Research Article

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Delirium risk of dexmedetomidine and midazolam in patients treated with postoperative mechanical ventilation: A meta-analysis

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Abstract: Objective: To evaluate by meta-analysis the effects of dexmedetomidine versus midazolam on postoperative delirium in patients that received postoperative mechanical ventilation. Methods: The electronic databases of PubMed, Web of Science, EMbase, CNKI, CBM, Cochrane library and WanFang were searched by two reviewers. All the clinical studies related to dexmedetomidine versus midazolam on postoperative delirium were screened and collected in this meta-analysis. The combined postoperative delirium risk between dexmedetomidine and midazolam groups was pooled by random effect model. The publication bias was assessed by Begg's funnel plot and Egger's line regression test. Results: A total of six studies including 386 subjects (202 in the dexmedetomidine group and 184 in the midazolam group) were finally included in this meta-analysis. All six studies reported adequate sequence generation. Three studies used blindness methods and 2 publications were free of selective reporting. However, only 1 publication reported allocation concealment. Because of significant heterogeneity across the studies (I^2=61.7%, p<0.05), the data were pooled by random effect model. Pooled data showed the postoperative delirium risk in the dexmedetomidine group was significantly lower than that of the midazolam group (RR=0.20 (095%CI:0.09~0.47, p<0.05)). The Begg's funnel plot showed obvious asymmetry at the bottom and Egger's line regression test also indicated significant publication bias (t=-6.51, p<0.05). Conclusion: Compared with midazolam, patients that received dexmedetomidine for postoperative mechanical ventilation sedation had less risk of developing delirium.

Keywords: Dexmedetomidine; Midazolam; Postoperative mechanical ventilation; Delirium; Meta-analysis

1 Introduction

Patients who receive major surgery are at increased risk of developing postoperative delirium as the result of, the administration of anesthetic agents and postoperative mechanical ventilation sedation [1,2]. Dexmedetomidine and midazolam are generally used for postoperative mechanical ventilation in patients who received major surgery. Several studies have compared the postoperative delirium risk for dexmedetomidine and midazolam in patients treated with postoperative mechanical ventilation [3-5]. Maldonado and his colleagues [3] conducted a prospective randomized controlled clinical trial to investigate the effects of postoperative sedation on the development of delirium in patients undergoing cardiac-valve procedures. Three postoperative sedation drugs were used: dexmedetomidine, propofol, or midazolam. They found that postoperative sedation with dexmedetomidine was associated with significantly lower rates of postoperative delirium and lower care costs. However, because of the small sample size and different surgery procedures, the conclusion was not conclusive. In our present meta-analysis, we searched the databases for all potential studies related to the comparison of delirium risk for dexmedetomidine and midazolam in patients treated with postoperative mechanical ventilation.

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2 Materials and methods

2.1 Publications identification

The electronic databases of Pubmed, Web of Science, EMbase, CNKI, CBM, Cochrane library and Wanfang were searched by two reviewers (Wang Peng and Zhang Ying). All the clinical studies related to dexmedetomidine versus midazolam on postoperative delirium were screened and collected in this meta-analysis. The publication search words were "dexmedetomidine", "midazolam", "delirium" AND "mechanical ventilation" as Medical Subject Headings (MeSH) and corresponding free text words.

2.2 Inclusion, exclusion criteria and data extraction

The inclusion criteria for this meta-analysis were: 1) clinical controlled trial study types; 2) patients treated with dexmedetomidine or midazolam for postoperative mechanical ventilation sedation; and 3) outcome of the included studies should include the incidence of delirium. The exclusion criteria were: 1) case report or review study type; 2) duplicated publications; 3) using other drugs for postoperative mechanical ventilation sedation; and 4) studies without enough data to calculate the postoperative delirium incidence rate.

2.3 Quality assessments

The methodological qualities for the 6 studies chosen were assessed by two authors (Wang Peng and Sha Shimin) according to the Cochrane Reviews Handbook with a six-item questionnaire:1)adequate sequence generation? 2)allocation concealment? 3)blinding? 4)incomplete outcome data addressed? 5)free of selective reporting? And 6) free of other bias? If the paper addressed the item, the quality assessment was marked with "Yes" for low risk. If the paper did not address the item, the quality assessment was marked with "No" for high risk.

2.4 Statistical analysis

Review Manager 5.0 and STATA/SE 12.0 were used to do all statistical analysis. Statistical heterogeneity among the included 6 publications was evaluated by chi-square (χ^2) test, and the inconsistency was demonstrated by I^2. If statistical heterogeneity existed (χ^2, $p<0.1$ or $I^2>50\%$), the random-effect model (Dersimonian-Laird method) was used to pool the data. Inversely, without significant heterogeneity among the included studies, the fixed-effect model was used to pool the data. The publication bias was evaluated by Begg's funnel plot and Egger's line regression test.

3 Results

3.1 Studies' characteristics

After searching the databases, a total of six studies [3-8] including 386 subjects (202 in the dexmedetomidine group and 184 in the midazolam group) were included in the final meta-analysis. The publication searching flowchart is shown in Figure 1. The paper publication years range from 2009 to 2013 with a minimum sample size of 20 and a maximum sample size of 100. The general characteristics of included studies are shown in Table 1.

3.2 Quality evaluation of each study

All of the six studies reported adequate sequence generation.Three3 studies used blindness methods and 2 publications were free of selective reporting. However, only 1 publication reported allocation concealment. The general methodological qualities of the included 6 studies are shown in Figure 2.

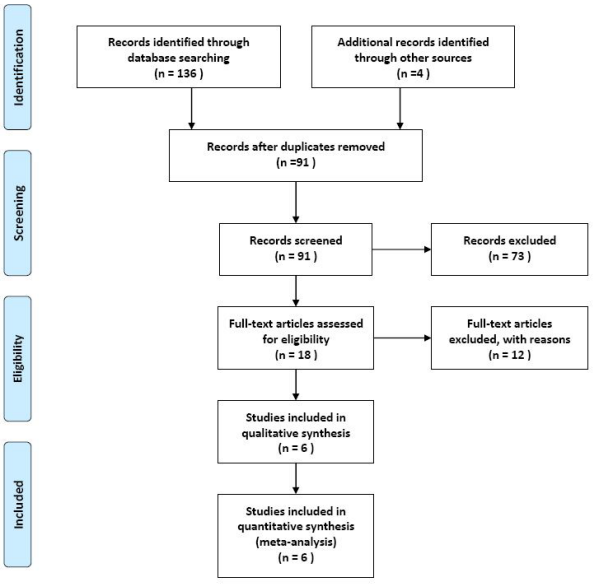

Figure 1: Publication searching flow-chart

Table 1: General information of included studies

Author	Year	No. (Dex/Mid)	Treatment		Quality
			Dex	Mid	
Maldonado JR	2009	30/30	1μg/kg, (0.2-0.7) μg/(kg·h)	0.1mg/kg, (0.04-0.1) mg/(kg·h)	(1),(3),(4), (5), (6)
Tao SY	2011	30/30	1μg/kg	0.05mg/kg	(1),(2),(4)
Zhao W	2011	10/10	(0.2-0.7) μg/(kg·h)	(0.03-0.13) mg/(kg·h)	(1)
Dan HC	2012	52/48	3.08μg/kg	0.37mg/kg	(1),(3),(4), (6)
Gu JX	2012	40/36	(0.2-0.7) μg/(kg·h)	(0.04-0.2) mg/(kg·h)	(1), (5)
Xiao Y	2013	20/20	1μg/kg	0.05mg/kg,	(1),(3),(4), (6)

(1)adequate sequence generation? (2)allocation concealment? (3)blinding? (4)incomplete outcome data addressed? (5)free of selective reporting? (6) free of other bias?

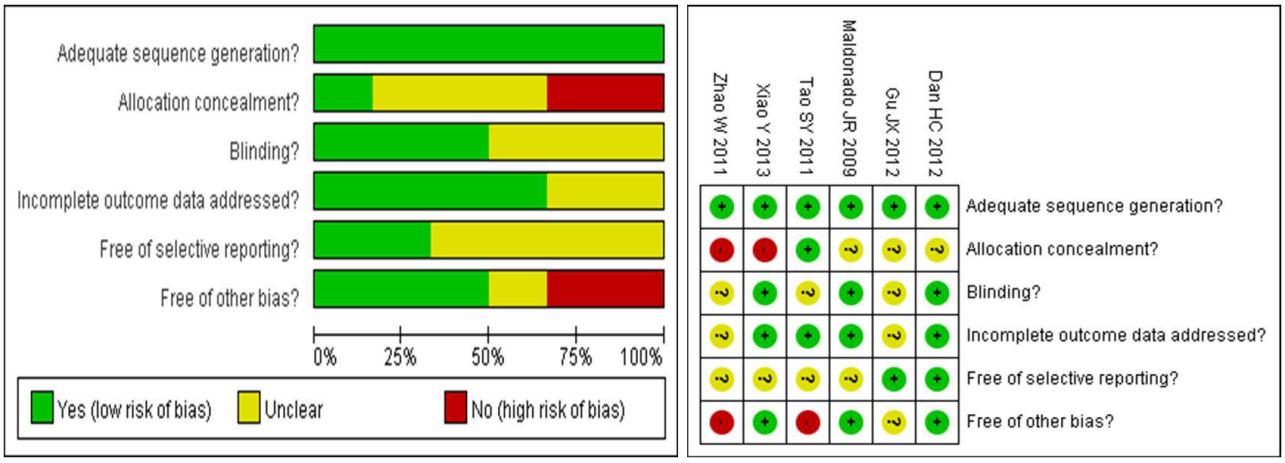

Figure 2: General quality of the included 6 studies.("+/Yes" for low risk; "-/No" for high risk; "?" for moderate risk)

3.3 Statistical heterogeneity

The statistical heterogeneity across the 6 studies was evaluated by chi-square (χ^2) test, and the inconsistency was demonstrated by I^2. Significant statistical heterogeneity was found across the studies with chi-square of 13.05 (I^2=61.7%, p<0.05).

3.4 Meta-analysis

Because of significant heterogeneity across the studies, the data was pooled by random effect model. Pooled data showed the postoperative delirium risk in dexmedetomidine group was significantly lower than that of the midazolam group (RR=0.20(95%CI:0.09~0.47, p<0.05), Figure 3).

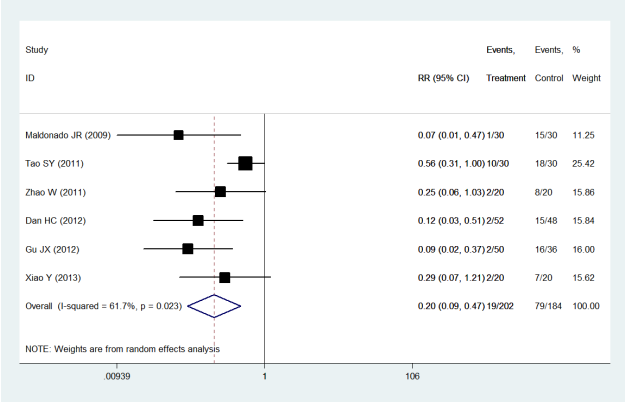

Figure 3: Forest plot of postoperative delirium risk between dexmedetomidine and midazolam group

3.5 Sensitivity analysis

Sensitivity analysis was performed by omitting each of the included studies. The results showed that the RR was

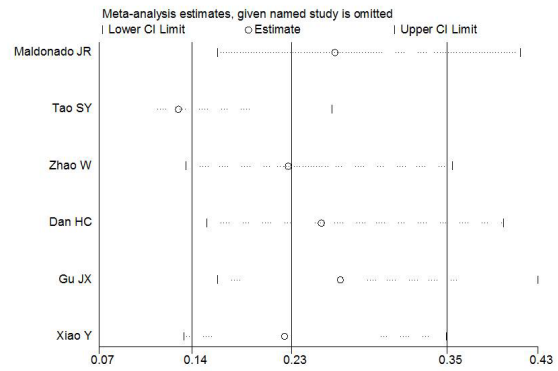

Figure 4: Forest plot of sensitivity analysis

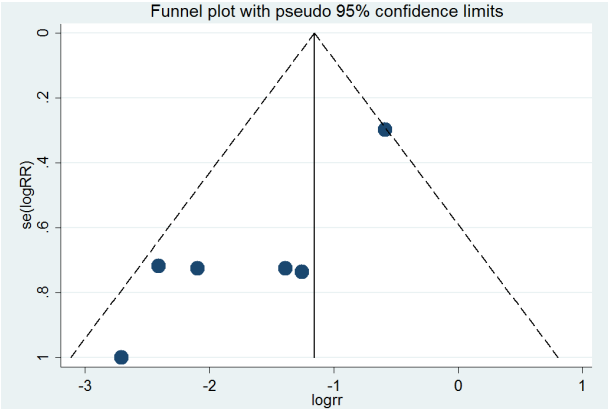

Figure 5: Begg's funnel plot for evaluation publication bias

not changed significantly by omitting each of the studies. This indicated the meta-analysis results were stable and not sensitive to any one of the 6 studies, Figure 4.

3.6 Publication bias

Publication bias was assessed by Begg's funnel plot and Egger's line regression test. The Begg's funnel plot showed obvious asymmetry at the bottom (Figure 5) and Egger's line regression test also indicated significant publication bias (t=-6.51, p<0.05).

4 Discussion

Postoperative delirium is common in patients who received postoperative mechanical ventilation sedation. Postoperative delirium is known as an acute organic mental syndrome which has been shown to affect up to 80% of patients who received postoperative mechanical ventilation or treated in intensive-care units (ICU) [9]. As has been reported, the risk factors for delirium included elderly age, sleep deprivation, metabolic abnormalities, alcohol or drug abuse and postoperative sedation [10, 11]. Several studies had reported that the development of postoperative delirium can increase the risk of morbidity, mortality, postoperative complications, and prolong the time of hospitalization [12]. Dexmedetomidine and midazolam are two kinds of drugs commonly used for postoperative mechanical ventilation sedation [13-15]. The risk of developing delirium with these two drugs was not completely clear. Several studies compared the postoperative delirium risk for dexmedetomidine and midazolam in patients treated with postoperative mechanical ventilation. Maldonado JR [3] and his colleagues reported a prospective randomized controlled trial comparing the postoperative delirium risk for patients that received dexmedetomidine, propofol or midazolam for postoperative sedation. They found that the incidence of postoperative delirium were 3% and 50% for receiving dexmedetomidine and midazolam respectively with statistical difference. However, Xiao et al [7] performed another study evaluating the postoperative delirium risk in patients who received dexmedetomidine or midazolam for postoperative mechanical ventilation sedation. They found that postoperative delirium risk between the two groups was not statistical different. These inconsistent results may be caused by weak statistical power because of the small sample size of each study.

In this meta-analysis, we investigated the effects of dexmedetomidine versus midazolam on postoperative delirium in patients who received postoperative mechanical ventilation. In this study, we included six clinical trials with 386 subjects (202 in the dexmedetomidine group and 184 in the midazolam group). The postoperative delirium risk in the dexmedetomidine group was significantly lower than that of midazolam group (RR=0.20(95%CI:0.09~0.47, p<0.05)). Compared with midazolam, patients that received dexmedetomidine for postoperative mechanical ventilation sedation had less risk of developing delirium.

Dexmedetomidine is one of most used drugs for analgesia and sedation in mechanical ventilated intensive care unit (ICU) patients and was approved by the Federal Drug Adminstration (FDA) in year 1999. Dexmedetomidine is known as a highly selective α2-adrenergic receptor agonist. It can bind to transmembrane G protein-binding adrenoreceptors in brain and spinal cord tissues [16, 17]. Clinically, dexmedetomidine has the effects of anal-

gesic and sedation without suppressing the respiratory system. So, dexmedetomidine is wildly used for postoperative mechanical ventilation sedation. And in our present meta-analysis, we also found that compared with midazolam, patients that received dexmedetomidine for postoperative mechanical ventilation sedation had less risk of developing delirium.

Several limitations were also observed in this meta-analysis. Firstly, only six studies were included in this meta-analysis. Secondly, significant statistical heterogeneity was found across the included studies which may decrease the statistical power. Thirdly, there was obvious publication bias in this meta-analysis. Because of the above limitations, well designed prospective randomized controlled trials are needed to further evaluate the delirium risk of dexmedetomidine and midazolam in patients treated with postoperative mechanical ventilation.

Conflict of interest statement: Authors state no conflict of interest

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