Clinical Effect of Dexmedetomidine in Preventing Postoperative Delirium in Patients Undergoing Cardiac Surger: A Meta-analysis of Randomized Controlled Trials

Feng Bai, Jixiang Tan, Anxin Chen, Yin Huang, Dong Wan
The First Affiliated Hospital of Chongqing Medical University, Chongqing 400000, China.

Abstract: **Objective** To evaluate the clinical effects of dexmedetomidine on preventing postoperative delirium in patients undergoing cardiac surgery by Meta-analysis. **Methods** PubMed, Cochrane Library Embase, Web of Science database were searched for randomized controlled trials (RCTs) of dexmedetomidine in the prevention of postoperative delirium in patients undergoing cardiac surgery. The experimental group was treated with dexmedetomidine, and the control group was intervened with placebo or other anesthetic drugs. The search time is from inception to 31 December 2022. Two reviewers evaluated the quality of the literature independently, and Meta-analysis was performed using RevMan5.3 software. A total of 15 RCTs were enrolled, including 3222 subjects, In which 1625 cases in the experimental group and 1597 cases in the control group. **Results** Meta-analysis results showed that dexmedetomidine could reduce the incidence of postoperative delirium in patients with cardiac surgery [relative risk ratio (RR) = 0.65, 95 % confidence interval (CI) (0.48, 0.87), P = 0.0004], but it may increase the risk of postoperative hypotension [RR = 1.23, 95%CI(1.11, 1.36), $P<0.001$] ,meanwhile the incidence of postoperative bradycardia [RR = 1.38, 95 % CI (0.7, 2.70), P = 0.04] and postoperative atrial fibrillation [RR = 0.92, 95 % CI (0.8, 1.07), P = 0.45] had no significant difference between two groups. **Conclusion** Dexmedetomidine has a certain effect on the prevention of postoperative delirium in patients undergoing cardiac surgery， it may increase the risk of postoperative hypotension, but not increase the incidence of postoperative bradycardia and postoperative atrial fibrillation. But this needs to be confirmed by more high-quality and large-sample studies.

Keywords*:* Dexmedetomidine; Postoperative Delirium; Cardiac Surgery; Meta-Analysis

Introduction

Delirium is a common clinical acute brain dysfunction, mainly manifested as attention disorder and acute consciousness fluctuation [1],it is usually caused by physical diseases, anesthesia, surgical trauma and so on. It has been reported that the incidence of postoperative delirium in patients undergoing cardiac surgery is 4.1 % to 54.9 %[2],It is closely related to increased mortality, prolonged hospital stay and a significant increase in medical costs [3].

The mechanism of delirium is very complex, mainly including neuroinflammatory response, brain metabolic disorder and so on. Among them, brain metabolic disorder is an important mechanism. Studies have shown that the locus coeruleus in the brain is involved in the occurrence of delirium [4].α_2 receptor agonists can prevent postoperative delirium by acting on the locus coeruleus. Dexmedetomidine is a highly selective α2-adrenoceptor agonist that exerts antisympathetic, sedative, and analgesic effects by activating α2-adrenergic receptors [5]. It has been observed that dexmedetomidine can reduce the incidence of delirium in patients after cardiac surgery [6]. However, a recent randomized controlled trial failed to reveal the beneficial effect of dexmedetomidine in preventing delirium after cardiac surgery [7]. In view of the inconsistent research results, it is difficult to conclude the preventive value of dexmedetomidine on delirium in patients after cardiac surgery; therefore, this study included new randomized controlled trials to explore the effect of dexmedetomidine on the occurrence of cardiac POST delirium through meta-analysis, in order to provide evidence-based basis for clinical decision-making on

the treatment of POST delirium.

1. Data and methods

1.1 Inclusion exclusion criteria

Inclusion criteria: (1) The subjects were older than 18 years old and underwent cardiac surgery. (2) The study compared dexmedetomidine with placebo or other anesthetics; (3) The incidence of POST delirium as the primary outcome or secondary outcome; (4) The study was a randomized controlled trial.

Excluded criteria: (1) Pediatric surgery and non-cardiac surgery; (2) Non-RCT studies such as retrospective studies and observational studies; (3) Failure to provide sufficient information or data.

1.2 Data source and retrieval strategy

Search PubMed, Cochrane Library, Embase and Web of Science for randomized controlled trials. The combination of subject words and free words is adopted. Search formulation ("dexmedetomidine") AND ("cardiac surgery"OR" CPB "OR "CABG" OR "coronary artery bypass" OR"aortic surgery") AND ("delirium"OR"postoperative delirium" OR"POD").

1.3 Data extraction and quality evaluation

Two researchers independently screened, extracted data and evaluated the quality, and then cross-checked. If there were differences, the third researcher would decide. The extracted contents included the first author, publication year.etc. The quality of the literature was evaluated according to the Jadad scale.

1.4 Statistical method

Meta-analysis was performed using RevMan5.3 software, and the relative risk (RR) of 95 % confidence interval (CI) was used as the evaluation index. The Q test I test was used to test the heterogeneity of the results. When the P value > 0.1 and the I2 value ≤ 50 %, there was no significant heterogeneity between the results of the study. The fixed effect model was used for analysis, and the random effect model was used for analysis. A forest map was created for each result, and a funnel plot was drawn to assess publication bias. $P < 0.05$ was considered statistically significant.

2. Result

2.1 Literature Retrieval Process and Results

A total of 192 related literatures were obtained by optimizing the initial search. After several screenings, 15 literatures were finally included in the study. **Figure 1.**

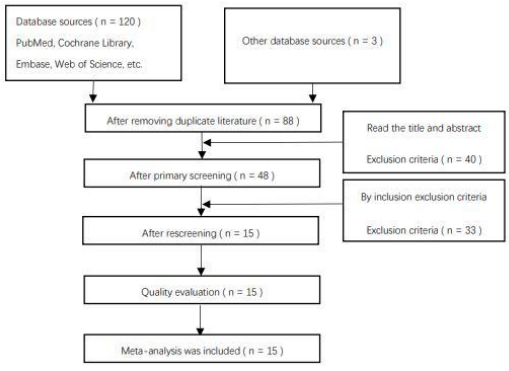

Figure 1 Literature screening flow chart

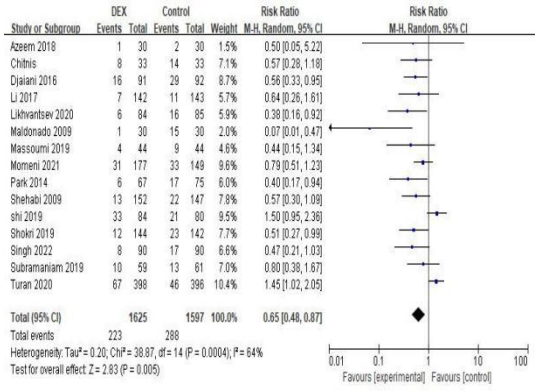

Figure 2 Incidence of postoperative delirium

2.2 Basic characteristics and quality evaluation of included studies

A total of 3222 patients with cardiac surgery were counted. **Table 1.**

Table 1 Basic characteristics of included studies

Author/Year	Number	Age（DEX/CONTROL）	Time of using drug	Control group	Main outcome	Secondary outcomes	Jadad score
Turan [7] 2020	794	63 ±11/ 62 ±12	INTRA+POST	placebo	POD	renal function.etc	3
Likhvantsev [8] 2020	169	62.6±6.7/ 62.4±7.2	INTRA+POST	placebo	POD	ICU stay.etc.	4
Shi [9] 2019	164	74.7±7.2/ 74.2±7.7	INTRA	propofol	POD	Delirium time.etc.	3
Shokri [10] 2019	286	63.75±3.29/ 64.38±4.81	INTRA+POST	clonidine	POD	length of ICU stay	4
Massoumi [11] 2019	88	61.8±7.9/ 61.3±8.9	INTRA+POST	placebo	POD	length of ICU stay.etc.	3
Subramaniam [12] 2019	120	64（63-72）; 69（63-74）/ 70（66-75）; 71（64-79）	POST	propofol	POD	POD duration.etc.	5
Azeem [13] 2018	60	65.3±4.8/ 66.7±5.6	POST	morphine	POD	Vital signs.etc.	4
Maldonado [14] 2009	90	55±16/ 58±18; 60±16;	POST	propofol、midazolam	POD	ICU and hospital stay.etc.	3
Shehabi [15] 2009	299	71.5（66-76）/ 71.0（65-75）	INTRA+POST	morphine	POD	ICU and hospital stay.etc.	4
Singh [16] 2022	180	60.3±8.1; 60.1±10.3	POST	propofol	POD	ICU length of stay.etc.	4
Djaiani [17] 2016	183	72.7±6.4/ 72.4±6.2	POST	propofol	POD	atrial fibrillation. etc.	3
Park [18] 2014	142	51.09±16.10/ 54.35±14.97	POST	remifentanil	POD	ICU and hospital stay.etc	2
Momeni [19] 2021	349	71 (61-81) ; 70 (59-81)	POST	placebo	POD	Delirium duration.etc	4
Li [20] 2017	285	66.4±5.4/ 67.5±5.3	INTRA+POST	placebo	POD	ICU and hospital stay.etc	4
Chitnis [21] 2022	66	78.7/ 78.8	POST	propofol	quality recovery	POD	4

DEX：dexmedetomidine；POD：postoperative delirium

2.3 Meta-analysis results

2.3.1 Main outcome: Incidence of postoperative delirium

The incidence of postoperative delirium in the dexmedetomidine group and the control group was 13.72 % (223 / 1625) and 18.03 % (288 / 1597).**Fig. 2**. Random effect model analysis showed that the incidence of postoperative delirium in the

dexmedetomidine group was lower than that in the control group, and the difference was statistically significant. Further subgroup analysis was divided into subgroups according to the time of administration. **Table 2.**

Table 2. Subgroup analysis of the effect of dexmedetomidine on the incidence of postoperative delirium

Subgroup	Number of study groups	Number of delirium	Result [95% CI]	Heterogeneity
Different administration time				
Intraoperative-postoperative sequential administration	6	236/1921	0.64[0.38,1.09]; *P*=0.10	I^2=71%; P=0.004
Only administered after surgery	8	221/1137	0.58[0.43,0.78]; *P*=0.0003	I^2=19%; P=0.28
Only administered during surgery	1	54/164	-	-
Different control drugs				
Placebo	5	230/1662	0.74[0.44,1.257]; *P*=0.26	I^2=69%; P=0.01
Other anesthetics	10	281/1560	0.59[0.41,0.87]; *P=0.007*	I^2=59%; P=0.009
Different age				
Elderly(≥ 60 years)	13	472/3020	0.62[0.47,0.81]; *P*=0.02	I^2=59%; P=0.003
Non-elderly(< 60 years)	2	39/202	0.20[0.03,1.19]; *P*=0.09	I^2= 66%; P=0.08

2.3.2 Adverse reactions: the incidence of postoperative hypotension, postoperative bradycardia and postoperative atrial fibrillation.

Of the 15 studies included in the meta-analysis, 9 compared the incidence of postoperative hypotension. Random effect model analysis showed that dexmedetomidine was associated with the incidence of postoperative hypotension, and the difference was statistically significant. **Fig. 3.**

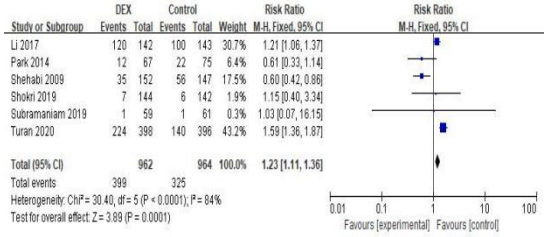

Figure 3 Incidence of postoperative hypotension

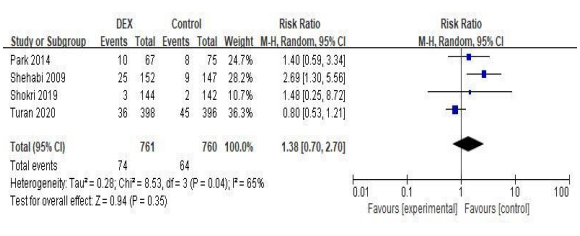

Figure 4 Incidence of postoperative bradycardia

Among the 15 studies included in the meta-analysis, 6 studies compared the incidence of postoperative bradycardia. Random effect model analysis showed that dexmedetomidine was not related to the incidence of postoperative bradycardia, and the difference was not statistically significant. **Fig 4.**

Among the 15 studies included in the meta-analysis, 5 studies reported the occurrence of atrial fibrillation. The fixed effect model was used for analysis. The results showed that dexmedetomidine was not related to the incidence of postoperative atrial fibrillation, and the difference was not statistically significant, Fig. 5.

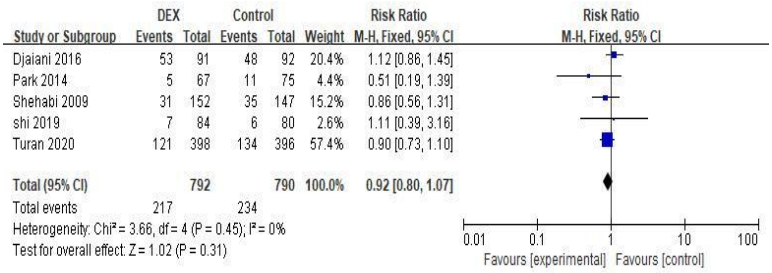

Figure 5 postoperative atrial fibrillation incidence

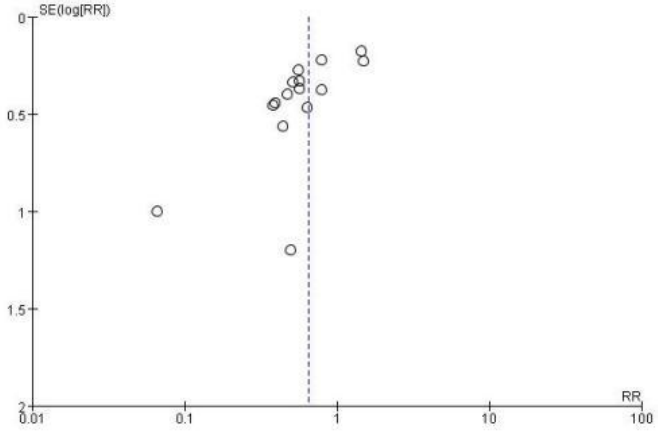

Figure 6 Postoperative delirium funnel plot

2.4 Publication bias analysis

The results showed that the two sides of the funnel plot were basically symmetrical, and there was no obvious publication bias between the studies. **Fig. 6**.

3. Discussion

Delirium is a common postoperative complication, which seriously affects the clinical prognosis of patients. Active prevention of delirium by non-drug and drug means is an important part of perioperative management [1]. The updated 2021 guidelines for the treatment of pain, agitation and delirium recommend the use of drugs such as dexmedetomidine to reduce the incidence of postoperative delirium [22].

Dexmedetomidine is a highly selective α2 receptor agonist with dual effects of analgesia and sedation. It is widely used in anesthesia and ICU analgesia and sedation. However, there are different conclusions on the preventive effect of dexmedetomidine on delirium in postoperative patients and critically ill patients, and the effect of dexmedetomidine on heart rate and blood pressure has also attracted much attention. In this study, patients after cardiac surgery were selected as the observation objects, and the latest clinical studies on the prevention of delirium in patients after cardiac surgery were included. Meta-analysis was used to obtain some valuable research results, which are worthy of further discussion.

3.1 Dexmedetomidine reduces the incidence of delirium after cardiac surgery

In this study, we conducted a meta-analysis of the newly published literature on dexmedetomidine for the prevention of delirium after cardiac surgery. A total of 3222 patients were enrolled. The results showed that dexmedetomidine could significantly reduce the incidence of delirium after cardiac surgery. In order to further clarify the influencing factors of dexmedetomidine in preventing delirium after cardiac surgery, the research group conducted subgroup analysis based on

administration time, control drug and age group. Studies have shown that age is an independent risk factor for postoperative delirium [23], however, the incidence of delirium after cardiac surgery is not affected by the age of patients, which may be related to the diversity and complexity of delirium risk factors and their causes [24]. The timing of dexmedetomidine given only after surgery can significantly reduce the incidence of delirium after cardiac surgery, and its preventive effect is limited only when used sequentially during and after surgery. This may be related to the postoperative use of dexmedetomidine can reduce the use of opioids or benzodiazepines, because opioids and benzodiazepines can significantly increase the incidence of postoperative delirium [25, 26] Therefore, the incidence of drug-induced delirium is reduced, and there is only one study on intraoperative administration, so it is not discussed. In order to clarify whether other anesthetics have the preventive effect of postoperative delirium, this study conducted a subgroup analysis. Dexmedetomidine was compared with placebo or other anesthetics. The results showed that placebo could not reduce postoperative delirium. Other anesthetics such as propofol and midazolam could not reduce the incidence of postoperative delirium. Dexmedetomidine showed a unique preventive effect on delirium, suggesting that dexmedetomidine may be a better choice when patients with risk factors for delirium after cardiac surgery need analgesic and sedative treatment.

3.2 Effects of dexmedetomidine on postoperative hypotension, bradycardia and atrial fibrillation

Maintaining hemodynamic stability after cardiac surgery is essential, but hypotension and bradycardia are the most common adverse reactions of dexmedetomidine [27]. Therefore, it is of great clinical significance to explore the effect of dexmedetomidine on blood pressure and heart rate in patients after cardiac surgery. This study suggests that postoperative hypotension may be an adverse reaction of dexmedetomidine used in cardiac surgery to prevent delirium, which is basically the same as that reported in the drug instructions of dexmedetomidine. Therefore, it is necessary to be alert to the occurrence of postoperative hypotension when dexmedetomidine is used to prevent delirium. The results of this meta-analysis showed that there was no significant difference in the incidence of postoperative bradycardia between the dexmedetomidine group and the control group, suggesting that dexmedetomidine was relatively safe in cardiac surgery and no obvious bradycardia occurred. However, this requires a comprehensive consideration of various factors such as the loading dose of dexmedetomidine and its administration rate, volume status, and the use of vasoactive drugs. In addition, atrial fibrillation is the most common complication after cardiac surgery [28], Although studies have shown that dexmedetomidine can reduce myocardial ischemia-reperfusion injury and prevent arrhythmia [29], However, the results of this study did not confirm that dexmedetomidine could reduce the incidence of atrial fibrillation after cardiac surgery. In view of the large heterogeneity of this study. In order to explore the source of heterogeneity, the research group conducted subgroup analysis of delirium in patients after cardiac surgery according to the administration time, age group and control drug. The results of heterogeneity test showed no significant change, so the administration time, age and control drug were not the main factors leading to significant heterogeneity. A reasonable explanation may be found from the perspective of sample size, dose, concentration and delirium assessment methods, but more high-quality clinical studies are needed to confirm it.

3.3 Limitations of the study

Some of the outcome indicators in the study are heterogeneous, and more homogeneity studies are needed to verify them in the future, and the optimal dose of dexmedetomidine to prevent delirium after cardiac surgery is discussed.

4. Conclusion

Dexmedetomidine can reduce the incidence of delirium in patients after cardiac surgery, and will not cause bradycardia and atrial fibrillation, but may increase the incidence of postoperative hypotension. However, the randomized controlled trials included in this study have great heterogeneity, and the above conclusions need to be confirmed by high-quality,

large-sample randomized controlled trials.

References

[1] Mattison MLP. Delirium [J]. Ann Intern Med, 2020, 173(7): Itc49-itc64.

[2] Chen H, Mo L, Hu H, et al. Risk factors of postoperative delirium after cardiac surgery: a meta-analysis [J]. J Cardiothorac Surg, 2021, 16(1): 113.

[3] Gleason LJ, Schmitt EM, Kosar CM, et al. Effect of Delirium and Other Major Complications on Outcomes After Elective Surgery in Older Adults [J]. JAMA Surg, 2015, 150(12): 1134-40.

[4] O'Neill E, Griffin ÉW, O'Sullivan R, et al. Acute neuroinflammation, sickness behavior and working memory responses to acute systemic LPS challenge following noradrenergic lesion in mice [J]. Brain Behav Immun, 2021, 94: 357-68.

[5] Gerresheim G, Schwemmer U. [Dexmedetomidine] [J]. Anaesthesist, 2013, 62(8): 661-74.

[6] Wang G, Niu J, Li Z, et al. The efficacy and safety of dexmedetomidine in cardiac surgery patients: A systematic review and meta-analysis [J]. PLoS One, 2018, 13(9): e0202620.

[7] Turan A, Duncan A, Leung S, et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial [J]. Lancet, 2020, 396(10245): 177-85.

[8] Likhvantsev VV, Landoni G, Grebenchikov OA, et al. Perioperative Dexmedetomidine Supplement Decreases Delirium Incidence After Adult Cardiac Surgery: A Randomized, Double-Blind, Controlled Study [J]. J Cardiothorac Vasc Anesth, 2021, 35(2): 449-57.

[9] Shi C, Jin J, Qiao L, et al. Effect of perioperative administration of dexmedetomidine on delirium after cardiac surgery in elderly patients: a double-blinded, multi-center, randomized study [J]. Clin Interv Aging, 2019, 14: 571-5.

[10] Shokri H, Ali I. A randomized control trial comparing prophylactic dexmedetomidine versus clonidine on rates and duration of delirium in older adult patients undergoing coronary artery bypass grafting [J]. J Clin Anesth, 2020, 61: 109622.

[11] Massoumi G, Mansouri M, Khamesipour S. Comparison of the incidence and severity of delirium and biochemical factors after coronary artery bypass grafting with dexmedetomidine: A randomized double-blind placebo-controlled clinical trial study [J]. ARYA Atheroscler, 2019, 15(1): 14-21.

[12] Subramaniam B, Shankar P, Shaefi S, et al. Effect of Intravenous Acetaminophen vs Placebo Combined With Propofol or Dexmedetomidine on Postoperative Delirium Among Older Patients Following Cardiac Surgery: The DEXACET Randomized Clinical Trial [J]. Jama, 2019, 321(7): 686-96.

[13] Azeem TMA, Yosif NE, Alansary AM, et al. Dexmedetomidine vs morphine and midazolam in the prevention and treatment of delirium after adult cardiac surgery; a randomized, double-blinded clinical trial [J]. Saudi J Anaesth, 2018, 12(2): 190-7.

[14] Maldonado JR, Wysong A, Van Der Starre PJ, et al. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery [J]. Psychosomatics, 2009, 50(3): 206-17.

[15] Shehabi Y, Grant P, Wolfenden H, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study) [J]. Anesthesiology, 2009, 111(5): 1075-84.

[16] Singh A, Garg V, Mehta Y, et al. Perioperative dexmedetomidine reduces delirium after coronary artery bypass graft surgery: A prospective, single-blind, observational study [J]. Ann Card Anaesth, 2022, 25(4): 490-7.

[17] Djaiani G, Silverton N, Fedorko L, et al. Dexmedetomidine versus Propofol Sedation Reduces Delirium after Cardiac Surgery: A Randomized Controlled Trial [J]. Anesthesiology, 2016, 124(2): 362-8.

[18] Park JB, Bang SH, Chee HK, et al. Efficacy and safety of dexmedetomidine for postoperative delirium in adult cardiac surgery on cardiopulmonary bypass [J]. Korean J Thorac Cardiovasc Surg, 2014, 47(3): 249-54.

[19] Momeni M, Khalifa C, Lemaire G, et al. Propofol plus low-dose dexmedetomidine infusion and postoperative delirium in older patients undergoing cardiac surgery [J]. Br J Anaesth, 2021, 126(3): 665-73.

[20] Li X, Yang J, Nie XL, et al. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial [J]. PLoS One, 2017, 12(2): e0170757.

[21] Chitnis S, Mullane D, Brohan J, et al. Dexmedetomidine Use in Intensive Care Unit Sedation and Postoperative Recovery in Elderly Patients Post-Cardiac Surgery (DIRECT) [J]. J Cardiothorac Vasc Anesth, 2022, 36(3): 880-92.

[22] Seo Y, Lee HJ, Ha EJ, et al. 2021 KSCCM clinical practice guidelines for pain, agitation, delirium, immobility, and sleep disturbance in the intensive care unit [J]. Acute Crit Care, 2022, 37(1): 1-25.

[23] Pinho C, Cruz S, Santos A, et al. Postoperative delirium: age and low functional reserve as independent risk factors [J]. J Clin Anesth, 2016, 33: 507-13.

[24] Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability [J]. Jama, 1996, 275(11): 852-7.

[25] Pavone KJ, Jablonski J, Cacchione PZ, et al. Evaluating Pain, Opioids, and Delirium in Critically Ill Older Adults [J]. Clin Nurs Res, 2021, 30(4): 455-63.

[26] Shi HJ, Yuan RX, Zhang JZ, et al. Effect of midazolam on delirium in critically ill patients: a propensity score analysis [J]. J Int Med Res, 2022, 50(4): 3000605221088695.

[27] Coursin DB, Coursin DB, Maccioli GA. Dexmedetomidine [J]. Curr Opin Crit Care, 2001, 7(4): 221-6.

[28] Wang X, Yao L, Ge L, et al. Pharmacological interventions for preventing post-operative atrial fibrillation in patients undergoing cardiac surgery: a network meta-analysis protocol [J]. BMJ open, 2017, 7(12): e018544.

[29] Hayashi Y, Sumikawa K, Maze M, et al. Dexmedetomidine prevents epinephrine-induced arrhythmias through stimulation of central alpha 2 adrenoceptors in halothane-anesthetized dogs [J]. Anesthesiology, 1991, 75(1): 113-7.