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Review Article

Evaluation of dexmedetomidine versus propofol sedation therapy in mechanically ventilated cardiac surgery patients: a systematic review and meta-analysis of randomized controlled trials and observational studies

Liuhui Chang[1], Hongwei Fang[2,3], Hong Xie[1], Chen Wang[1], Jiang Zhu[1], Ming Li[4], Xiangrui Wang[3], Youjia Xu[5]

Departments of [1]Anesthesiology, [4]Experimental Center, [5]Orthopedics, The Second Affiliated Hospital of Soochow University, 1055 Sanxiang Road, Suzhou 215123, Jiangsu, China; [2]Department of Anesthesiology, Bengbu Medical College, Bengbu, Anhui, China; [3]Department of Anesthesiology, Renji Hospital, School of Medicine, Shanghai Jiaotong University, 1630 Dongfang Road, Shanghai 200127, China

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Abstract: Background: During mechanical ventilation, adequate sedation is a vital factor after cardiac surgery; dexmedetomidine is applied to provide a better efficacy of sedation therapy. However, the prognosis is still controversial in clinical. This meta-analysis aims to compare the effects of dexmedetomidine with propofol administration for MV cardiac surgery patients. Methods: We searched multiple electronic databases including PubMed, Embase, Google Scholar and The Cochrane Library and Cochrane Central Register of Controlled Trials, and the results were updated to July 2015. All statistical analysis was performed by Review Manager, and the Cochrane Collaboration's software was used for preparation and maintenance of Cochrane systematic reviews. Results: Eight trials (three RCTs and five observational studies of 1392 patients) were included, with a sample size ranging from 56 to 582. Pooled analysis suggested that dexmedetomidine had no correlation with decreased duration in MV among cardiac surgery patients in RCTs (WMD: 0.41 D; 95% CI: -1.58-0.76; P = 0.24), but statistically reduced the duration of MV in the observational studies (WMD: -3.80 D; 95% CI: -5.48–2.11; P = 0.15). No statistically significant shorter length of ICU was associated with dexmedetomidine in cardiac surgery patients in two RCTs (WMD: -0.48 D; 95% CI: -1.55-0.59; P = 0.006). Conclusions: Dexmedetomidine has an indispensable role in achieving effective sedation in cardiac surgery patients. Current evidences demonstrate that dexmedetomidine decreases the duration of MV in cardiac surgery patients. Nevertheless, most results relying on the data from observational studies only might cause the selection bias.

Keywords: Dexmedetomidine, propofol, general anesthetics, cardiac surgery, mechanically ventilated, randomized controlled trials, meta-analysis

Introduction

As we all know, the primary goal of sedation in postoperative cardiac surgery patients includes sustaining patient's comfort and anxiety, minimizing pain and cardiac instability is secondary to sympathetic discharge [1]. During mechanical ventilation (MV), adequate sedation is a vital factor to provide comfort to patient [2-4]. Proper sedation and analgesia can decrease MV duration, the length of intensive care unit (ICU) and/or hospital stays, and physiologic stress responses; in this way, the cost of overall health care can be reduced [5-7]. More and more analgesics and sedatives are utilized for postoperative cardiac surgery patients to achieve the aforementioned goals. Nonetheless, considering the safety, efficacy, and cost-effectiveness, there is not any consensus in terms of a preferred agent [8, 9]. Currently, propofol and dexmedetomidine are widely used as sedatives in clinical practice.

Propofol is a hypnotic and sedative drug which is approved for short and long-term sedation therapy in MV post-surgical patients [10, 11].

Propofol also affords more superiority over benzodiazepines such as ease of weaning and adjustment, faster onset, and rapid awakening of neurologic assessments and extubation [12]. Nevertheless, due to potential adverse effects associated with high doses and long-term use, patient selection limits the widely use of it [13, 14].

Dexmedetomidine, a highly selective α-2 adrenergic agonist, occasionally combined with midazolam, was used to provide a better sedation, antianxiety, and analgesic properties [8]. In 1999, dexmedetomidine was authorized for patients during the first 24 hours of MV by the Food and Drug Administration (FDA) [15-17]. Currently, dexmedetomidine has been used in the clinic. However, doctors are concerned about the safety of dexmedetomidine, which limits its widespread utilization in more patients [18]. Meanwhile, latest literature has noted that dexmedetomidine has some advantaged properties (analgesic and opioid sparing effects), and these qualities contribute to earlier extubation, so dexmedetomidine is considered as a preferred selection for cardiac surgery patients [9].

Several studies made the comparison between dexmedetomidine and propofol in terms of their drug effects in cardiac surgery patients. However, studies have illustrated conflicting consequences of MV duration when dexmedetomidine was used to treat cardiac surgery patients. Furthermore, owing to small sample sizes, individual research results were not accurate enough. Therefore, we systematically gathered all the available clinical research results together, and figured out the process as much as possible. Here, we performed a meta-analysis of all associated studies to assess the clinical efficacy of dexmedetomidine and propofol in cardiac surgery patients.

Materials and methods

Participants

This meta-analysis focused on adult patients (age > 18) who scheduled for coronary artery bypass graft surgery (CABG).

Interventions

During the clinical trials, patients had accepted postoperative sedation with only dexmedetomidine or propofol. The ventilator weaning protocols of cardiac surgery patients for dexmedetomidine or propofol was coincident during the study period.

Types of outcome measures

The primary outcome was MV duration; others including length of ICU and/or in-hospital stay, opioid drugs requirement, mortality and hemodynamic changes among patients were also recorded at the same time.

Types of studies

We concluded all studies comparing dexmedetomidine with propofol for MV cardiac surgery patients' sedation in Randomized controlled trials (RCTs) or observational studies (prospective or retrospective cohort studies). Agreement regarding studies was evaluated using the Cohen *k* statistic [19]. We excluded studies published in abstracts, commentaries, editorials, reviews or other improper articles.

Study selection

We employed the Cochrane risk of bias tool, and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement methodology for guarantee, and a systematic review and meta-analysis of RCTs [20]. Related articles were selected through multiple electronic databases including PubMed, Embase, Google Scholar and The Cochrane Library and Cochrane Central Register of Controlled Trials (CENTRAL). The electronic search was conducted by two reviewers (L.H Chang and H.W Fang) working independently. Studies were considered without time limit, besides, their language must be English. We performed the latest updated search in July 2015. Key words included: "Dexmedetomidine" and "Propofol" and "Intensive Care Unit" and "Cardiac Surgical Procedures". The major international conference was hand-searched journal. We manually searched the related articles and reference lists to avoid omissions. The abstracts of all articles were identified as potential related retrieval and were examined in the study selection process. If an article required further evaluation, we contacted the paper author by e-mail or telephone, then we could request for further detailed data.

Inclusion criteria

The foremost objective of this meta-analysis was to estimate the influence of dexmedetomidine and propofol for cardiac surgery patients, with respect to patient outcomes and adverse events. Only studies that accorded with all of the following criteria were inclusive: (1) the setting was patients' age > 18 and patients undergoing isolated, primary, elective cardiac surgery; (2) the trials compared dexmedetomidine with propofol for only calmative therapy; (3) outcomes included duration of MV, length of ICU or in-hospital stay, opioid drugs requirement rates, mortality or hemodynamic changes (hypotension, bradycardia, hypertension and/or other effects); and (4) excessive data to calculate relative risk (RR) or mean difference (MD) with 95% confidence interval (95% CI).

Exclusion criteria

We also eliminated studies if they (1) included patients with hypoevolutismus, cognitive disorder, behavioral or psychological impairment, severe diseases of the central nervous system including brain tumors or uncontrolled epilepsy, (2) used dexmedetomidine or propofol for anesthesia plus other drugs simultaneously in the identical group, and (3) did not report the particular results. Divisions caused by the selection process were settled after consensus-based discussion.

Data extraction

This part was done by the same two investigators, worked independently, which eligibility, quality and outcomes were assessed and recorded; any divisions being solved by consensus-based discussion referred to a third investigator (Y.J Xu). We extracted the following study features: first author, publication year, country, study design, number of participants, protocol of dexmedetomidine or propofol, duration of MV, length of ICU and/or hospital stay, mortality, opioid drugs requirement rates and so on.

Quantitative data synthesis

We used The Cochrane risk of bias tool to evaluate the risk of bias for each RCT [21], and Cohort studies were evaluated using the Newcastle-Ottawa Scale [22].

In order to carry out the quality assessment of these studies contained in the present meta-analysis, we adopted the Review Manager (REVMAN) software (version 5.2; The Nordic Cochrane Centre, Copenhagen, Denmark) constructed the 'risk of bias' table. The table included six parameters of bias, sequence generation (representing selection bias), allocation concealment (representing selection bias), blinding (representing performance bias or detection bias), incomplete data (representing attrition bias), and selective reporting (representing reporting bias). To classify its risk of bias, each parameter would be split into one of the three different levels ("low", "high" or "unclear").

Meta-analysis and statistical methods

Duration of MV, Length of ICU and/or hospital stay data were recorded respectively as mean (± standard deviation [SD]) in days. Opioid drugs requirement rates were recorded as events in percentage. For continuous outcomes (Duration of MV, Length of ICU and/or hospital stay), the weighted mean difference (WMD) with 95% confidence interval (CI) was calculated. Besides, if the 95% confidence interval (CI) was not equal to 0 for the WMD or 1 for the OR, we considered the WMD or OR was statistically significant.

In terms of the formula supplied by Hozo et al. [23], we reckoned with the mean and square deviation of the studies in which only median, size, and range was recorded. We adopted the formula offered in the Cochrane Handbook for Systematic Reviews of interventions (chapter 7), and evaluated the mean and square deviation of the studies in which only median, size, and interquartile range (IQR) was recorded [24].

Publication bias was analyzed and viewed examination of dissymmetry in funnel plots. To identify the potential influence of each single study, sensitivity analysis was analyzed by removing the single study in sequence.

In this article, all statistical analysis was performed by Review Manager, the Cochrane Collaboration's software preparation and maintenance of Cochrane systematic reviews. Depending on the lack or existence of significant heterogeneity, statistical method was selected severally fixed effect or random effect model.

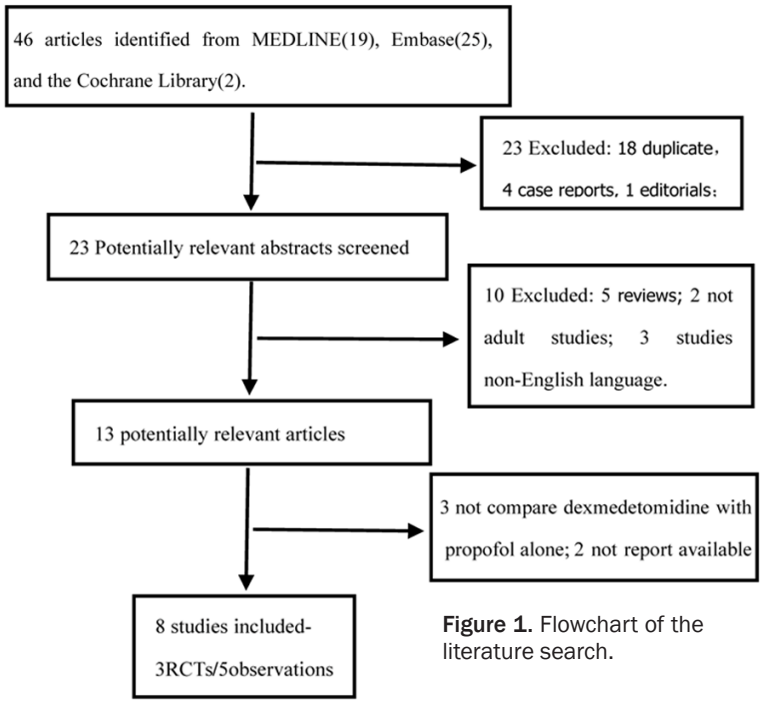

Figure 1. Flowchart of the literature search.

P-values < 0.10 were considered to be proof of heterogeneity, higher χ^2 and I^2 values prompted higher levels of inconsistencies, then the random effects model was utilized to compute. The summary estimates and 95% CIs were also calculated for assessment.

Results

Study characteristics

Firstly, by using keywords search of the electronic libraries, we chose 46 potentially relevant studies in a preliminary stage (**Figure 1**). With retrieval and review of the articles' abstract, 23 studies were excluded depending on the title or abstract. Moreover, 3 articles were excluded due to study design (i.e., not comparing dexmedetomidine with propofol alone), and 2 more studies were excluded because they did not examine. Therefore, 8 studies [25-32], a sample size ranged from 56 to 582, with a total number of 1392 patients were enrolled in the meta-analysis. Evaluated trials included data published between October 2003 and February 2014. All of the 8 studies were published in English from USA. The studies above, three were RCTs [25-27], and five were cohort studies [28-32]. The characteristics of the identified studies were presented in **Table 1**. Risk assessment of RCTs was set in **Table 2**, and the Observational studies were shown in **Table 3**.

Duration of MV

Randomized controlled trials: Data collected from RCTs [25-27] were pooled (**Figure 2**), and no statistically significant shorter duration of MV was associated with DEX administration in cardiac surgery patients (WMD: 0.41 D; 95% CI: -1.58-0.76; *P* = 0.24). There was evidence of low heterogeneity (χ^2: 2.84; I^2: 30%).

Observational studies: Within observational studies [28-32] (**Figure 2**), DEX was associated with reducing duration of MV in cardiac surgery patients (WMD: -3.80 D; 95% CI: -5.48--2.11; *P* = 0.15). There was also evidence of low heterogeneity (χ^2: 6.67; I^2: 40%).

Length of ICU stay

Length of ICU stay was evaluated in 6 studies, including two RCTs [26, 27] and four observational studies [29-32]. No statistically significant shorter length of ICU was associated with dexmedetomidine administration in cardiac surgery patients in two RCTs (WMD: -0.48 D; 95% CI: -1.55-0.59; *P* = 0.006). But there was evidence of high heterogeneity (χ^2: 7.54; I^2: 87%). However, in the four observational studies, all of them showed a shorter mean length of ICU in the dexmedetomidine group. The pooled mean difference between dexmedetomidine and propofol group was -0.51 D (95% CI: -0.93 to -0.09; *P* = 0.02), which suggested a statistically significant difference between the two groups. However, the χ^2 and I^2 were 10.39 and 71%, which indicated high heterogeneity among the studies (**Figure 3**).

Length of hospital stay

Five [27, 29-32] of the included studies provided data of the length of hospital stay. Dexmedetomidine significantly decreased the length of hospital stay in cardiac surgery patients (WMD: -2.02 D; 95% CI: -3.77--0.27; *P* <

Table 1. Characteristics of studies included in the meta-analysis

Included studies /year/country	Patients Age/number (Male)	Surgery Procedure	Studies design	Intervention		Outcomes used in this meta-analysis
				Dexmedetomidine	Propofol	
Daniel /2003/USA	Adults/ Dex: 148 (NR); Pro: 147 (NR)	CABG	RCT	Received 1.0 g/kg of DEX over 20 minutes and then 0.2 to 0.7 g/kg/h to maintain a Ramsay sedation score > 3 during assisted ventilation and > 2 after extubation	Received PRO-based care according to each investigator's standard practice	MV duration, opioid agents use rates
Stephanie /2005/USA	Adults/ Dex: 43 (35); Pro: 46 (38)	CABG	Prospective RCT	DEX (1 μg/kg [actual body weight] loading dose intravenously administered over 15 mins, followed by a 0.4 μg/kg/h intravenous infusion)	Pro (5 μg/kg/min intravenous infusion titrated within the range of 0.2-0.7 μg/kg/h or 5-75 μg/kg/min)	MV duration, length of ICU
Jose´R /2009/USA	Adults/ Dex: 40 (26); Pro: 38 (22)	Cardiac-valve operations	Prospective RCT	DEX loading dose: 0.4 μg/kg, a infusion: 0.2-0.7 μg/kg/h	PRO: 25-50 μg/kg/min	MV duration, length of ICU, length of hospital stay
Jeffrey F /2009/USA	Adults/ Dex: 50 (38); Pro: 50 (38)	CABG and/ or valvular surgery	Retrospective Cohort study	Loading doses are not used; doses are started at 0.2 μg/kg/h	PRO use was guided by the individual anesthesiologist	MV duration, opioid agents use rates
Kevin E /2010/USA	Adults/ Dex: 28 (23); Pro: 28 (16)	Cardiac surgery	Prospective Descriptive study	The mean initial DEX infusion rate was 0.6 + 0.1 μg/kg/h	the mean initial PRO rate was 1.5 + 0.6 μg/kg/h	MV duration, length of ICU, length of hospital stay, opioid agents use rates
Heather /2013/USA	Adults/ Dex: 53 (39); Pro: 73 (45)	MIDCAB	Retrospective Before-after study	NR	NR	MV duration, length of ICU, length of hospital stay, opioid agents use rates
James A /2013/USA	Adults/ Dex: 291 (200); Pro: 291 (190)	Cardiac valve and/or CABG surgery	Retrospective analysis	NR	NR	MV duration, length of ICU, length of hospital stay
Brandi N /2014/USA	Adults/ Dex: 42 (38); Pro: 42 (38)	CABG surgery	Retrospective Cohort study	The mean total ventilation dose for DEX was 398 μg with a mean dose rate of 0.5 μg/kg/h	The total ventilation dose of PRO was 2,613 mg with a mean dose rate of 35 μg/kg/min	MV duration, length of ICU, length of hospital stay

NR = not reported; RCT = randomized controlled trial; DEX = dexmedetomidine; PRO = propofol; CABG = Coronary Artery Bypass Graft; MIDCAB = Minimally Invasive, Direct Coronary Artery Bypass.

Table 2. Risk of bias assessment of included RCT

Included studies	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Daniel/2003	Low	Low	Unclear	Low	Low	Low
Stephanie/2005	Low	Low	Unclear	Low	Low	Low
Jose´R/2009	Low	Low	Low	Low	Low	Low

0.00001). However, the χ^2 and I^2 were 45.4 and 91%, respectively, which indicated high heterogeneity among the studies (**Figure 4**).

Opioid drugs requirement rates

Four [25, 28-30] of the included studies provided data of opioid drugs requirement rates. DEX did not decrease the risk of opioid drugs requirement rates in cardiac surgery patients (RR: 0.67; 95% CI: 0.17-2.70; $P < 0.00001$) (**Figure 5**).

Publication bias

Using the duration of MV, through the funnel figure we evaluated potential publication bias as a destination. The funnel plot did not show the existence of publication bias (**Figure 6**).

Discussion

Main finding

Our meta-analysis, including three RCTs and five observational studies, investigated the

Table 3. Risk of bias assessment of the observational studies

Included studies	Selection				Comparability	Outcome			Total Score
	Exposed Cohort	Nonexposed Cohort	Ascertainment of Exposure	Outcome of Interest		Assessment of Outcome	Length of Follow-up	Adequacy of Follow-up	
Jeffrey F/2009	*	*	*	*	*	*	*	...	7
Kevin E/2010	*	*	*	...	*	*	*	...	6
Heather/2013	*	*	*	*	*	*	*	*	8
James A/2013	*	*	*	*	*	*	*	...	7
Brandi N/2014	*	*	*	*	**	*	*	*	9

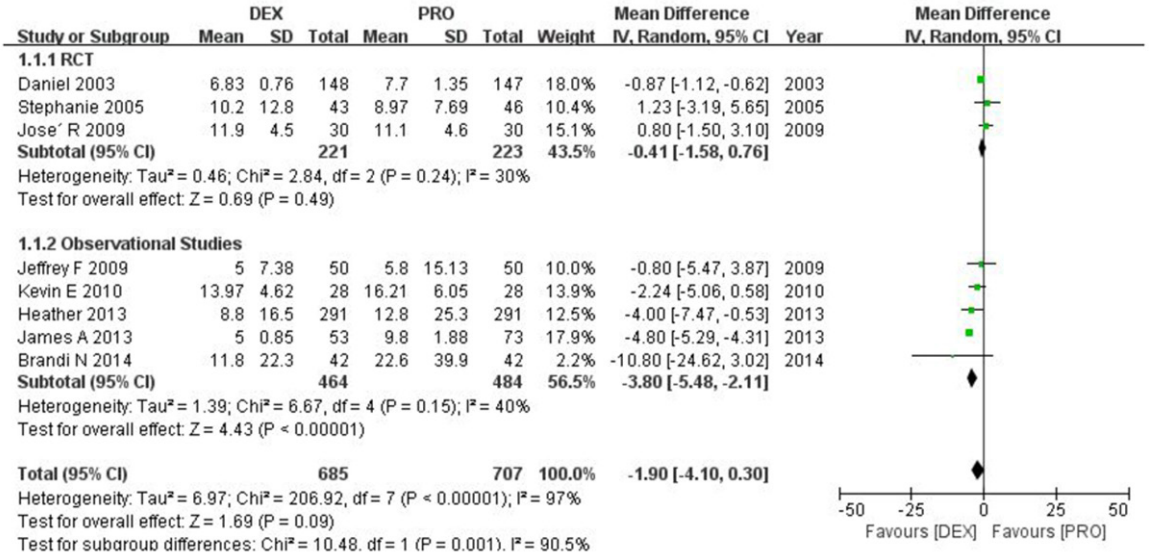

Figure 2. Effects of dexmedetomidine versus profol on MV duration in mechanically ventilated cardiac surgery patients.

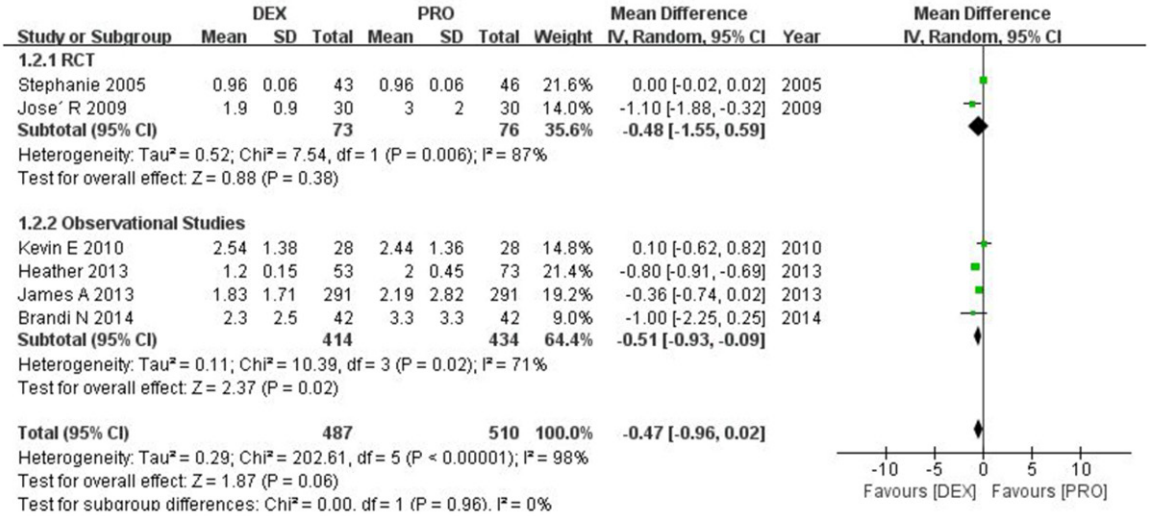

Figure 3. Effects of dexmedetomidine versus profol on length of ICU in mechanically ventilated cardiac surgery patients.

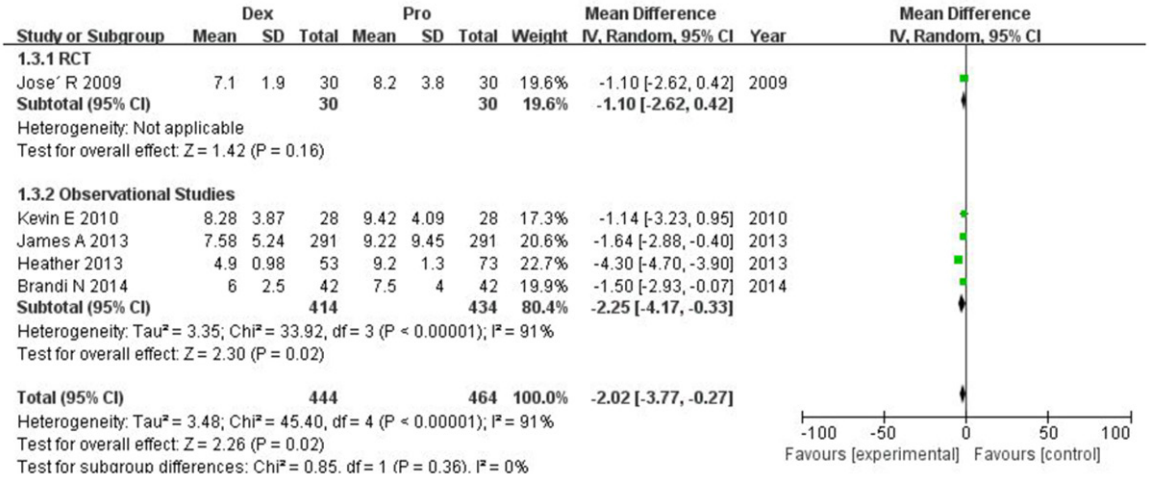

Figure 4. Effects of dexmedetomidine versus profol on length of hospital stay in mechanically ventilated cardiac surgery patients.

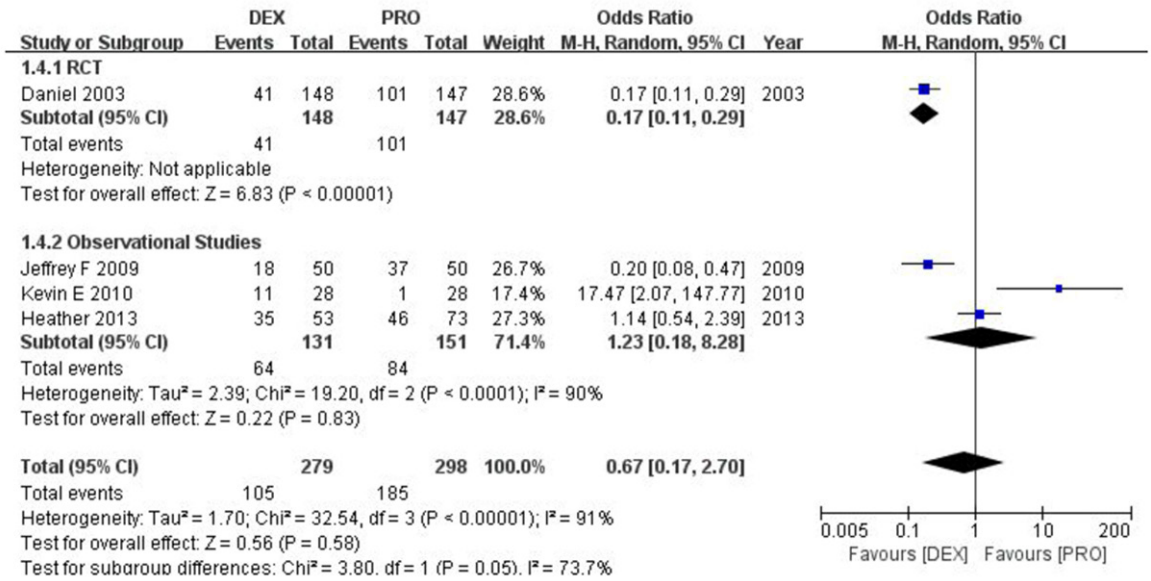

Figure 5. Effects of dexmedetomidine versus profol on opioid drugs requirement rates in mechanically ventilated cardiac surgery patients.

effect of dexmedetomidine and propofol on the duration of MV and length of ICU stays of cardiac surgery patients. The analysis showed that dexmedetomidine did not reduce the duration of MV, length of ICU stay and the frequency of opioid drugs requirement in cardiac surgery patients, compared to propofol. Moreover, the analysis also revealed that dexmedetomidine has a shorter length of hospital stay compared to propofol in cardiac surgery patients.

Currently, in the ICU, midazolam, benzodiazepines, lorazepam and propofol were the most commonly used sedative and hypnotic agents, and anesthetics such as morphine and fentanyl were the most widely used analgesics [33]. Although these drugs had been approved, several studies focus on their drug complications, especially when we need to prolong use of critically ill patients [34]. Advantages of propofol are short duration of action and rapid onset after therapy, and faster awakening, extubation as well [35]. In addition, the medical cost of propofol was much lower than other sedatives. However, considering the defect of analgesic activity of propofol, an auxiliary opioid therapy

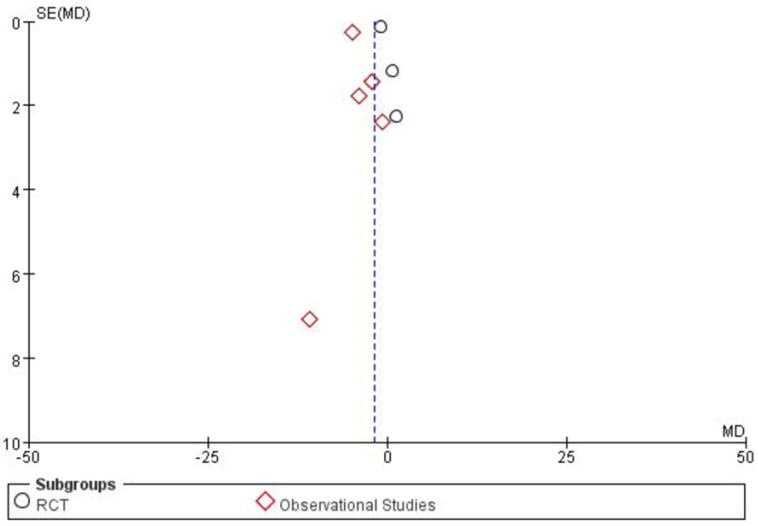

Figure 6. Effects of dexmedetomidine versus profol MV duration in mechanically ventilated cardiac surgery patients.

was necessary. What's worse, propofol could cause significant respiratory depression and may increase the side effects of opioid analgesics [36].

Wijeysundera DN et al. [37] investigated the effects of α-2 adrenergic receptor agonists, including dexmedetomidine, in perioperative mortality and cardiovascular complications undergoing cardiac surgery patients. Unlike the GABA receptor agonist, dexmedetomidine exerted its pharmacological effects through a unique combination of α-2 receptors. Dexmedetomidine may reduce the demand for opiates, and thus reducing the risks of excessive sedation associated with it [38].

Differences between propofol and dexmedetomidine had been investigated in several studies in cardiac surgery patients [39-41]. It was demonstrated that no significant difference on duration of MV between these two drugs. However, some other studies reported a significantly shorter duration of MV compared to propofol, when analyzed as a categorical or continuous variable [30-32].

To fast-track surgical patients, randomized controlled trials had demonstrated: due to the pharmacological properties of dexmedetomidine, such as easy to awaken and reduction of opioid drugs utilization, which made DEX as an attractive choice [35]. However, studies on dexmedetomidine compared to propofol-based sedation therapy, did not show significant clinical improvements in terms of the length of stay in cardiac surgery patients [42]. One retrospective database analysis reported that among post-cardiac surgery patients, dexmedetomidine was associated with significantly lower mortality, shorter duration of MV, fewer days in the ICU, and reducing hospital costs as well [43].

Similar to clonidine, pharmacological characteristics of dexmedetomidine offered potential analgesic effect and lower opioid requirements compared with the propofol-based regimen. In Jeffrey's study, compared with the use of propofol, dexmedetomidine group exhibited lower opioid consumption; moreover, a large proportion of dexmedetomidine-treated patients did not need opioid drugs [28]. Even though, Kevin's study showed that, in comparison with propofol-based patients, dexmedetomidine patients required more morphine drugs virtually [29]. Our meta-analysis showed that only four articles recorded the opioid drugs requirement rates. In contrast with propofol, dexmedetomidine did not significantly reduce opioid drugs requirement rates.

Wiyeysundera DN et al. [37] summarized that: during cardiac surgery, α-2 adrenergic receptor agonists were correlated to the reduced number of ischemic episodes, the risk of myocardial infarction and mortality. Their research also highlighted the risk of hypotension in the cardiac surgery, and no statistically significant increase of the incidence of bradycardia, hypotension, heart failure or others.

We acknowledged that several limitations are worth discussing in this meta-analysis. Firstly, only three relevant individual RCTs and five observational studies were integrated with the results. Secondly, among all included studies, managements of dexmedetomidine and propofol sedation were not the equivalent method (**Table 1**). This may be considered as a source of heterogeneity. Thirdly, some observational studies were retrospective chart study and

managed in a single institution. Moreover, our results may be influenced if studies included two different cohorts of patients and changes in clinical staff during the various study timeframes. In addition, the impact of publication bias could not be neglected. Finally, some drugs belonged to these two kinds of sedatives but related to other important parameters, were not included in this meta-analysis. Lack of data may make this research underpowered to test and cannot reveal a statistically significant difference.

Conclusions

In summary, dexmedetomidine must have an indispensable function in MV cardiac surgery patients. Compared to propofol, however, dexmedetomidine did not conspicuously induce the duration of MV in cardiac surgery patients in RCTs. Larger samples, higher quality and adequately powered RCTs of dexmedetomidine are warranted with a focus on the MV duration, length of ICU and/or hospital stay, opioid drugs requirement rates and the incidence of delirium analysis.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xiangrui Wang, Department of Anesthesiology, Renji Hospital, School of Medicine, Shanghai Jiaotong University, 1630 Dongfang Road, Shanghai 200127, China. Tel: +86-21-68383198; Fax: +86-21-50903239; E-mail: xiangruiwang@gmail.com; Dr. Youjia Xu, Departments of Orthopedics, The Second Affiliated Hospital of Soochow University, 1055 Sanxiang Road, Suzhou 215123, China. E-mail: xuyoujia@medmail.com.cn

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