

Review

Efficacy and safety of sedation with dexmedetomidine in critical care patients: A meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Dexmedetomidine may help physicians target a low level of sedation. Unfortunately, the impact of dexmedetomidine on major endpoints remains unclear in intensive care unit (ICU).

Material and methods: To evaluate the association between dexmedetomidine use with efficacy and safety outcomes, two reviewers independently identified randomized controlled trials comparing dexmedetomidine with other sedative agents in non-post-cardiac surgery critically ill patients in the PubMed and Cochrane databases. Random effects models were considered if heterogeneity was detected using the DerSimonian and Laird estimation method. Statistical heterogeneity between results was assessed by examining forest plots, confidence intervals (CI) and by using the I^2 statistic. The risk of bias was assessed using the risk of bias tool.

Results: This meta-analysis included 1994 patients from 16 randomized controlled trials. Comparators were lorazepam, midazolam and propofol. Dexmedetomidine was associated with a reduction in ICU length of stays (WMD = -0.304 ; 95% CI [-0.477 , -0.132]; $P = 0.001$), mechanical ventilation duration (WMD = -0.313 , 95% CI [-0.523 , -0.104]; $P = 0.003$) and delirium incidence (RR = 0.812 , 95% CI [0.680 , 0.968]; $P = 0.020$). Dexmedetomidine is also associated with an increase in the incidence of bradycardia (RR = 1.947 , 95% CI [1.387 , 2.733]; $P = 0.001$) and hypotension (RR = 1.264 ; 95% CI [1.013 , 1.576]; $P = 0.038$).

Conclusions and relevance: In this first meta-analysis including only randomized controlled trials related to ICU patients, dexmedetomidine was associated with a 48 h reduction in ICU length of stay, mechanical ventilation duration and delirium occurrence despite a significant heterogeneity among studies. Dexmedetomidine was also associated with an increase in bradycardia and hypotension.

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1. Introduction

In intensive care units (ICUs), sedation is aimed at reducing discomfort, metabolic demands during organ failure and increasing tolerance towards mechanical ventilation [1]. Sedation should

be considered as a tool helping physicians care for critically ill patients. The most recent clinical practice guidelines in the USA used the term “management of pain, agitation and delirium”, rather than “sedation”, in the title [2]. Only those patients with acute respiratory distress syndrome (ARDS) or with brain injury and intracranial hypertension require deep sedation. Notwithstanding these recommendations, observational studies have shown that patients are still deeply sedated in our ICU [3–5]. The occurrence of deep sedation in the first 48 hours after initiation of mechanical ventilation is associated with an increase

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in long-term mortality [6,7]. In a recent pilot study, Shehabi et al. [8] demonstrated that an early, goal-directed to target, light sedation is feasible and safe. In this algorithm, early goal-directed sedation was provided via dexmedetomidine.

Dexmedetomidine is an α -2 receptor agonist with sedative, analgesic and anxiolytic properties [9] that is used for light to mild sedation. Although dexmedetomidine is a first line drug for sedation in ICUs [2], its impact on patient outcomes remains undetermined. New trial results, such as the large randomized controlled trials (RCTs) published by Jakob and al. [10], have yet to be included in any meta-analysis of RCTs in ICU patients. Thus, this updated meta-analysis compared dexmedetomidine with other sedative agents in terms of duration of mechanical ventilation, length of stay in the ICU, delirium, mortality and adverse events.

2. Methods

2.1. Populations, comparators, outcomes

This meta-analysis included only RCTs of adult patients admitted to ICUs that compared dexmedetomidine with another sedative agent, with or without opioid association. RCTs of patients who underwent cardiac surgery, and trials of sedation started preoperatively in patients who required postoperative admissions, were excluded.

The main study outcomes were efficacy outcomes: ICU length of stay and duration of mechanical ventilation. Secondary outcomes were safety outcomes: rates of death, bradycardia, hypotension and delirium.

2.2. Search strategy for identification of studies

We searched the PubMed and the Cochrane databases, using the following keywords dexmedetomidine, sedation, intensive care, and postoperative. Trials published between January 2000 and June 2014 in English or French were included.

2.3. Study selection

Titles and abstracts of studies identified by searching the PubMed and Cochrane databases were screened to determine if they met the inclusion criteria. The full texts of articles that met the inclusion criteria were read, and relevant data extracted.

2.4. Data abstraction and management

Two reviewers (JMC and AM) independently extracted data, including outcomes of interest, demographics of the enrolled patient population, inclusion and exclusion criteria for each study, the comparative drug used, the number of patients in each group, sedation targets and posology. Discrepancies between reviewers were resolved through consensus discussions. Data were managed using Microsoft Excel 2010 (Microsoft corporation, Redmond, WA, USA).

2.5. Measures of treatment effect

Efficacy outcomes (length of ICU stay, duration of mechanical ventilation, and incidence of delirium) were the primary study outcomes. Safety outcomes (rates of bradycardia and hypotension requiring interventions, and in-hospital mortality) were the secondary study outcomes. All outcomes were planned before data extraction. All statistical analyses were performed using Comprehensive Meta-analysis software (version 2, Biostat Corporation). Random effects models were considered if heterogeneity was detected using the DerSimonian and Laird estimation method.

Statistical heterogeneity between results was assessed by examining forest plots, confidence intervals and by using the I^2 statistic, the most common (and easily interpretable) metric for measuring the magnitude of between-study heterogeneity. I^2 values range between 0% and 100%, with < 25% considered as low, 25–50% considered as modest, and > 50% considered as high [10]. This statistical method generally assumes heterogeneity when the P -value of the I^2 test is < 0.05. Publication bias was assessed by a funnel plot [11]. Categorical outcomes are reported as relative risks (RR) with their associated 95% confidence intervals (CI); continuous outcomes are reported as weighted mean differences (WMD). All analyses were performed to independently assess propofol, benzodiazepines (BZD) and global effects (propofol + BZD).

3. Results

Among the 260 studies initially identified, 15 articles describing 16 RCTs were included [8,10,12–24], with one of the articles reporting two RCTs [10]. The study flowchart is shown on Fig. 1. The 16 RCTs included 1994 patients from 19 countries. Seven studies compared dexmedetomidine with propofol alone [10,12,13,19,20,22,24], five with midazolam alone [10,15,17,21,23], two with either propofol or midazolam [8,18], one with lorazepam [14] and one with haloperidol [16]. Six studies evaluated patients admitted to ICUs postoperatively [12,13,15,20,22,24], with one evaluating women admitted after caesarean section [15]. Eight studies were blinded, [10,13,14,17,18,23,24]

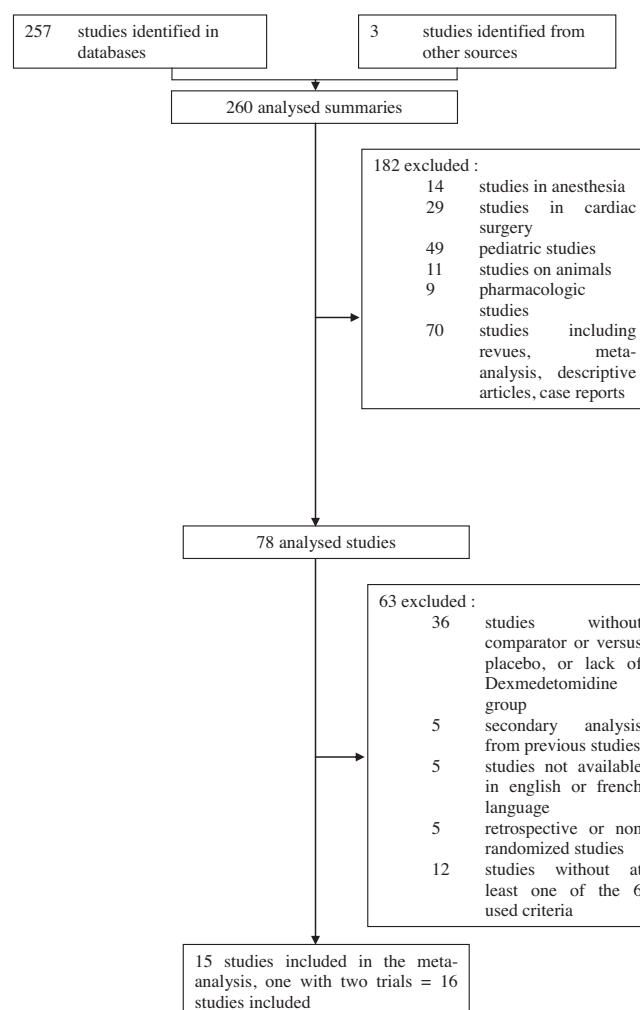


Fig. 1. Flowchart showing study inclusion and exclusion for the meta-analysis.

Table 1
Description of the trials included in the meta-analysis.

Source	Year of publication	Countries involved	Population	Inclusion criteria	Exclusion criteria	Number of patients	Posology	Control	Number of patients	Posology	Target sedation	Blinding	Criteria
Venn and Grounds [12]	2001	United Kingdom	Complex major abdominal or pelvic surgery	Requirement for a minimum of 8 h artificial ventilation		10	Loading dose: 2.5 µg/kg/h over 10 min. Maintenance infusion: 0.2–2.5 µg/kg/h	Propofol	10	Loading dose: 1 mg/kg over 10'. Maintenance: 1–3 mg/kg/h	RSS > 2	Non-blinded	Bradycardia Mortality
Elbaradie et al. [13]	2004	Egypt	Major thoracic, abdominal or pelvic cancer surgeries	Minimum of 6-hour postoperative sedation and ventilation	Neurosurgical procedures, known allergy to propofol or dexmedetomidine, known or suspected pregnancy, gross obesity (over 50% above ideal body weight), severe hepatic or renal disease where the neurologic condition was difficult to evaluate, spinal or epidural anaesthesia, history of corticosteroid therapy within the last 3 months, or uncontrolled diabetes	30	Loading dose: 2.5 µg/kg/h over 10 min. Maintenance infusion: 0.2–0.5 µg/kg/h	Propofol	30	Loading dose: 1 mg/kg. Maintenance: 0.5–1 mg/kg	RSS 2–5	Blinded	Bradycardia Hypotension
Pandharipande et al. [14]	2007	United States	Medical and surgical ICU	Need for mechanical ventilation more than 24 hours	Neurological disease (previous stroke, cerebral palsy, etc) that would confound the diagnosis of delirium, active seizures, Childs-Pugh class B or C liver disease, moribund state with planned withdrawal of life support, family or physician refusal, alcohol abuse, active myocardial ischemia, second- or third-degree heart block, severe dementia, benzodiazepine dependency, pregnancy or lactation, and severe hearing disabilities or inability to understand English to allow delirium evaluations	52	Maintenance infusion: 0.15–1.5 µg/kg/h	Lorazepam	51	Maintenance infusion: 1–10 mg/h		Double-blinded	Bradycardia Delirium Hypotension Length of stay Mortality
Esmaglu et al. [15]	2009	Turkey	Eclampsia patients	Caesarean delivery and need for ventilatory support	Chronic hypertension; cardiac, neurological, hepatic, renal, or endocrinal disease; or allergic reactions to the medicine used during the treatment or developed the Haemolysis, Elevated Liver Enzymes and Platelets (HELLP) syndrome	20	Loading dose: 1 µg/kg over 20 min. Maintenance infusion: 0.7 µg/kg/h	Midazolam	20	Loading dose: 0.05 mg/kg. Maintenance: 0.1 mg/kg	RSS 2–3	Non-blinded	Length of stay
Reade et al. [16]	2009	Australia	Medical and surgical ICU	Patients considered as requiring mechanical ventilation only because their degree of agitation required such a high dose of sedative medication that extubation was not possible	Patients who could not be extubated even if their agitation was corrected	10	Optional loading dose: 1 µg/kg over 20 min. Maintenance infusion: 0.2–0.7 µg/kg/h	Haloperidol	10	Optional loading dose: 2.5 mg/kg. Maintenance infusion: 0.5–2 mg/kg	RASS 0	Non-blinded	Bradycardia Hypotension Length of stay Length of ventilation Mortality

Table 1 (Continued)

Source	Year of publication	Countries involved	Population	Inclusion criteria	Exclusion criteria	Number of patients	Posology	Control	Number of patients	Posology	Target sedation	Blinding	Criteria
Riker et al. [17]	2009	United States, Australia, Brazil, Argentina, New-Zealand	Medical and surgical ICU	Patients aged 18 years or older; intubated and mechanically ventilated for less than 96 hours prior to start of study drug with an anticipated ventilation and sedation duration of at least 3 more days	Trauma or burns as admitting diagnoses; dialysis of all types; pregnancy or lactation; neuromuscular blockade other than for intubation; epidural or spinal analgesia; general anaesthesia 24 hours prior to or planned after the start of study drug infusion; serious central nervous system pathology (acute stroke, uncontrolled seizures, severe dementia), acute hepatitis or severe liver disease (Child-Pugh class C); unstable angina or acute myocardial infarction; left ventricular ejection fraction less than 30%; heart rate less than 50 bpm; second- or third-degree heart block; or systolic blood pressure less than 90 mmHg despite continuous infusions of 2 vasopressors before the start of study drug infusion	244	Optional loading dose: 1 µg/kg. Maintenance infusion: 0.8 µg/kg/h	Midazolam	122	Optional loading dose: 0.05 mg/kg. Maintenance infusion: 0.06 mg/kg/h	RASS –2/+1	Double-blinded	Bradycardia Delirium Hypotension Length of stay Length of ventilation Mortality
Ruokonen et al. [18]	2009	Finland, Switzerland	Medical and surgical ICU	Age > 18 years; mechanical ventilation, need for sedation for > 24 h after randomization, expected ICU stay > 48 h	Acute severe neurological disorder; mean arterial pressure < 55 mmHg despite volume and vasopressors; heart rate < 50 bpm; AV-conduction block II–III (unless pacemaker installed); hepatic Sequential Organ Failure Assessment (SOFA) score > 2; bilirubin > 101 µmol/L; lactation or positive pregnancy test; muscle relaxation, loss of hearing or vision, any other condition interfering with RASS assessment; use of α2-agonists or antagonists at the time of randomization	41	Loading dose: 0.8 µg/kg over 60 min. Maintenance infusion: 0.25–1.4 µg/kg/h	Midazolam or Propofol	44	Loading dose: 2.4 mg/kg/60'. Maintenance: 0.8–4 mg/kg/h. M loading dose: 0.12 mg/kg/60'. M maintenance: 0.04–0.2 mg/kg/h	RASS –3/–1 or RASS –4	Double-blinded	Bradycardia Delirium Hypotension Length of stay Length of ventilation Mortality
Memiş et al. [19]	2009	Turkey	Septic shock	Clinical and laboratory criteria of septic shock; patients conventionally resuscitated and haemodynamically stable	Known allergy to propofol or dexmedetomidine; patients with known or suspected brain death; unstable haemoglobin levels (change in haemoglobin > 0.5 g/dL); significant arrhythmias; acute myocardial ischemia (continuous ST-segment analysis); patients requiring continuous renal replacement therapy; pregnancy; and age below 18 years	20	Loading dose: 1 µg/kg over 10'. Maintenance infusion: 0.2–2.5 µg/kg/h	Propofol	20	Loading dose: 1 mg/kg over 15'. Maintenance: 1–3 mg/kg/h	RSS < 2	Non-blinded	Length of stay Mortality
Tasdogan et al. [20]	2009	Turkey	Admission after ileus surgery	Patients requiring postoperative sedation and ventilation, with two criteria for sepsis	Known allergy to propofol or dexmedetomidine; possible or confirmed pregnancy; presence of one of the following conditions at randomization: haemodynamic instability (defined as a systolic blood pressure < 100 mmHg), heart failure (New York Heart Association class III or IV), renal failure (Rifle classification), liver failure (manifested by serum total protein concentration < 3 g/dL, and total bilirubin > 5 mg/dL), and known or suspected brain death	20	Loading dose: 1 µg/kg over 10'. Maintenance infusion: 0.2–2.5 µg/kg	Propofol	20	Loading dose: 1 mg/kg over 15'. Maintenance: 1–3 mg/kg/h	RSS < 2	Non-blinded	Length of stay Length of ventilation Mortality

Table 1 (Continued)

Source	Year of publication	Countries involved	Population	Inclusion criteria	Exclusion criteria	Number of patients	Posology	Control	Number of patients	Posology	Target sedation	Blinding	Criteria
Huang et al. [21]	2012	China	Acute cardiogenic respiratory failure under NIV	Patients older than 18 years of age; signs and symptoms consistent with acute cardiogenic pulmonary oedema; NIV failure due to patient refusal to continue NIV because of discomfort, claustrophobia or marked agitation	Poor respiratory state requiring immediate intubation; a clear alternative primary diagnosis such as pneumonia; severely altered consciousness; any patient requiring an immediate lifesaving intervention such as cardiopulmonary resuscitation, airway control, cardioversion or inotropic support; any patient requiring thrombolysis or percutaneous coronary intervention for acute ST-segment elevation myocardial infarction	33	Optional loading dose: 1 µg/kg. Maintenance infusion: 0.2–0.7 µg/kg/h	Midazolam	29	Optional loading dose: 0.05 mg/kg. Maintenance: 0.05–1 mg/kg	RSS 2–3	Non-blinded	Bradycardia Delirium Hypotension Length of stay Mortality
Jakob et al. [10]	2012	Belgium, Finland, Germany, Netherlands, Russia, Switzerland, United Kingdom	Medical and surgical ICU	Age 18 years or older; invasive mechanical ventilation, clinical need for light to moderate sedation using midazolam or propofol infusion expected to last for 24 hours or longer after randomization, and randomization within 72 hours of ICU admission and within 48 hours of starting continuous sedation	Acute severe neurological disorder, mean arterial pressure less than 55 mmHg despite appropriate intravenous volume replacement and vasopressors, heart rate less than 50 bpm, atrioventricular-conduction grade II or III (unless pacemaker installed), and use of α2-agonists or antagonists within 24 hours prior to randomization	249	Maintenance infusion: 0.2–1.4 µg/kg/h	Midazolam	251	Maintenance infusion: 0.03–0.2 mg/kg/h	RASS –3/0	Double-blinded	Bradycardia Delirium Hypotension Length of stay Length of ventilation Mortality
Jakob et al. [10]	2012	Belgium, Finland, Germany, Netherlands, Russia, Switzerland, United Kingdom	Medical and surgical ICU	Age 18 years or older; invasive mechanical ventilation, clinical need for light to moderate sedation using midazolam or propofol infusion expected to last for 24 hours or longer after randomization, and randomization within 72 hours of ICU admission and within 48 hours of starting continuous sedation	Acute severe neurological disorder, mean arterial pressure less than 55 mmHg despite appropriate intravenous volume replacement and vasopressors, heart rate less than 50 bpm, atrioventricular-conduction grade II or III (unless pacemaker installed), and use of α2-agonists or antagonists within 24 hours prior to randomization	251	Maintenance infusion: 0.2–1.4 µg/kg/h	Propofol	249	Maintenance infusion: 0.3–4 mg/kg/h	RASS –3/0	Double-blinded	Bradycardia Delirium Hypotension Length of stay Length of ventilation Mortality
Terao et al. [22]	2011	Japan	Extensive cervical spine surgery	Patients undergoing extensive cervical spine surgery who required postoperative endotracheal intubation and mechanical ventilation under sedation overnight	Preoperative endotracheal intubation, patients younger than 18 years of age	16	Loading dose: 0.1 µg/kg/min over 10'. Maintenance infusion: 0.4 µg/kg/h	Propofol	16	Loading dose: 0.1 mg/kg/min over 10'. Maintenance: 1 mg/kg/h	RSS 2–4	Non-blinded	Length of stay Length of ventilation

Table 1 (Continued)

Source	Year of publication	Countries involved	Population	Inclusion criteria	Exclusion criteria	Number of patients	Posology	Control	Number of patients	Posology	Target sedation	Blinding	Criteria
Shehabi et al. [7]	2013	Australia, New-Zealand	Medical and surgical ICU, mainly medical	Patients intubated within the previous 12 hours, expected to require mechanical ventilation for longer than 24 hours, and required immediate and ongoing sedation	Age less than 18 years; pregnancy proven or suspected; primary neurological injury; diagnosis likely to result in prolonged weakness; drug overdose; burn injury; acute liver failure; dementia, or psychiatric illness; need for ongoing neuromuscular blockade, palliative care, or treatment limitations; inability to communicate in English; mean blood pressure less than 55 mmHg; heart rate less than 55 bpm; high-grade AV block in the absence of functioning pacemaker	21	Maintenance infusion: 0–1.5 µg/kg/h	Midazolam or Propofol	16	Dose titrated to achieve the desired level of sedation	RASS –2/+1	Non-blinded	Delirium Length of stay Length of ventilation Mortality
MacLaren et al. [23]	2014	United States	Medical and surgical ICU, mainly medical	Patients requiring mechanical ventilation and receiving a benzodiazepine infusion with an anticipated need of at least 12 additional hours of sedation at a Riker sedation agitation score of 3 to 4, qualified for daily awakenings	Age less than 18 or greater than 85 years; administration of benzodiazepines for purposes other than sedation; administration of neuromuscular blockers for more than 12 hours; administration of epidural medications; active myocardial ischemia; second- or third-degree heart block; haemodynamic instability; active neuromuscular disease; Childs-Pugh class C liver disease; alcohol abuse within 6 months of study eligibility; baseline dementia; solid organ transplant; pregnancy; moribund state with planned withdrawal of life support; enrolment in another therapeutic study; or known or suspected severe adverse reactions to any benzodiazepines, dexmedetomidine, or clonidine	11	Maintenance infusion: 0.15–1.5 µg/kg/h	Midazolam	12	Maintenance infusion: 1–10 mg/kg/h	Riker 3–4	Double-blinded	Bradycardia Delirium Hypotension Length of stay Length of ventilation Mortality
Chen et al. [24]	2014	China	Oral and maxillofacial surgery (OMS)	Patients aged 18–50, ASA I to II, requiring postoperative nasal endotracheal intubation under overnight sedation	Pregnant or lactating women, respiratory or cardiac, bradycardia (baseline heart rate < 60 bpm), arterioventricular block or hypotension (baseline systolic arterial pressure < 90 mmHg), abuse of alcohol or drugs, intolerance to or allergy to dexmedetomidine or propofol, inability or refusal to give informed consent	33	Loading dose: 1 µg/kg for 10 min. Maintenance: 0.4 µg/kg/h in the recovery room, then 0.2–0.7 µg/kg/h in the ICU	Propofol	33	Loading dose: 0.1 mg/kg for 10'. Maintenance: 1–2 mg/kg/h		Double-blinded	Bradycardia Hypotension

ICU: intensive care unit.

and 11 used a loading dose [12,13,15–22,24]. Dexmedetomidine infusion rates ranged from 0 to 2.5 µg/kg/h. Characteristics of the various included studies are shown in Table 1.

3.1. Efficacy outcomes

There was significant heterogeneity concerning the length of stay in the ICU (global $I^2 = 56\%$; propofol $I^2 = 67\%$; BZD $I^2 = 42\%$). Sedation with dexmedetomidine was associated with a 48 hour-reduction of length of stay in the ICU versus benzodiazepines and propofol (WMD = -0.304 ; 95% CI $[-0.477, -0.132]$; $P = 0.001$) (Fig. 2). There was no difference between propofol and BZD (Random effect analysis BZD 95% CI $[-0.544, -0.021]$, propofol 95% CI $[-0.635, -0.079]$, $P = 0.704$).

Heterogeneity for the duration of mechanical ventilation was also observed (global $I^2 = 63.3\%$; propofol $I^2 = 68\%$; BZD $I^2 = 39\%$), although duration was two days significantly shorter for patients given dexmedetomidine (WMD = -0.313 , 95% CI $[-0.523, -0.104]$; $P = 0.003$). There was no difference between propofol and BZD (Random effect analysis BZD 95% CI $[-0.709, 0.0]$ propofol 95% CI $[-0.589, -0.015]$, $P = 0.778$).

Dexmedetomidine was associated with a significant reduction in delirium incidence (RR = 0.812, 95% CI $[0.680, 0.968]$; $P = 0.020$; global $I^2 = 32\%$; propofol $I^2 = 0\%$; BZD $I^2 = 39\%$) (Fig. 3). There was no difference between propofol and BZD (Random effect analysis BZD 95% CI $[-1.855, 0.064]$ propofol 95% CI $[-1.186, 0.236]$, $P = 0.6$).

3.2. Safety outcomes

Dexmedetomidine did not influence mortality rate (RR = 1.009; 95% CI $[0.833, 1.221]$; $P = 0.931$; $I^2 = 0\%$). There was no difference

between propofol and BZD (Random effect analysis BZD 95% CI $[0.865, 1.35]$ propofol 95% CI $[0.572, 1.207]$, $P = 0.237$). Use of dexmedetomidine was significantly associated with increased rates of bradycardia (RR = 1.947, 95% CI $[1.387, 2.733]$; $P = 0.001$; global $I^2 = 39.7\%$, propofol $I^2 = 24\%$; BZD $I^2 = 34\%$) and hypotension (RR = 1.264; 95% CI $[1.013, 1.576]$; $P = 0.038$; global $I^2 = 30\%$; propofol $I^2 = 7\%$; BZD $I^2 = 45\%$). There was no difference between propofol and BZD for both parameters with respectively (Random effect analysis BZD 95% CI $[1.447, 3.343]$, propofol 95% CI $[0.867, 2.749]$, $P = 0.331$) and (Random effect analysis BZD 95% CI $[0.966, 1.759]$, propofol 95% CI $[0.797, 1.943]$, $P = 0.866$).

4. Discussion

This meta-analysis demonstrated that compared with midazolam and propofol, the use of dexmedetomidine was associated with a 48 hour-reduction in ICU length of stay and duration of mechanical ventilation. Dexmedetomidine was associated with a significant reduction in delirium incidence. However, bradycardia and hypotension were more frequently reported with the use of dexmedetomidine.

Our study was different from 3 previously published meta-analyses as concerns certain endpoints. First, we included only RCTs performed in ICUs and excluded the preoperative administration of dexmedetomidine. Second, studies related to post-cardiac surgery patients were excluded because in this setting, patients have a reduced ICU length of stay and are ventilated only for few hours. Moreover, inflammation associated with the latte is related to a specific pathway (extracorporeal circulation and ischemia-reperfusion). Therefore, findings from post-cardiac surgery ICU patients are not extrapolated to general ICU patients.

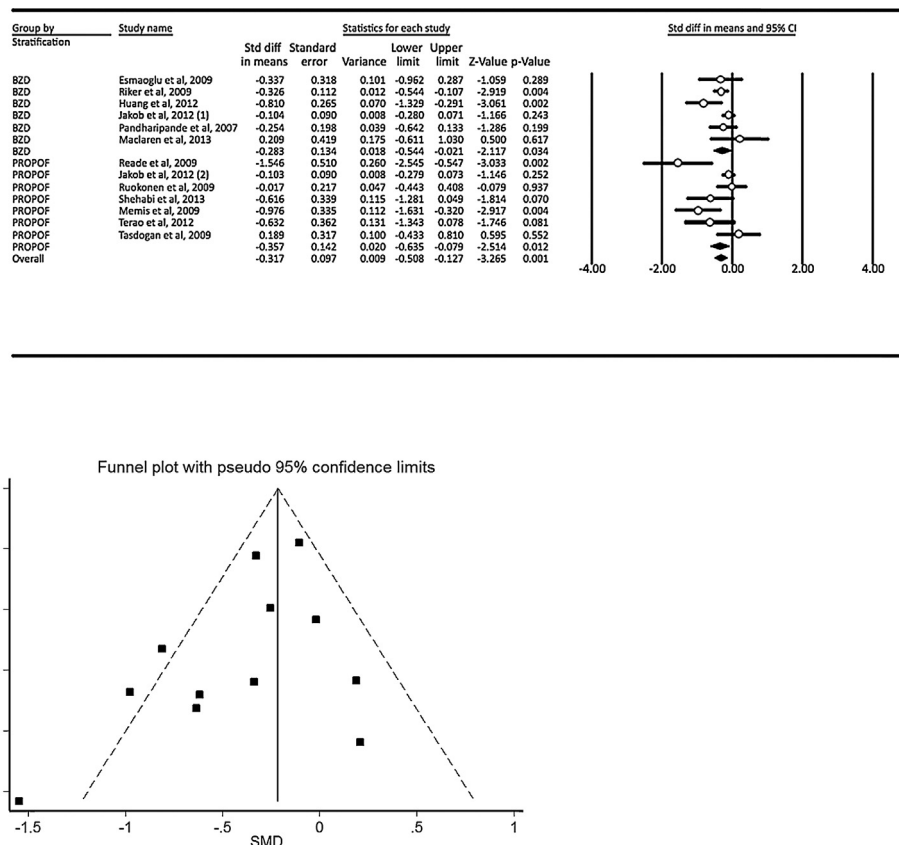


Fig. 2. Effect of dexmedetomidine on the length of stay and related funnel plot.

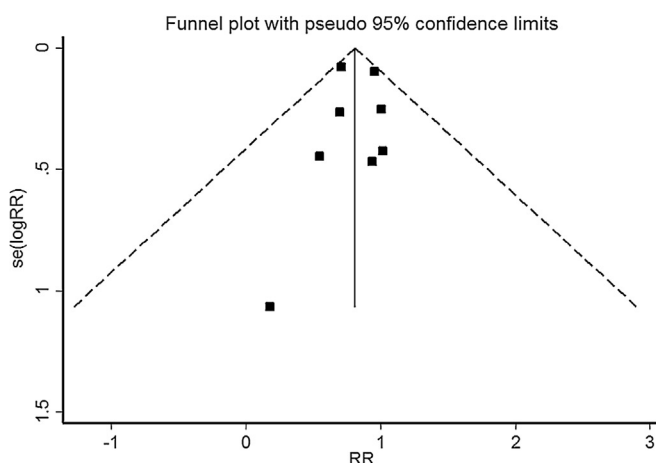
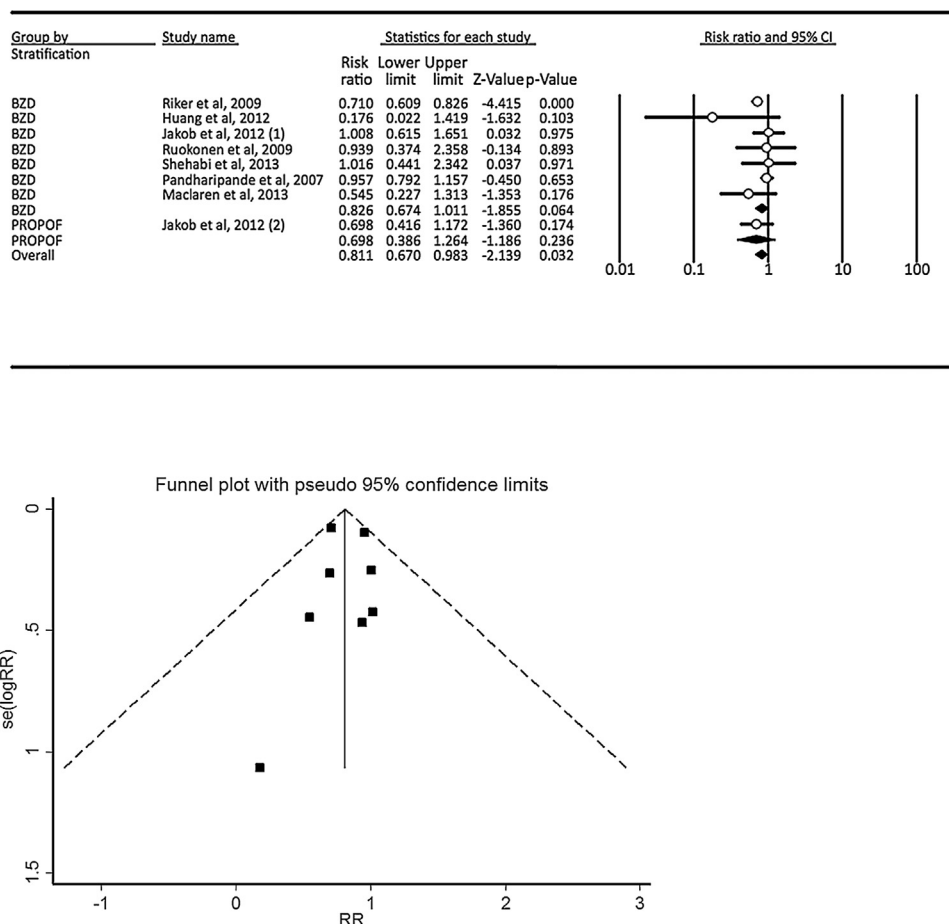


Fig. 3. Effect of dexmedetomidine on delirium incidence and related funnel plot.

Third, 2 large double-blinded RCTs were included and obviously have influenced our results [10].

The reduction in length of ICU stay confirms the results of three previously published meta-analyses [25], but only one of these has also shown that dexmedetomidine reduced the duration of mechanical ventilation [26]. In contrast to other hypnotics, dexmedetomidine induces minimal and non-clinically relevant changes in respiratory drive [9]. Since patients must be awake or aroused prior to performing spontaneous breathing tests [27], beginning the weaning process earlier results in earlier spontaneous breathing tests in awake patients. Regardless of the comparator, patients on dexmedetomidine are more likely to be awake, aroused and communicating [10].

The lower incidence of delirium with dexmedetomidine is in good agreement with the results of one meta-analysis [25] and the results of a study based on post-cardiac ICU patients [28]. The inclusion of new, large RCTs probably explains why the present meta-analysis did not report findings similar to previous ones [29]. The reduction of sedation-induced delirium is suitable from a pathophysiological point of view. In contrast to other hypnotics, the mechanism of action of dexmedetomidine is not mediated by GABA receptors. Modulation of GABA receptor activity is a well-known trigger of delirium mediated by sleep pathway disturbances [30]. This reduction of delirium incidence may partly explain the reduction in length of stay and duration of mechanical ventilation associated with dexmedetomidine [31]. Nevertheless, certain limitations related to delirium evaluation must be stressed. The criteria used to assess delirium vary among studies, and include delirium days, delirium free days, and delirium prevalence.

In addition, methods of evaluation vary, with some studies using the CAM-ICU instrument and others mixed criteria [32].

The mechanism of action of dexmedetomidine involves its binding to α_2 -receptors, which may explain the increased rate of bradycardia in these patients. Similar findings were observed in one previous meta-analysis [26]. Use of a loading dose and high infusion doses have been reported as risk factors for bradycardia [22,29]. Eleven studies included in our meta-analysis used a loading dose, with a mean of 1 $\mu\text{g/kg}$ in 10 to 60 minutes, although some patients received loading doses as high as 2.5 $\mu\text{g/kg}$. Infusion doses were as high as 2.5 $\mu\text{g/kg/h}$. Avoiding loading doses may reduce the incidence of bradycardia. Many treatments associated with dexmedetomidine in ICUs can worsen bradycardia, including treatments with anti-arrhythmic agents and opioids. Bradycardias in these studies were rarely severe, with reductions in infusions allowing heart rates to return to normal range [17,18]. Most of the studies included in our meta-analyses excluded patients with a low heart rate at admission and those with atrioventricular blockades without pacing. In contrast to other meta-analyses, we observed significant hypotension associated with dexmedetomidine. However, this result had borderline significance.

This study has several limitations. Although we excluded studies that involved post-cardiac-surgery ICU patients, the included studies were heterogeneous. Most studies included both medical and surgical patients, whereas others included medical patients only, reflecting the heterogeneous populations admitted to ICUs. Sedation protocols also differed among studies, with differences including the type of comparative hypnotic, the use or not of a loading dose or an adjunct opioid, and the possibility of

another rescue hypnotic. Only half of the studies were blinded, and sedation objectives differed. Interestingly, previous meta-analyses found that the dexmedetomidine-associated benefits in regards to length of stay and duration of ventilation **did not affect mortality** rates. However, even this criterion differed among studies, and included deaths prior to discharge from the hospital, or after 28 or 30 days or 3 months. Overall, **no study was designed to show a statistical difference in mortality**. Moreover, the time to randomization was long in all studies, with the exception of a preliminary study by Shehabi [8]. The time to randomization was up to 96 hours in SEDCOM and 72 hours in MIDEX and PRODEX, allowing non-protocol sedatives to be used unchecked in the first 3 to 4 days. An early goal-directed sedation may be able to show changes in mortality, but this issue will be addressed in the SPICE III trial (NCT01728558).

5. Conclusion

In conclusion, in association with significant heterogeneity among the included studies, dexmedetomidine (as compared to midazolam and propofol) was associated with a 48 hour-reduction in length of ICU stay and duration of mechanical ventilation, as well as a decrease in incidence of delirium. Dexmedetomidine was also associated with increased incidences of bradycardia and hypotension. Awareness of these adverse events must be raised, even if our meta-analysis is not able to describe their clinical relevance.

Disclosure of interest

AM, BP, SP and SC declare that they have no competing interest.
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