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Application of Dexmedetomidine in Cardiopulmonary Bypass Prefilling

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Abstract

Objective: The purpose of this study was to explore the application of dexmedetomidine (Dex) in cardiopulmonary bypass.

Methods: A total of 60 patients undergoing elective cardiopulmonary bypass were divided into control (C) group and Dex group. In the Dex group, appropriate amount of Dex was added into the membrane lung prefilling solution before anesthesia induction, while those in control group were given normal saline. The levels of mean arterial pressure (MAP) and heart rate (HR) at different times were measured. The levels of cardiac troponin I (CTNI), malondialdehyde (MDA), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α) at different points (T0/T1/T2/T3/T4) in both groups were measured by enzyme-linked immunosorbent assay kits.

Results: The intraoperative and postoperative levels of MAP and HR in the 2 groups were significantly lower than those preoperatively ($P < .05$). The levels of MAP and HR in the Dex group were significantly lower than those of the C group ($P < .05$). The levels of CTNI/MDA/IL-6/TNF-α at different points in both groups were significantly higher than those at T0 ($P < .05$). The serum levels of CTNI, MDA, IL-6, and TNF-α in the Dex group at T1/T2/T3/T4 were significantly lower than those in the C group ($P < .05$). The rate of arrhythmia in the Dex group was significantly lower than that in the C group ($P < .05$).

Conclusion: Dexmedetomidine has a stable effect in cardiopulmonary priming solution.

Keywords
dexmedetomidine, cardiopulmonary bypass, priming solution, postoperative cognitive, blood pressure level

Introduction

Cardiopulmonary bypass (CPB) refers to the life support technology that uses a series of artificial pipes to connect the large blood vessels and the artificial heart lung machine to drain the blood of the body's return heart vein to the outside and then to the internal artery system after oxygenation.[1] Presently, CPB technology is often used in open-heart and large blood vessel surgery, which can make the operation field achieve the goal of "no blood, quiet."[2] Clinical research has found that[3] in the process of heart disease, patients receiving surgical treatment are prone to be injured by surgery and have many body stress reactions, which may cause sympathetic excitation and other changes. Cardiopulmonary bypass open-heart surgery is one of the most severe trauma operations in clinical practice.[4] Surgical stimulation and other operations during the operation can lead to serious stress response. Therefore, it is a hot spot of clinical research to properly regulate the stress response of CPB during open-heart surgery and ensure the smooth operation. Dexmedetomidine (Dex) is a highly selective α2-adrenergic receptor agonist.[5] Dexmedetomidine has analgesic, sedative, and antisympathetic effects on the central nervous system. To some extent, it is beneficial to control the clinical dosage of opioids after surgery. In the past clinical CPB heart surgery, Dex was injected through the patient's internal jugular vein 30 minutes before anesthesia induction, but rapid injection of Dex[6] may cause increased blood pressure and decreased heart rate (HR). In this study, Dex was added to CPB pulmonary

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membrane priming solution to replace the previous treatment of intravenous injection of Dex. The purpose of this study was to observe whether Dex can effectively improve the problem of blood pressure rise and to study the effect of CPB in pulmonary membrane priming solution.

Patients and Methods

Patients

From September 2017 to September 2018, 60 patients with selective operation of CPB heart surgery were included in this study. With the consent of the medical ethics committee, the patients and their families were informed and signed informed consent. According to the random digital method, the patients were divided into control group and Dex group. Criteria for inclusion are as follows: all patients met the classification of American Society of Anesthesiologists,[7] all of them were grade II and III, and all of them received cardiac surgery for the first time. Exclusion criteria are patients with recent surgical treatment, patients with severe respiratory diseases, patients with liver and kidney dysfunction, and patients with coagulation dysfunction and other surgical contraindications.

Research Methods

Before anesthesia induction, Dex 1 μg/kg was added into the membrane lung priming solution in the Dex group and was continuously infused at the rate of 0.5 μg/kg/h until the end of operation. Equivalent 0.9% normal saline was added into the membrane lung priming solution in the control group before anesthesia induction.

Observation Index

The mean arterial pressure (MAP) was measured by automatic ambulatory monitoring device, and HR was detected by HR monitor before, during, and after operation. Before anesthesia induction (T0), before CPB (T1), during CPB (T2), immediately after CPB (T3), and 12 hours after CPB (T4), 2 mL of patients' peripheral arterial blood samples were taken, centrifuged at 3000 r/min for 10 minutes, and stored at −20 °C for testing. The concentrations of cardiac troponin I (CTNI), malondialdehyde (MDA), interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) were measured with commercial kits (Nanjing Jiancheng Bioengineering Research Institute) by enzyme-linked immunosorbent assay. The cognitive function, occurrence of arrhythmia, and dosage of anesthetic (midazolam and propofol) in the 2 groups were compared. Mini-Mental State Examination was used to evaluate the cognitive function.

Statistical Analysis

SPSS19.0 statistical software was used for data processing. The counting data were expressed as percentage, the comparison between groups was compared by χ^2 test, the measurement data of normal distribution were expressed as mean ± SD, and the comparison between groups was done by Fisher exact test. $P < .05$ was statistically significant.

Table 1. Comparison of the Changes in Mean Arterial Pressure and Heart Rate Between the 2 Groups in Different Periods (n = 30, Means ± SD).

Group	Time	MAP (mm Hg)	HR (times/minute)
Control group	Preoperative	92.78 ± 6.42	86.61 ± 8.66
	Intraoperative	80.26 ± 5.75[a]	79.51 ± 6.34[a]
	Postoperative	87.36 ± 6.08[a]	81.64 ± 5.45[a]
Dex group	Preoperative	93.52 ± 6.37	86.23 ± 8.25
	Intraoperative	71.47 ± 4.61[a,b]	64.72 ± 5.36[a,b]
	Postoperative	78.01 ± 5.13[a,b]	72.11 ± 6.17[a,b]
t		6.492	5.728
P		.000	.000

Abbreviations: Dex, dexmedetomidine; HR, heart rate; MAP, mean arterial pressure.
[a]$P < .05$, compared with the group before treatment.
[b]$P < .05$, compared with the control group.

Results

General Information

The average age of 60 patients was 43.64 ± 5.76 years. The male to female ratio was 36:24, and the average weight was 56.25 ± 4.56 kg. There were 17 patients with coronary artery bypass grafting under CPB, 10 patients with mitral valve replacement, 11 patients with main artery dissection, 10 patients with aortic valve replacement, and 12 patients with thoracic aortic aneurysm. The patients in the control group had an average age of 44.25 ± 5.82 years, with a sex ratio of 19:11 and an average weight of 58.25 ± 4.71 kg. The patients in the Dex group had an average age of 42.77 ± 5.91 years with a sex ratio of 17:13 and an average weight of 54.94 ± 4.12 kg. There was no significant difference between the 2 groups ($P > .05$).

Comparison of the Changes in MAP and HR at Different Points Between the 2 Groups

The levels of MAP and HR in the 2 groups were significantly lower than those before operation ($P < .05$). The levels of MAP and HR in the Dex group were significantly lower than those in the control group ($P < .05$; Table 1).

Comparison of CTNI, MDA, IL-6, and TNF-α at Different Time Points Between the 2 Groups

The levels of CTNI, MDA, IL-6, and TNF-α at T1 to T4 were significantly higher than those at T0 ($P < .05$). The levels of CTNI, MDA, IL-6, and TNF-α at T1 to T4 were significantly lower than those in the control group ($P < .05$; Table 2).

Table 2. Comparison of CTNI, CK-MB, IL-6, and TNF-α Levels at Different Time Points Between the 2 Groups (n = 30, Means ± SD).

Group	Time	CTNI (ng/mL)	MDA (nmol/L)	IL-6 (ng/mL)	TNF-α (ng/L)
Control group	T0	0.27 ± 0.03	5.84 ± 1.48	0.08 ± 0.02	4.18 ± 0.72
	T1	2.14 ± 0.07[a]	8.87 ± 2.67[a]	0.11 ± 0.02[a]	6.30 ± 0.82[a]
	T2	5.96 ± 2.06[a]	13.75 ± 3.57[a]	0.31 ± 0.09[a]	18.37 ± 0.89[a]
	T3	7.42 ± 2.35[a]	18.06 ± 3.62[a]	0.96 ± 0.15[a]	26.18 ± 0.84[a]
	T4	8.96 ± 2.32[a]	20.92 ± 3.86[a]	0.86 ± 0.13[a]	20.32 ± 0.79[a]
Dex group	T0	0.28 ± 0.03	5.88 ± 1.45	0.07 ± 0.02	4.14 ± 0.67
	T1	1.55 ± 0.13[a,b]	7.08 ± 2.52[a,b]	0.09 ± 0.03[a,b]	6.12 ± 0.55[a,b]
	T2	3.67 ± 2.08[a,b]	9.38 ± 1.63[a,b]	0.25 ± 0.07[a,b]	12.87 ± 0.81[a,b]
	T3	3.05 ± 1.28[a,b]	8.07 ± 2.45[a,b]	0.76 ± 0.19[a,b]	20.17 ± 0.76[a,b]
	T4	2.62 ± 0.32[a,b]	7.75 ± 1.61[a,b]	0.64 ± 0.16[a,b]	15.64 ± 0.75[a,b]
t		1.452	2.163	1.547	1.699
P		.001	.000	.000	.000

Abbreviations: Dex, dexmedetomidine; CTNI, cardiac troponin I; MDA, malondialdehyde; IL-6, interleukin 6; TNF-α, tumor necrosis factor α.
[a]$P < .05$, compared with the group before treatment.
[b]$P < 0.05$, compared with the control group.

Table 3. Comparison of General Conditions Between the 2 Groups During Treatment, Means ± SD/n (%).

				Dosage of anesthetic (mg)	
Group	n	Postoperative cognitive function score (points)	Arrhythmia after operation (case)	Midazolam	Propofol
Control group	30	24.35 ± 0.51	5 (16.67)	10.62 ± 2.09	710.43 ± 13.75
Dex group	30	26.92 ± 0.43[a]	2 (6.67)[a]	7.08 ± 1.57[a]	630.11 ± 11.38[a]
t	–	4.892	7.433	5.162	12.728
P	–	.014	.000	.004	.000

Abbreviation: Dex, dexmedetomidine.
[a]$P < .05$, compared with the control group.

Comparison of General Conditions Between the 2 Groups During Treatment

During the treatment, the scores of cognitive function in the Dex group were significantly higher than those in the control group ($P < .05$). The rate of arrhythmia in the Dex group was significantly lower than that in the control group ($P < .05$). The dosage of anesthetic in the Dex group was significantly lower than that in the control group ($P < .05$; Table 3).

Discussion

Arrhythmia is a common postoperative complication of CPB.[8] Arrhythmia not only affects the hemodynamics of patients but also leads to poor prognosis, which may delay the treatment process. In this study, the rate of postoperative arrhythmia in the Dex group was significantly lower than that in the control group, suggesting that adding Dex into CPB priming solution can significantly improve the postoperative arrhythmia and improve the stability of postoperative hemodynamics.

This may be related to the mechanism of Dex; as an α2-adrenergic receptor agonist, Dex can selectively bind to α2-adrenergic receptor in the presynaptic phase of sympathetic nerve endings,[9] thus inhibiting the synthesis and release of noradrenaline, reducing the level of catecholamine after CPB heart surgery and finally effectively reduce the incidence of tachycardia. In addition, Dex can selectively bind to α2 receptor on nucleus tractus solitarius of medulla oblongata through parasympathetic effect. It contributes to enhance vagus nerve activity, inhibit the production of cardiac cyclic adenosine monophosphate, and finally improve postoperative arrhythmia. At the same time, it was found that the blood pressure of patients undergoing CPB heart surgery would decrease due to the decrease in blood viscosity and the dilution of catecholamine concentration in plasma. However, with the prolongation of CPB time, the stress response in patients will be gradually strong, which will lead to the increase in catecholamine secretion level in plasma, and finally, the blood pressure of patients undergoing CPB heart surgery will gradually rise. In the results of this study, the map and HR levels of the 2 groups during and after operation were significantly lower than those of the group before operation, and the map and HR levels of the Dex group during and after operation were significantly lower than those of the control group, which was consistent with the conclusions of research of Fangjun et al.[10] All of the above suggest that adding Dex to the membrane lung precharge can play a role of sympathetic block, reduce the concentration of epinephrine in the blood, so as to reduce the resistance of systemic circulation, effectively avoid the early hypotension at the beginning of CPB, slow down the HR and blood pressure, and avoid the sudden drop of HR.

Cardiopulmonary bypass cardiac surgery can cause myocardial injury, even myocardial ischemia–reperfusion injury. At this time, it will activate a large number of neutrophils in the body, promote the excessive production of oxygen-free radicals, and eventually lead to damage of oxidative stress. At present, CTNI is a regulatory protein regulating muscle relaxation and contraction during myocardial contraction, which can directly reflect the severity of myocardial damage in the body. Malondialdehyde, as the main product of membrane lipid peroxidation, can reflect the level of oxygen-free radicals to a certain extent, so as to assess the extent of oxidative stress damage in cells.[11] The results showed that the levels of serum CTNI and MDA in the 2 groups were significantly higher than those before anesthesia induction, and the levels of serum CTNI and MDA in the Dex group were significantly lower than those in the control group. This may be related to α2 receptor blocking of Dex, and it can activate protein kinase and extracellular signal regulated protein kinase, so as to improve myocardial function and reduce myocardial infarction area to the greatest extent. Dexmedetomidine was added into the membrane lung precursory fluid to reduce the degree of myocardial injury and avoid the damage of the structure of myocardial cell membrane, so as to reduce the level of serum CTNI. At the same time, Yagmurdur et al[12] and other studies have shown that Dex can inhibit MDA production and reduce the degree of ischemia–reperfusion injury. The results of this study showed that the dosage of anesthetic in the Dex group was significantly lower than that in the control group, which suggested that the dosage of sedative anesthetics could be reduced by adding Dex into the membrane lung precharge because Dex had better sedative and analgesic effects, antianxiety and hypnotic effects, had no inhibition of respiration, significantly inhibited sympathetic nerve activity, and also reduced the inhibition of anesthetic drugs on the heart during CPB operation. In the process of CPB heart operation, factors such as the depth of anesthesia or surgical injury may lead to cognitive dysfunction,[13] which is not conducive to the rapid recovery of patients after operation, and reduce the risk of postoperative complications. At the same time, CPB intraoperative stimulation may cause systemic inflammatory response and even lead to severe central inflammatory response, mainly including pro-inflammatory response and anti-inflammatory response. It was found that[14] pro-inflammatory response factor can activate microglia and inhibit the formation of hippocampal nerve, which makes it difficult to repair the nerve dysfunction and ultimately leads to the decline in cognitive function of patients. According to related literature,[15] the rise in pro-inflammatory factors is closely related to the decline in cognitive function, while TNF-α and IL-6 can directly reflect the inflammatory response of the body, especially IL-6 has the best correlation with cognitive dysfunction. In the results of this study, the serum levels of IL-6 and TNF-α in the 2 groups at T1 to T4 were significantly higher than those before anesthesia induction, and the serum levels of IL-6 and TNF-α in the Dex group at T1 to T4 were significantly lower than those in the control group. This is because Dex can directly inhibit the release of pro-inflammatory factors IL-6 and TNF-α. At the same time, it can also indirectly inhibit pro-inflammatory factors by inhibiting apoptosis protein caspase. In addition, the results showed that the score of cognitive function in the Dex group was significantly higher than that in the control group because Dex added into the membrane lung priming solution can inhibit the release of inflammatory mediators caused by CPB cardiac surgery stimulation, reduce the dosage of midazolam and other anesthetics, shorten the postoperative recovery time of patients, and significantly reduce the risk of postoperative cognitive dysfunction.

There are some disadvantages in this study. The sample size of this study is small. Furthermore, the mechanism that Dex has a stable effect in cardiovascular pricing solution has not been explored. This leads to the need for further study.

In conclusion, Dex has a stable effect in CPB priming solution, and it can effectively control blood pressure level, reduce myocardial injury, and is conducive to rapid recovery after operation, which is worth popularizing.

Declaration of Conflicting Interests

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References

1. Madhavan S, Siew-Pang C, Wei-Chuan T, et al. Cardiopulmonary bypass time: every minute counts. *J Cardiovasc Surg (Torino)*. 2018;59(2):274-281.
2. Moscarelli M, Condello I, Fattouch K, et al. Dopamine optimizes venous return during cardiopulmonary bypass and reduces the need for postoperative blood transfusion. *ASAIO J*. 2019;65(8):882-887.
3. Qiang Z, Wei Z. Effect of dexmedetomidine on hemodynamics in patients with rheumatic heart disease and pulmonary hypertension undergoing valve replacement. *Chine J Hosp Pharm*. 2014;34(6):469-472.
4. Loebe M, Loczlewski S, Brunkhorst FM, Harke C, Hetzer R. Procalcitonin in patients undergoing cardiopulmonary bypass in open heart surgery-first results of the Procalcitonin in Heart Surgery study (ProHearts). *Intensive Care Med*. 2000;26(suppl 2):S193-S198.
5. Zheng Z, Dan C, Haiyan L, et al. Myocardial protective effect of dexmedetomidine in elderly patients undergoing off-pump coronary artery bypass grafting. *Chine Pharm*. 2016;27(20):2836-2838.
6. Klamt JG, Vicente WV, Garcia LV, Ferreira CA. Hemodynamic effects of the combination of dexmedetomidine-fentanyl versus midazolam-fentanyl in children undergoing cardiac surgery with cardiopulmonary bypass. *Rev Bras Anestesiol*. 2010;60(4):350-362.

7. Yifei S, Jiange H, Wenqian Z, et al. Comparison of the effects of propofol and sevoflurane combined anesthesia on postoperative cognitive dysfunction in elderly patients undergoing heart valve surgery under cardiopulmonary bypass. *Chine J Anest*. 2016;36(4):399.
8. Tingting N, Min Y, Lina Y, et al. The effect of dexmedetomidine on the prognosis of patients undergoing cardiopulmonary bypass. *Chine J Anesth*. 2016;36(7):785-789.
9. Xu Wei T, Yu Wen L. Clinical application progress of dexmedetomidine. *Med Rev*. 2017;23(9):1830-1834.
10. Fangjun W, Jianhua H, Shuang Y, et al. Effect of dexmedetomidine on hemodynamics during cardiopulmonary bypass in patients undergoing cardiac surgery. *China Pharm*. 2017;28(2):204-209.
11. Lingling J, Xianwen H, Lijun B, et al. Effect of dexmedetomidine pretreatment on myocardial ischemia in patients undergoing valve replacement. *J Anhui Med Universe*. 2017;52(6):859-863.
12. Yagmurdur H, Ozcan N, Dokumaci F, Kilinc K, Yilmaz F, Basar H. Dexmedetomidine reduces the ischemia-reperfusion injury markers during upper extremity surgery with tourniquet. *J Hand Surg Am* .2008;33(6):941-947.
13. Newman MF, Kirchner JL, Phillips-Bute B.Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med*. 2001;10(4):81-82.
14. Changchun Z, Yuming W. Effect of dexmedetomidine on postoperative rehabilitation of patients undergoing valve replacement under general anesthesia and cardiopulmonary bypass. *Guangdong Med J*. 2016;37(18):2702-2706.
15. Yihong X, Shiliang S, Jiang Q, et al. Effect of dexmedetomidine on postoperative cognitive dysfunction in patients undergoing cardiopulmonary bypass. *Chine J Neuromed*. 2016;15(4):391.