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Original Article

Dexmedetomidine versus midazolam/propofol sedation reduces delirium in the intensive care unit: a systematic review and meta-analysis of randomized controlled trials

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Abstract: *Background:* Delirium is a serious complication for intensive care unit (ICU) patients. Preventing delirium by dexmedetomidine administration for sedative is still controversial. This meta-analysis aims to analyze the different occurrence of delirium between dexmedetomidine and midazolam/propofol administration for ICU patients. *Methods:* We searched multiple electronic databases including Embase, PubMed, Google Scholar, and The Cochrane Library and Cochrane Central Register of Controlled Trials (CENTRAL), and the results were updated in December 2016. All statistical analysis utilizing Review Manager was performed, and the Cochrane Collaboration's software was used only for preparation and maintenance of Cochrane systematic reviews. We employed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement methodology for validation. *Results:* Eight studies, with a sample size ranged from 23 to 998, for a total number of 2182 participants were included in this meta-analysis. Pooled subgroup analysis suggested that dexmedetomidine had an intense correlation with reducing the occurrence of delirium compared with midazolam/propofol administration for ICU patients (OR: 0.47; 95% CI: 0.26-0.84; $P < 0.00001$). Both the duration of mechanical ventilation (MV) and Length of ICU stay statistically significant shorter was associated with dexmedetomidine for ICU patients (Weighted Mean Difference [WMD]: -2.27 D; 95% confidence interval [CI]: -3.59 to -0.95; $P < 0.00001$) and (WMD: -1.62 D; 95% CI: -1.75 to -1.50; $P = 0.03$). *Conclusions:* Current evidence demonstrates that dexmedetomidine, administered as sedative agent for ICU-MV patients, is related to conspicuously lower rates of delirium, shorter duration of MV, and length of ICU. Nevertheless, the overall outcomes of this meta-analysis can be impacted by drug interactions, neurocognitive assessment method, and clinical heterogeneity.

Keywords: Delirium, dexmedetomidine, midazolam, propofol, intensive care unit, randomized controlled trials, meta-analysis

Introduction

Delirium is a neurobehavioral syndrome, caused by transient abnormal abort of secondary neuronal activity and lead to systemic dysfunction [1-3]. As early as 1964, delirium was first mentioned as postcardiotomy delirium in the postoperative cardiac surgery patients [4]. Postoperative delirium (POD) is an acute organic psychiatric syndrome, the incidence of which is rather high in both medical and surgical patients [5, 6], and even much higher among ICU patients (up to 80%) [7, 8], especially elderly patients being at the greatest risk. Delirium would raise mortality and decrease cognitive function in the long term. Furthermore, agitated delirium is represented particularly in patients who have received MV due to the increasing risk of self-extubation and removal of other essential medical devices. It would be a crucial therapeutic advance to identify an agent that shortens the duration of established delirium.

Currently, 2 classes of medicines are mainly used for sedative action: γ-aminobutyric acid (GABA) agonists, including lorazepam, midazolam, and propofol, including α-2-adrenoreceptor agonists, such as clonidine and dexmedetomi-

dine. While α-2-agonists offer satisfying sedation and analgesia with little or even no respiratory inhibition, they increasingly substitute the GABA agonists as more effective medications for analgesia and sedation. Consequently, different choices between the 2 classes of medications would arouse the different influences on the occurrence of delirium, the duration of MV, the length of ICU stay, and the cost of health care [9].

Dexmedetomidine, as a highly selective α-2-adrenoreceptor agonist, is widely applied for sedation management in the clinic and especially exhibits an anesthetic-sparing effect [10]. Back to 1999, dexmedetomidine was firstly authorized for sedation management in patients during the first 24 hours of MV by the Food and Drug Administration (FDA) [11-13]. Then, it was utilized to make sedation for ICU patients clinically, particularly during the early postoperative period [14]. Several clinical trials have already demonstrated its efficacy and safety. Because of its excellent sedation with few adverse events such as cardiovascular instability or respiratory depression, dexmedetomidine may be an effective alternative to facilitate smooth tracheal extubation. Furthermore, it has also been documented that dexmedetomidine could weaken the plasma catecholamine responses in intubation and extubation phases [15, 16].

Actually, the treatment guidelines of pain, agitation and delirium require reducing MV time and the stay length in ICU, so it is necessary for clinicians to minimize or even substitute benzodiazepines with either propofol or dexmedetomidine in ICU patients [17]. Nevertheless, a Cochrane review recently reported that no evidence supported the beneficial effect of dexmedetomidine on decreasing the risk of POD in seriously ill patients owing to inadequate assessment of delirium, absent delirium as the primary measure outcome, or the high heterogeneity of those clinical trials [18]. Furthermore, individual research results were equally not accurate enough due to various reasons. Therefore, we set out to systematically gather all the available clinical research results. Here, we evaluated the risk of delirium in medical/surgical ICU patients with dexmedetomidine and midazolam/propofol management by a meta-analysis of all associated studies.

Materials and methods

This was a systematic review and meta-analysis of previously published Randomized Controlled Trials (RCTs), ethical approval and patient written informed consent were not required.

Participants

This meta-analysis focused on adult patients (age > 18 years) who required mechanical ventilation and received sedation drug infusion in the medical or surgical ICU.

Interventions

During the clinical trials, patients accepted sedation with dexmedetomidine or midazolam/propofol. The ventilator weaning protocols of ICU patients for dexmedetomidine or midazolam/propofol was consistent during the study period.

Types of outcome measures

The primary outcome was the incidence of delirium. Others symptoms included MV duration 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 midazolam/propofol for ICU patients' sedation in RCTs. Agreement regarding studies was assessed using the Cohen *k* statistic [19]. We excluded studies published in abstracts, commentaries, editorials, cohort studies, reviews or other improper articles.

Study selection

We employed the Cochrane risk of bias tool and the PRISMA statement methodology for validation, and a systematic review and meta-analysis of RCTs [20]. Related articles were selected through multiple electronic databases including Embase, PubMed, Google Scholar, The Cochrane Library, and Cochrane Central Register of Controlled Trials (CENTRAL). The electronic search was conducted by two reviewers retrieving independently (SP. Xing and J Ding). Studies were considered without time limit and the language must have been English. We performed

the latest updated search in December 2016. Key words included: "Dexmedetomidine" and "Propofol" and "Midazolam" and "Intensive Care Unit" and "Randomized controlled trial". Major international conferences were handsearched by journal. We manually searched the related papers and reference lists in order to avoid omission. The abstracts of all articles were cited as potential related retrieval and were examined in the study selection process. If an article required further evaluation, we would contact the paper author by telephone or e-mail, and then we could require additional detailed data.

Inclusion criteria

The foremost objective of this meta-analysis was to estimate the clinical effects of dexmedetomidine and propofol/midazolam for ICU tracheal intubated patients, with respect to patients' delirium occurrence and other adverse events. Only studies that accorded with all of the following criteria were inclusive: (1) the setting was patients' age > 18 and tracheal intubated patients; (2) the trials compared dexmedetomidine with midazolam/propofol for only calmative therapy; (3) outcomes included the incidence of delirium, duration of MV, length of ICU or in-hospital stay, opioid drugs requirement rates, mortality or hemodynamic changes (hypotension, bradycardia, hypertension and/or other side effects); and (4) data calculated relative risk (RR) or mean difference (MD) with 95% confidence interval (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 midazolam/propofol for anesthesia plus other drugs simultaneously or subsequently in the identical group, and (3) did not report the detail data. Divisions caused by the selection process were settled after consensus-based discussion.

Data extraction

This part was made by the same two investigators that worked independently to assess eligibility, quality, and outcomes. Any disagreements were solved by consensus-based discussion and referred to a third investigator (DX. Wen). We extracted the following trial characteristics: first author, country, publication year, number of participants, study design, protocol of dexmedetomidine or midazolam/propofol, the incidence of delirium, 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]. In order to carry out the quality assessment of these studies contained in the present meta-analysis, we used 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, and allocation concealment (both representing selection bias), blinding (representing performance bias or detection bias), incomplete data (representing attrition bias), and selective reporting (representing reporting bias). Meanwhile, to classify its risk of bias, each parameter was be split into one of three different levels ("low", "high" or "unclear").

Meta-analysis and statistical methods

The incidence of delirium was recorded as events in percentage. Length of ICU and/or hospital stay data were recorded respectively as mean (± standard deviation [SD]) in days. For continuous outcomes (length of ICU and/or hospital stay), the WMD with 95% CI was calculated. Additionally, if the 95% 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 Hozo' formula [22], we reasoned that 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.

Publication bias was analyzed and examination by dissymmetry in funnel plots. To make out the potential impact of each single clinical trial,

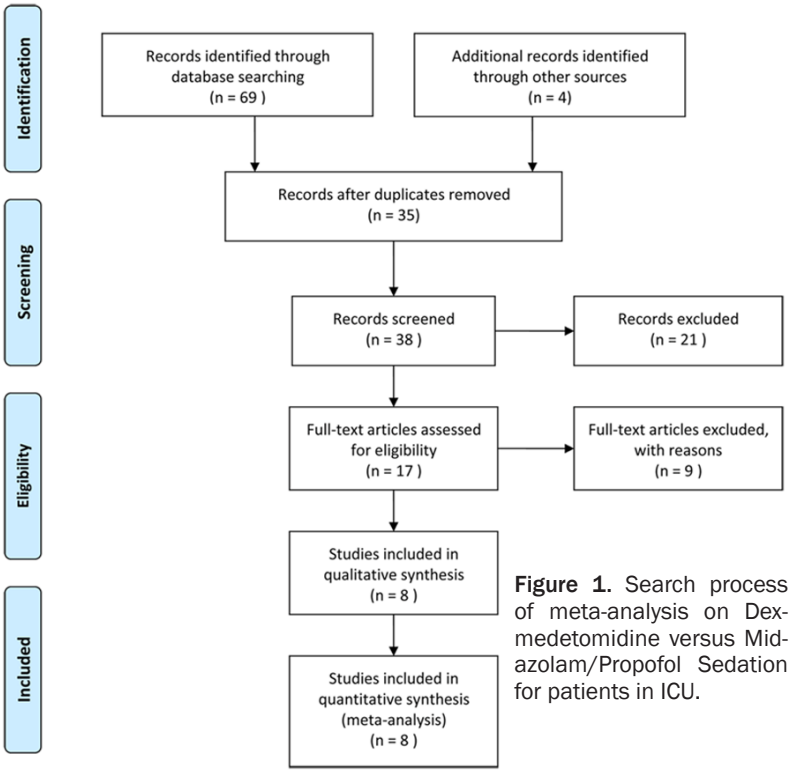

Figure 1. Search process of meta-analysis on Dexmedetomidine versus Midazolam/Propofol Sedation for patients in ICU.

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. Being dependent on the lack or existence of significant heterogeneity, statistical methods were selected for several fixed effect or random effect models. *P*-values < 0.10 were considered to be proof of heterogeneity, higher X^2 and I^2 values prompted higher levels of inconsistencies, then the subgroup analysis and the random effects model were utilized to statistical analysis or compute. The summary estimates and 95% CIs were also calculated for assessment.

Results

Study characteristics

First, by using keywords search of the electronic libraries and adding records identified through other sources, we chose 73 potentially relevant studies in a preliminary stage (**Figure 1**). With retrieval and review of the articles' abstract, 35 studies were excluded depending on the title or abstract. Moreover, 21 articles were excluded: 13 reviews; 2 not adult studies; 6 studies non-English language. Then, we analyzed each study, 9 Excluded: 7 not compared dexmedetomidine with midazolam/propofol; 1 not reported available data; 1 not RCT. Therefore, 8 studies [23-30], with a sample size ranging from 23 to 998, with a total number of 2182 patients were enrolled in the meta-analysis. Evaluated trials included data published between September 2008 and February 2016. All of the studies were published in English from different country. All of the studies were RCTs and the characteristics of the identified studies were presented in **Table 1**. Risk assessment of RCTs was established in **Figures 2** and **3**.

The incidence of delirium

Data collected from RCTs were pooled (**Figure 4**) [23-30]. Dexmedetomidine was associated with reducing the incidence of delirium in ICU patients (OR: 0.47; 95% CI: 0.26-0.84; $P < 0.00001$). However, there was also evidence of high total heterogeneity about the subgroup differences among the studies (X^2: 11.06; I^2: 81.9%).

Duration of MV

Data also collected from RCTs were pooled (**Figure 5**) [23-30], and statistically significant shorter duration of MV was associated with dexmedetomidine administration in ICU patients compared with propofol/midazolam (WMD: -2.27 D; 95% CI: -3.59 to -0.95; $P < 0.00001$). However, the X^2 and I^2 were 5.44 and 63.3%, which indicated high heterogeneity among the studies (**Figure 5**).

Length of ICU stay

Six [23, 25, 27-30] of the included studies provided data of the Length of ICU stay, and all of

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

Included studies/ year/country	Patients		Studies design	Intervention		Outcomes used in this meta-analysis
	Age (Mean ys)	Number (Male)		Dexmedetomidine	Midazolam/Propofol	
Maldonado JR et al. [23]/2009/USA	Dex: 55; Mid/Pro: 59.	Dex: 40 (26); Mid/Pro: 78 (49).	Prospective RCT	DEX loading dose: 0.4 μg/kg, drip 0.2-0.7 μg/kg/h.	PRO: 25-50 μg/kg/min; MID: drip (0.5-2 mg/h).	The incidence of Delirium, MV duration, length of ICU.
Ruokonen E et al. [24]/2008/Swit	Dex: 64; Mid/Pro: 68.	Dex: 41 (32); Mid/Pro: 44 (38).	RCT	DEX: 0.8 μg/kg/h for 1 h and then adjusted stepwise at 0.25, 0.5, 0.8, 1.1, and 1.4 μg/kg/h.	PRO: 2.4 mg/kg/h for 1 h and then adjusted stepwise at 0.8, 1.6, 2.4, 3.2, and 4.0 mg/kg/h. MID: boluses (1-2 mg), starting at 3 boluses/h for 1 h, and thereafter 1-4 boluses per hour, or as a continuous infusion at 0.12 mg/kg/h for 1 h, followed by adjustments at 0.04, 0.08, 0.12, 0.16, and 0.20 mg/kg/h.	The incidence of Delirium, MV duration.
Riker RR et al. [25]/2009/USA	Dex: 61.5; Mid: 62.9.	Dex: 244 (125); Mid: 122 (57).	Prospective RCT	DEX: 0.2-1.4 μg/kg/h.	MID: 002-0.1 mg/kg/h.	The incidence of Delirium, MV duration, length of ICU.
Yapici N et al. [26]/2010/Turkey	Dex: 58.905; Mid: 61.617.	Dex: 38 (13); Mid: 34 (14).	RCT	DEX: 0.3-0.7 μg/kg/min.	MID: 0.05-0.2 mg/kg/h.	The incidence of Delirium, MV duration.
Jakob SM et al. [27]/2012/Swit	Dex: 65; Mid/Pro: 65.	Dex: 500 (313); Mid/Pro: 498 (341).	RCT	DEX: 0.2-1.4 μg/kg/min.	PRO: 0.3-4.0 mg/kg/h; MID: 0.03-0.2 mg/kg/h.	The incidence of Delirium, MV duration, length of ICU.
Lachaine J et al. [28]/2012/Canada	Dex: NR; Mid: NR.	Dex: 244 (NR); Mid: 122 (NR).	Prospective RCT	DEX: 0.2-1.4 μg/kg/min.	MID: 0.02-0.1 mg/kg/h.	The incidence of Delirium, MV duration, length of ICU.
MacLaren R et al. [29]/2013/USA	Dex:58.3; Mid: 57.8.	Dex: 11 (6); Mid: 12 (7).	RCT	DEX: 0.15-1.5 μg/kg/min.	MID: 1-10 mg/h.	The incidence of Delirium, MV duration, length of ICU.
Djaiani G et al. [30]/2016/USA	Dex: 72.7; Pro: 72.4.	Dex: 91 (68); Pro: 92 (70).	Prospective RCT	DEX: 0.4 μg/kg bolus followed by 0.2 to 0.7 μg/kg/h infusion.	PRO: 25-50 μg/kg/min.	The incidence of Delirium, MV duration, length of ICU.

NR = not reported; RCT = randomized controlled trial; MV = Mechanical ventilation; DEX = dexmedetomidine; MID = midazolam; PRO = propofol.

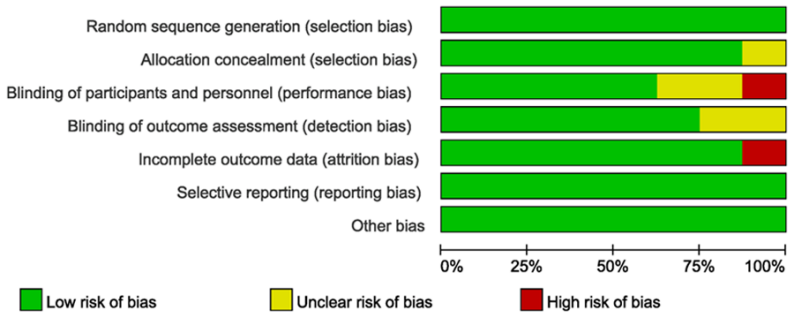

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

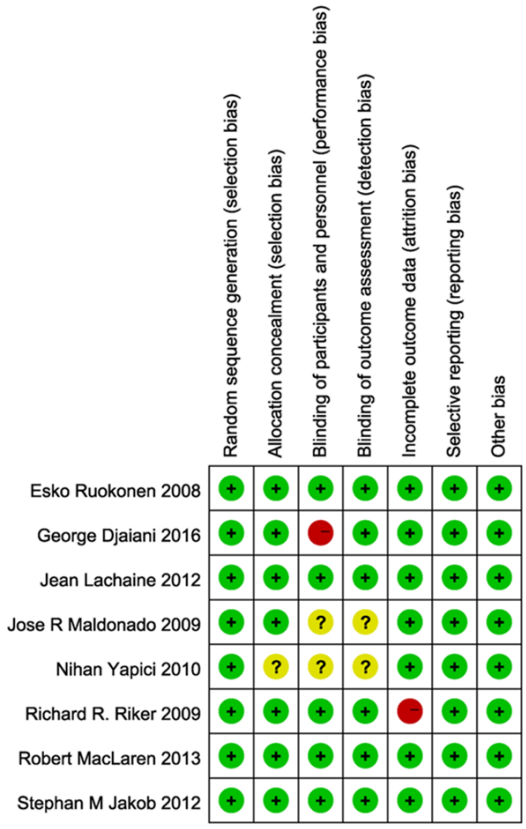

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

them showed a shorter mean length of ICU in the dexmedetomidine group. The pooled mean difference between dexmedetomidine and propofol/midazolam group was -1.62 D (95% CI: -1.75 to -1.50; P = 0.03), which suggested a statistically significant difference between the two groups. However, there was evidence of high heterogeneity (X^2: 13.48; I^2: 92.6%) among the studies (**Figure 6**).

Publication bias

Utilizing the length of ICU stay, through the funnel figure we evaluated potential publication bias as a destination. The funnel plot did not show the existence of publication bias (**Figure 7**).

Discussion

Main findings

Our meta-analysis, involving eight RCTs, investigated the sedation effect of dexmedetomidine and propofol/midazolam for the incidence of delirium in ICU patients, which indicated that dexmedetomidine made positive contribution to decreasing the occurrence of delirium, curtailing the duration of MV and the length of ICU stay comparing with propofol/midazolam in ICU patients.

Delirium

Currently, the most widely applied sedative and hypnotic medications are midazolam, benzodiazepines, lorazepam, and propofol. In the ICU, the most commonly used anesthetics are morphine and fentanyl [31]. Although these medications have been adopted in patients, more attention should still be focused on their adverse complications, especially when used in critically ill patients [32].

As is well-known, propofol has obvious advantages including short duration of action, hrapid onset after therapy, faster awakening after extubation, and especially its cost is much lower than other sedatives. However, propofol also has no negligible shortcomings such as leading to significant respiratory depression, aggravating the side effects of opioid analgesics and so on. Considering these defects of analgesic activity of propofol, it is quite necessary to establish an auxiliary opioid therapy [33]. While dexmedetomidine, unlike other anesthetics, induces a sedative state that is mostly similar to the human natural sleep. Patients could experience a clinically effective sedation when they received dexmedetomidine administration. However, patients are uniquely arousable and easily to be calm, which is not ordinarily

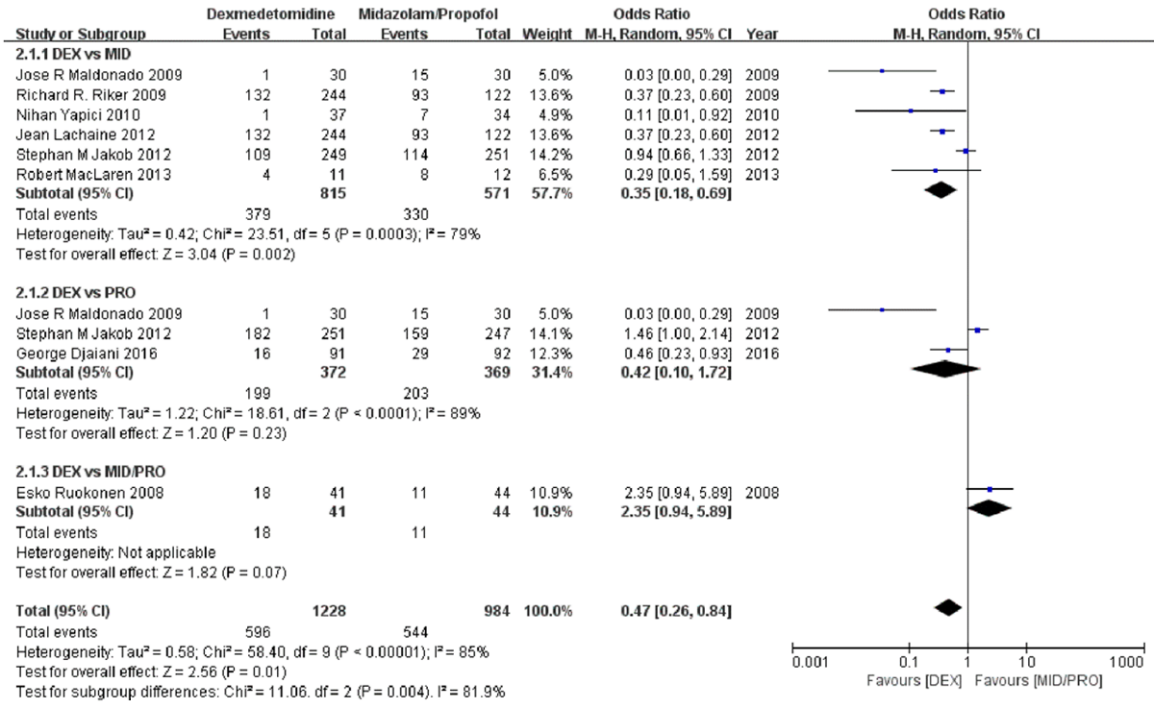

Figure 4. Forest plot of the effect of dexmedetomidine compared with midazolam/propofol sedation in ICU patients on the incidence of delirium. Diamond summary estimate is presented last for each outcome. Square size is proportional to study weight in this random effects meta-analysis. M-H indicates Mantel-Haenszel.

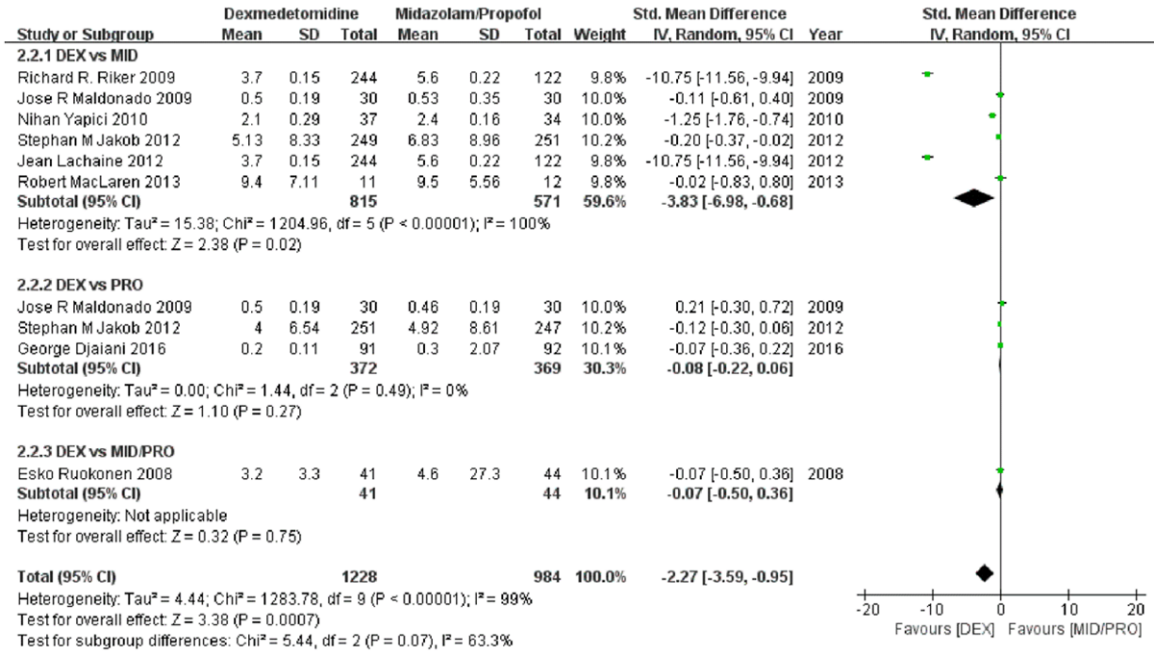

Figure 5. Forest plot of the effect of dexmedetomidine compared with midazolam/propofol sedation in ICU patients on the duration of MV in days. Diamond summary estimate is presented last for each outcome. Square size is proportional to study weight in this random effects meta-analysis. IV indicates inverse variance.

observed in any other clinically available sedatives [26].

Several studies have investigated the different impacts between propofol/midazolam and dex-

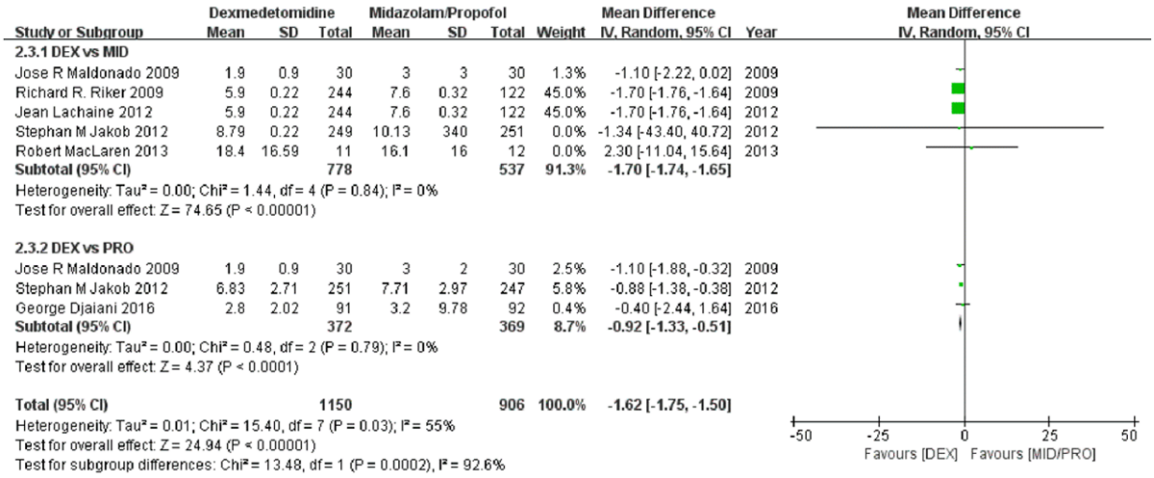

Figure 6. Forest plot of the effect of dexmedetomidine compared with midazolam/propofol sedation in ICU patients on the length of ICU stay in days. Diamond summary estimate is presented last for each outcome. Square size is proportional to study weight in this random effects meta-analysis. IV indicates inverse variance.

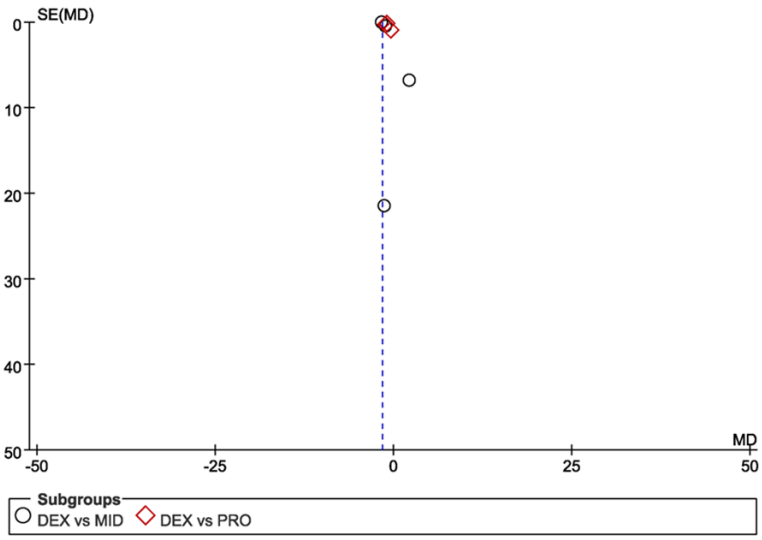

Figure 7. Funnel plot of comparison.

medetomidine in ICU patients [24, 25, 27, 30]. Among them have demonstrated that no significant differences or increasing emergency of delirium in ICU patients with these medications for sedation. Others, in contrast, have reported that dexmedetomidine would reduce the incidence of delirium compared with propofol/midazolam, when analyzing the incidence as a categorical or continuous variable [29, 30]. In marked contrast to propofol, dexmedetomidine protected or even promoted the impaired cognitive function in patients [34]. All of these seemingly conflictive results may be correlative with the equivocal definition of delirium.

The following specific characteristics of dexmedetomidine can be considered as the explanation for the lower occurrence rate of delirium in the dexmedetomidine group.

1) Dexmedetomidine is a highly selective and specific α-2-adrenoreceptor agonist [3, 35, 36].

2) Dexmedetomidine has an effect on presynaptic noradrenergic transmission [37, 38].

3) Dexmedetomidine provides sedation with little or even no respiratory depression [39].

4) Dexmedetomidine is absent of clinically significant anticholinergic effects [40-42].

5) Dexmedetomidine decreases the opioid requirements - an average of 40% lower [43, 44].

6) Dexmedetomidine is considered to provide a more physiological sleep-wake cycle for ICU patients [45, 46].

Ultimately, both in an animal ischemia model [47] and patients undergoing cardiac surgery [48], dexmedetomidine showed significant neuroprotective effects [49]. The combination of the above-mentioned characters of dexmede-

tomidine is related to the lower incidence and shorter duration of delirium. Hence, it is quite acceptable that administration of dexmedetomidine during the perioperative stage contributed to decreasing mortality after cardiac surgery [50], which is also in accordance with the results of our study.

As reported by many other studies, GABAergic agents, such as propofol and midazolam, have played segmental role in the occurrence and development of delirium, and even deteriorated further [51, 52]. Studies have demonstrated that administration of medications for postoperative sedation may be correlative with delirium by 1) disturbing physiological sleep patterns; 2) inducing a central mediated acetylcholine-deficient state; and 3) interfering with central cholinergic muscarinic transmission on the basal forebrain and hippocampus level [51, 53]. These may illuminate why midazolam or propofol induced incremental rates of delirium [52, 54].

MV and ICU

Postoperative sedation practices have sought an evolutionary process to get the target that patients were set a more balanced method of hypnotic and analgesia-based sedation. Recently, it has been demonstrated by several studies that the occurrence of delirium in cardiac surgery patients is reduced with the administration of dexmedetomidine, and has presented the benefits of this therapy in accelerating extubation for ICU patients [55].

Furthermore, Robert et al. found that, compared to benzodiazepines, dexmedetomidine could reduce the new-onset delirium as measured by the Intensive Care Delirium Screening Checklist (ICDSC), which is consistent with other previous studies that estimated delirium by the Confusion Assessment Method ICU. Additionally, part of this research indicates that the duration of MV itself may impact the incidence of delirium, with the shorter duration having the lower occurrence [25, 27, 56]. Furthermore, we found that despite similar length of ventilation, less delirium occurred with dexmedetomidine treatment.

Stephan and colleagues [27] observed that dexmedetomidine tended to decrease the mechanical ventilation time compared to midazolam but not propofol, while it reduced the extubation time compared to both midazolam and propofol. According to the studies, it is possible that patients' ability to exchange the painful feeling to the nursing staff has been enhanced with dexmedetomidine treatment, which has contributed to the earlier extubation [27].

Accordingly, compared with standard sedation, dexmedetomidine may exhibit relevant benefits in clinical which make patients better arousability and easier to express pain perception so that clinicians would make more appropriate use of opioids and facilitate earlier mobilization and quicker functional recovery [27].

RCTs have demonstrated in fast-track surgical patients: dexmedetomidine may be the more attractive choice in consideration of its unique pharmacological properties, including easy awakening and reduction of opioid drugs utilization. Moreover, other studies also showed significantly clinical improvements in terms of the length of ICU stay, when comparing the sedation effects between dexmedetomidine and propofol/midazolam. Similarly, our database analysis reports that dexmedetomidine makes contribution to shorter duration of MV, fewer days in ICU, and other benefits as well significantly.

Adverse effect

The ICU environment makes patients prefer to develop agitation and/or delirium on account of noradrenergic hyperfunction. Obviously, unsatisfying sedation can evoke an intense stress response, catecholamine release or even agitation, and also result in tachypnea, tachycardia, and hypertension [26].

Despite the fact that it has been a standard clinical practice to use propofol for postoperative sedation after cardiac surgery for over a decade, dexmedetomidine presents a more attractive alternative. It is the sympatholytic characteristic of dexmedetomidine that decreases plasma epinephrine and norepinephrine levels, and attenuates the high-dynamic physiological response to stress. Unlike other sedatives that are regularly utilized for the critically ill patients, dexmedetomidine has a peculiar mechanism of action displaying anxiolytic, sedative, and analgesic effect with little or even no respiratory depression [57].

Koroglu et al. [58] found that compared to midazolam, dexmedetomidine had a better quality of sedation and a higher degree of satisfaction, especially no significant adverse effects on hemodynamic or respiratory function. Siobal et al. [59] explained the reason why their patients who had failed previous attempts in extubation and could successful extubation after dexmedetomidine infusion that α-2-receptor stimulation cannot induce respiratory depression, while, dexmedetomidine maybe mitigates the transition of autonomous respiration for agitated patients' sedation.

The hemodynamic stress reaction arising from MV may be inhibited by dexmedetomidine, which may eliminate the emergence of agitation when the effect of sedation is phasing down. Therefore, this may be convenient for earlier extubation in some patients [26]. In consideration of the side effects, bradycardia was more familiar in dexmedetomidine treated patients, while hypertension and tachycardia were more familiar in midazolam treated patients [25].

In summary, Wiyeysundera et al. [48] reported that: α-2-adrenergic receptor agonists could make a contribution to the reduced number of ischemic episodes, the risk of myocardial infarction, and death. Their research also emphasized the risk of hypotension in the cardiac surgery, and had no statistically significant differences in terms of increasing the occurrence of bradycardia, hypotension, heart failure, or others.

Limitations

We acknowledge that some limitations are worth to be considered in this meta-analysis. First of all, only eight relevant individual RCTs were involved in the analytical results. Additionally, it was not the right equivalent method for patients (medical/surgical/trauma) with the sedation management of dexmedetomidine and propofol/midazolam among all included studies (**Table 1**). This may be reconciled as a source of heterogeneity affecting the accuracy. Afterwards, if the studies that included two different cohorts of patients and have changed the clinical staff during the various study time frames, our results may be influenced potentially. In addition, the impact of publication bias cannot be easily neglected. Last but not least, additional important parameters related to the two sedatives were not considered in this meta-analysis, which may make this research results underpowered to verify and not reveal a statistically significant difference.

Conclusions

In summary, dexmedetomidine has already played an indispensable role in sedation among ICU patients. Furthermore, dexmedetomidine, as the sedative agent, is associated with conspicuously lower rates of delirium, shorter duration of MV and length of ICU stay, comparing with propofol/midazolam. Despite all of those, in order to ensure the specific clinical application value of dexmedetomidine, it is still necessary to organize larger samples, higher-quality and adequately powered RCTs of dexmedetomidine in terms of focusing on the emergence of delirium, the MV duration, the length of ICU and/or hospital stay, and opioid drugs requirement.

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Disclosure of conflict of interest

None.

Abbreviations

ICU, Intensive Care Unit; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MV, mechanical ventilation; WMD, Weighted Mean Difference; CI, confidence interval; GABA, γ-aminobutyric acid; FDA, Food and Drug Administration; RCTs, Randomized Controlled Trials; CENTRAL, Cochrane Central Register of Controlled Trials; RR, relative risk; MD, mean difference; CI, confidence interval; REVMAN, Review Manager; SD, standard deviation; IQR, interquartile range; POD, Postoperative Delirium; ICDSC, Intensive Care Delirium Screening Checklist; IV, inverse variance; M-H, Mantel-Haenszel.

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