 4 cases (13.3%) in dexmedetomidine group had delirium.

The preoperative MMSE scores between the two groups of patients were not statistically different (P > 0.05); however, in control group, the MMSE score at postoperative 1 week were statistically different from the preoperative score (P < 0.05). MMSE scores of two groups showed no significant difference in the scores

Table 4. The comparison of MMSE scores between two groups of patients

Group	Preoperative	After 1 week
Control Group	28.12±1.24	26.42±1.61*
Dexmedetomidine Group	28.27±1.42	28.19±1.53#

Note: *P < 0.05, *vs.* preoperative value; #P < 0.05, *vs.* control group.

Table 5. The Comparison of the concentrations of TNF-α, S-100β protein and NSE between two groups of patients at each time point

Group	TNF-α (pg/L)	S-100β Protein (μg/L)	NSE (μg/L)
Dexmedetomidine Group			
T1	0.35±0.02	0.16±0.05	6.5±1.5
T2	0.46±0.04*,#	3.82±1.15*,#	17.4±4.7*,#
T3	0.73±0.06*,#	4.09±1.19*,#	20.1±4.1*,#
Control Group			
T1	0.34±0.02	0.15±0.04	6.3±1.8
T2	0.54±0.06*	4.13±1.18*	21.2±4.1*
T3	0.84±0.09*	5.49±1.07*	24.2±4.3*

Note: *P < 0.05, *vs.* T1; #P < 0.05, *vs.* control group at the same point.

before the operation, but at postoperative 1 week, the two groups were significantly different ($P < 0.05$), see **Table 4**. There were 12 patients (40%) in control group developed cognitive impairment while there were only 4 patients (13.3%) in Dexmedetomidine group developed cognitive impairment.

Comparison of levels of TNF-α, plasma S100β and NSE in two groups of patients

At T1, there were no significant differences in TNF-α, S-100β protein and NSE levels between the two groups ($P > 0.05$). Compared with T1, the level of TNF-α, S-100β protein and NSE at T2 and T3 of both groups were significantly increased ($P < 0.05$). The level of TNF-α, S-100β protein and NSE in Dexmedetomidine group at T2 and T3 were significantly lower than those of the control group ($P < 0.05$), See **Table 5**.

Discussion

Due to the non-physiological oxygenation and perfusion, local cerebral hypoxic ischemia or embolism during cerebral valve replacement surgery under CPB can induce inflammatory cascade, causing central nervous system damage and increased incidence in postoperative neuropsychological complications [9-11]. Therefore, maintaining the balance between supply and demand of oxygen in patients undergoing brain surgery and improving cerebral blood flow and cerebral oxygen metabolism, can reduce brain function impairment after heart valve replacement surgery under CPB.

Blood flows to internal jugular bulb via retrosigmoid approach, not including the external jugular vein blood, and detection of $SjvO_2$ can indirectly reflect cerebral oxygen metabolism [12, 13]. The normal range of $SjvO_2$ is 55%-75%, $SjvO_2$ > 75% suggesting an increased cerebral oxygen or brain blood flow, while < 55% suggesting a relative low cerebral oxygen supply or cerebral blood flow; either decrease in oxygen supply or increase in oxygen consumption of brain can cause the drop of $SjvO_2$ level. Calculating $Da\text{-}jvO_2$ and $CERO_2$ can reflect the correlation between oxygen consumption and cerebral blood flow [14, 15]. $CERO_2$ level will not be affected by hemoglobin content, and is suitable for the evaluation of the balance of cerebral oxygen supply and demand during operation; $CERO_2$ reduction suggests a decreased cerebral metabolic rate of oxygen, which means leftover in oxygen consumption in cerebral blood flow; $CREO_2$ elevation, however suggests an increased cerebral oxygen uptake, which means insufficient cerebral oxygen consumption in cerebral blood flow. This study showed that the $SjvO_2$ in two groups of patients were significantly higher at T2 than the value at T1, while $Da\text{-}jvO_2$ and $CERO_2$ were significantly lower than the values at T1; the $SjvO_2$ in dexmedetomidine group at T2 and T3 were significantly higher than those of the control group ($P < 0.05$). Thus, in heart valve replacement surgery under CPB, dexmedetomidine may reduce cerebral oxygen consumption by reducing cerebral oxygen metabolism, and further improve brain oxygenation and the hypoxia tolerance of brain tissue, to play a protective effect on cerebral tissues.

Study has shown that the intravenous infusion of Dexmedetomidine 1 μg/kg prior to conven-

tional induction of anesthesia and followed by 0.4 μg/kg/h infusion until the end of the operation can reduce perioperative inflammatory response of patients with acute brain injury [16]. TNF-α, an important cytokine of inflammation response and tissue damage in CPB, plays a key role in postoperative organ injury mechanisms. The levels of cytokines, such as TNF-α, can directly reflect the severity of systemic inflammatory response syndrome after CPB, which is closely related to the occurrence of postoperative complications [17, 18]. S-100β and NSE protein mainly exist in gliocytes in central nervous system with a very low concentration under normal circumstances; however, under the circumstances of brain trauma or CPB, gliocytes damage and blood-brain barrier function disorder will result in increased concentration of S-100β and NSE, which will increase with the severity of trauma increased [19, 20]. Combined detection of NSE and S-100β can reflect brain injury during CPB. The results of this study showed that compared with T1, concentrations of TNF-α, S-100β protein and NSE in two groups were significantly increased at T2 and T3 ($P < 0.05$). The concentrations of TNF-α, S-100β protein and NSE in Dexmedetomidine group at T2, T3 were significantly lower than those of the control group ($P < 0.05$), indicating that dexmedetomidine can significantly improve the situation of brain damage in heart valve replacement surgery under CPB, which is possibly achieved by inhibiting the inflammatory response.

Delirium and cognitive impairment occurs more frequently in cardiac surgery; Dextromethorphan can not only stabilize hemodynamic condition and protect vital organs, but also reduce the incidence of postoperative neurological symptoms [21]. A study shows that dexmedetomidine can not only prevent the occurrence of postoperative delirium, but also has a good treatment effect on postoperative delirium developed in ICU [22]. In the present study, the postoperative delirium score of control group (18.6±6.2) was significantly higher than that of dexmedetomidine group (15.8±4.2), the difference was statistically significant ($P < 0.05$); at postoperative 1 week, the difference in MMSE score between the two groups was significantly different ($P < 0.05$). In this study, the incidence of postoperative delirium and cognitive impairment in Dexmedetomidine was lower than that of control group; however, due to the small sample size, we still need clinical trials with large samples size to further verify.

In conclusion, Dexmedetomidine can significantly improve brain oxygen metabolism and postoperative neurological symptoms in heart valve replacement surgery under CPB, which shows a cerebral protective effect to a certain extent. However, due to small sample size, we still need more clinical trials to prove its application value in heart valve replacement surgery.

Disclosure of conflict of interest

None.

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References

[1] 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 2015; 8: 21166-21172.

[2] Priye S, Jagannath S, Singh D, Shivaprakash S and Reddy DP. Dexmedetomidine as an adjunct in postoperative analgesia following cardiac surgery: A randomized, double-blind study. Saudi J Anaesth 2015; 9: 353-358.

[3] Pouard P and Bojan M. Neonatal cardiopulmonary bypass. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2013; 16: 59-61.

[4] Zamani MM, Keshavarz-Fathi M, Fakhri-Bafghi MS, Hirbod-Mobarakeh A, Rezaei N, Bahrami A and Nader ND. Survival benefits of dexmedetomidine used for sedating septic patients in intensive care setting: A systematic review. J Crit Care 2016; 32: 93-100.

[5] Lundblad M, Trifa M, Kaabachi O, Ben Khalifa S, Fekih Hassen A, Engelhardt T, Eksborg S and Lonnqvist PA. Alpha-2 adrenoceptor agonists as adjuncts to peripheral nerve blocks in children: a meta-analysis. Paediatr Anaesth 2016; 26: 232-238.

[6] Karaman Y, Abud B, Tekgul ZT, Cakmak M, Yildiz M and Gonullu M. Effects of dexmedetomidine and propofol on sedation in patients after coronary artery bypass graft surgery in a fast-track recovery room setting. J Anesth 2015; 29: 522-528.

[7] Ding XD, Zheng NN, Cao YY, Zhao GY and Zhao P. Dexmedetomidine preconditioning attenuates global cerebral ischemic injury following asphyxial cardiac arrest. Int J Neurosci 2016; 126: 249-256.
[8] Luo X, Zheng X and Huang H. Protective effects of dexmedetomidine on brain function of glioma patients undergoing craniotomy resection and its underlying mechanism. Clin Neurol Neurosurg 2016; 146: 105-108.
[9] De Somer F. Recent advances in the comprehension and the management of perioperative systemic host response during cardiopulmonary bypass. Recent Pat Cardiovasc Drug Discov 2012; 7: 180-185.
[10] Augoustides JG. The inflammatory response to cardiac surgery with cardiopulmonary bypass: should steroid prophylaxis be routine? J Cardiothorac Vasc Anesth 2012; 26: 952-958.
[11] Ford AH and Almeida OP. Pharmacological interventions for preventing delirium in the elderly. Maturitas 2015; 81: 287-292.
[12] Schoeler M, Loetscher PD, Rossaint R, Fahlenkamp AV, Eberhardt G, Rex S, Weis J and Coburn M. Dexmedetomidine is neuroprotective in an in vitro model for traumatic brain injury. BMC Neurol 2012; 12: 20.
[13] Sato K, Kimura T, Nishikawa T, Tobe Y and Masaki Y. Neuroprotective effects of a combination of dexmedetomidine and hypothermia after incomplete cerebral ischemia in rats. Acta Anaesthesiol Scand 2010; 54: 377-382.
[14] Guo JR, Shen HC, Liu Y, Xu F, Zhang YW, Zhang JP and Yang DW. Effect of acute normovolemic hemodilution combined with controlled low central venous pressure on cerebral oxygen metabolism of patients with hepalobectomy. Hepatogastroenterology 2014; 61: 2321-2325.
[15] Zhang X, Hu Q, Liu Z, Huang H, Zhang Q and Dai H. Comparison between nitroglycerin and remifentanil in acute hypervolemic hemodilution combined with controlled hypotension during intracranial aneurysm surgery. Int J Clin Exp Med 2015; 8: 19353-19359.
[16] Zhang H, Lu Y, Liu M, Zou Z, Wang L, Xu FY and Shi XY. Strategies for prevention of postoperative delirium: a systematic review and meta-analysis of randomized trials. Crit Care 2013; 17: R47.
[17] Ji F, Li Z, Nguyen H, Young N, Shi P, Fleming N and Liu H. Perioperative dexmedetomidine improves outcomes of cardiac surgery. Circulation 2013; 127: 1576-1584.
[18] Wang X, Ji J, Fen L and Wang A. Effects of dexmedetomidine on cerebral blood flow in critically ill patients with or without traumatic brain injury: a prospective controlled trial. Brain Inj 2013; 27: 1617-1622.
[19] Zheng L, Fan QM and Wei ZY. Serum S-100-beta and NSE levels after off-pump versus on-pump coronary artery bypass graft surgery. BMC Cardiovasc Disord 2015; 15: 70.
[20] Sun J, Li J, Cheng G, Sha B and Zhou W. Effects of hypothermia on NSE and S-100 protein levels in CSF in neonates following hypoxic/ischaemic brain damage. Acta Paediatr 2012; 101: e316-320.
[21] Mo Y and Zimmermann AE. Role of dexmedetomidine for the prevention and treatment of delirium in intensive care unit patients. Ann Pharmacother 2013; 47: 869-876.
[22] Evered L, Scott DA, Silbert B and Maruff P. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. Anesth Analg 2011; 112: 1179-1185.