TITLE: Dexmedetomidine for Sedation of Patients in the ICU or PICU: Review of Clinical Effectiveness and Safety

DATE: 16 January 2014

CONTEXT AND POLICY ISSUES

Sedation of ICU patients is often essential for ICU patients to maximize survival, reduce ICU and hospital stay, and facilitate mechanical ventilation.[1] The standard of care for sedation include benzodiazepine sedatives and propofol.[1] Some drawbacks of the available sedative agents include patients' agitation and delirium. To overcome these drawbacks, it has been suggested that dexmedetomidine can be an appropriate alternative to traditional sedatives for maintaining light to moderate sedation.[1,2] However, the Health Canada approved label for dexmedetomidine provides warnings that the drug is associated with hypotension, clinically significant episodes of bradycardia, and sinus arrest.[3]

The objective of the current review is to evaluate the evidence surrounding the use of dexmedetomidine for sedation in intensive-care units.

RESEARCH QUESTION

What is the clinical effectiveness and safety of dexmedetomidine for sedation of patients in the ICU/PICU compared with traditional sedatives?

KEY FINDINGS

Four meta-analyses, one systematic review, and five randomized-controlled trials were included in this review. The available evidence indicates the use of dexmedetomidine was associated with decreased ICU stay and decreased time on mechanical ventilation. However, it was associated with higher rates of bradycardia than comparators.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between January 1, 2008 and December 3, 2013.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed for relevance. Full texts of any relevant titles/abstracts were retrieved, and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult and pediatric patients requiring sedation in ICU/PICU
Intervention	Dexmedetomidine
Comparator	Traditional sedatives such as midazolam, lorazepam, propofol, ketamine, and narcotics
Outcomes	Efficacy: Length of stay in ICU/PICU; duration of mechanical ventilation; time to extubation; other clinical benefits. Safety: Incidence of delirium or severe agitation and adverse events
Study Designs	Health technology assessment, systematic reviews, meta-analyses, and randomized-controlled trials

Exclusion Criteria

Studies were excluded if they evaluated dexmedetomidine for sedation in settings other than the ICU, such as during surgical operations. Additionally, primary trials were excluded for this review if they were used in one of the included systematic reviews or meta-analyses. Studies that evaluated pain as the only outcome were also excluded.

Critical Appraisal of Individual Studies

The methodological quality of the included systematic reviews and meta-analyses was evaluated using the "assessment of multiple systematic reviews" (AMSTAR).[4] AMSTAR is an 11-item checklist that has been developed to ensure reliability and construct validity of systematic reviews. The randomized controlled trials included in this review were evaluated using the SIGN50 checklist for the controlled studies.[5]

For the included studies a numeric score was not calculated. Instead, the strengths and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 211 potential citations were identified by searching the bibliographic database, with 195 citations being excluded during the title and abstract screening based on their irrelevance to the question of interest. The full text documents of the remaining 16 articles were retrieved. Two additional articles were identified by grey literature and hand search. Of the 18 articles, seven did not meet the inclusion criteria and were excluded; leaving 11 articles that reported five systematic reviews and meta-analyses and five unique randomized-controlled trials. The remaining article reported additional results from an included randomized-controlled trial.

A PRISMA diagram demonstrating the study selection process is presented in Appendix I.

Summary of Study Characteristics

Details on studies characteristics are tabulated in Appendix II.

Eleven articles that addressed the research question were included in this report; these included one systematic review,[6] four systematic reviews with meta-analyses,[7-10] and six articles reporting randomized controlled trials.[11-16]. Two articles reported one randomized controlled trial;[15,16] both articles were reviewed, but the review considered them as one trial only.

The included studies evaluated the use of dexmedetomidine for sedation in patients treated in an intensive care unit; however, the medical condition for which sedation was indicated was not systematically reported or considered in the analyses. The identified conditions were cardiac surgery in the Lin meta-analysis[9] and Prasad's RCT,[13] elective or non-elective surgery in Tan's meta-analysis[10] and Aydogan's RCT,[11] and acute cardiogenic pulmonary edema and hypoxia in Huang's RCT.[14] The meta-analysis by Frazer et al. excluded studies conducted on cardiac or critically ill obstetrical patients.

The sedation protocols and regimens varied among the included studies; the sedation doses for dexmedetomidine ranged from 0.15 to 0.5 mcg/kg/h. Titration methods differed from one study to another, and they could not be grouped in specific categories; however, most of the included studies reported that the titration depended on clinical sedation evaluation methods such as the RAMSAY test.

Comparators included benzodiazepine sedatives, non-benzodiazepine sedatives, or opioids. Frazer's meta-analysis used two benzodiazepines as comparators, midazolam and lorazolam.[7] The systematic review by Mo et al. and the meta-analysis by Lin et al. evaluated studies with the three categories of comparators including lorazepam,[6] propofol,[6,9] midazolam,[6,9] haloperidol,[6] and morphine.[6,9] Xia et al. included studies in their meta-analysis that had propofol as comparator.[8] Three RCTs, by Aydogan,[11] Maclaren,[12] and Huang,[14] used midazolam as comparator. The RCT by Prasad et al. used fentanyl as the comparative agent.[13] Finally, Mirski et al. compared dexmedetomidine with propofol in their RCT.[15]

Summary of Critical Appraisal

Details on studies appraisal are tabulated in Appendix III.

The four meta-analyses were based on systematic reviews of literature that was conducted by at least two investigators for each meta-analysis.[7-10] The quality of the included RCTs was evaluated in the four meta-analyses.[7-10] One meta-analysis by Tan et al. evaluated the clinical heterogeneity in the included studies by conducting subgroup analysis for patients undergoing elective surgery and for non-elective critically ill patients;[10] the remaining three meta-analyses evaluated the heterogeneity using statistical methods only.[7-9] However, the heterogeneity in the sedation protocols and differences in comparators were not considered or evaluated in the four meta-analyses.[7-10]

The systematic review by Mo et al. included studies if they evaluated the primary outcome, delirium, using objective monitoring tools.[6] However, the review did not specify how the literature search and data extraction were conducted. Moreover, the review did not evaluate the methodological quality of the included studies.[6]

The five included RCTs employed double-blind design;[11-15] the sample size was based on power calculation in four RCTs.[11-13,15] Limitation of the included RCTs included unclear allocation concealment methods in four trials,[11,13-15] and five trials shared a common shortage in specifying whether the statistical analysis was conducted by using the intention to treat or per-protocol datasets.[11-15] The generalizability of patient characteristics in the included studies could not verified in three meta-analyses[7-9] and the systematic review.[6] This was because these studies did not report the exclusion criteria in each of the included studies. The meta-analysis by Tan at al.[10] reported the exclusion criteria in the included 24 studies; the included studies presented a large spectrum of ICU patients, and the findings of this meta-analysis are likey generalizable to the general ICU patients. Four of the included RCTs reported extensive exclusion criteria, which may affect the generalizability of their findings;[11-14] the remaining RCT did not report exclusion criteria, and the external validity could not be fully assessed.[15]

Summary of Findings

Details on study findings are tabulated in Appendix IV.

Length of ICU stay

ICU stay was reported in the four meta-analyses and two RCTs.[2,8-11,14] Three meta-analyses reported statistically significant lower length of ICU stay associated with dexmedetomidine;[7,8,10] the difference in ICU stay between dexmedetomidine and comparators ranged from 0.5 to 1.5 days. The meta-analysis by Lin et al. reported numerically (statistically not significant) lower duration of ICU stay (3.4 days) with dexmedetomidine.[9] Aydogan's RCT on adolescent patients undergoing surgery for scoliosis reported same length of ICU stay with dexmedetomidine and midazolam;[11] however, Huang' RCT reported statistically significant lower ICU stay of 3.6 days in the dexmedetomidine group compared with midazolam.[14]

Duration of mechanical ventilation

Four meta-analyses and two RCT reported results for duration of mechanical ventilation.[7-10,13,14] The meta-analyses by Frazer et al.[7] and Lin et al.[9] reported statistically significant lower duration of mechanical ventilation for patients sedated with dexmedetomidine than the comparator groups; the difference was 1.8 days and 2.7 hours respectively.[7,9] Tan's meta-analysis reported numerically lower time on mechanical ventilator for dexmedetomidine than comparators,[10] while Xia et al. reported numerically higher time of mechanical ventilation for dexmedetomidine.[8]

The two RCTs in patients by Aydogan et al. (adolescent patients undergoing scoliosis surgery) and Prasad et al. (pediatric patients undergoing cardiac surgery) reported statistically significant lower mechanical ventilation time for the dexmedetomidine group of 118 hours (versus midazolam) and 4 hours (versus fentanyl) respectively.[11,13]

Mortality

Mortality was evaluated in the four meta-analyses, and the four reports did not show any statistically significant difference in the incidence of mortality between dexmedetomidine and the comparators.[7-10]

Delirium

The four meta-analyses, the systematic review, and four RCTs reported the incidence of delirium.[6-12,14,15] Two meta-analyses reported statistically significant lower incidence of delirium in the dexmedetomidine groups compared with comparators; the associated risk ratio was 0.40 and 0.36 in Xia's and Lin's meta-analysis respectively. The meta-analyses by Frazer et al. and Tan et al. reported numerically lower incidence rates of delirium associated with dexmedetomidine than comparators.[7,10]

The systematic review by Mo et al. reported that the incidence of delirium was not statistically different between dexmedetomidine and comparators in six trials, and it was statistically significantly lower in the dexmedetomidine group than with midazolam or propofol in one study.[6]

Aydogan's RCT on pediatric patients undergoing scoliosis surgery reported statistically significant lower rates of delirium in the dexmedetomidine groups than with midazolam (12.5% versus 31.3%).[11] The two RCTs by MacLaren and Huang reported a numerically lower incidence of delirium associated with dexmedetomidine than midazolam.[12,14] Mirski et al. reported one case of delirium but they did not identify in which group this case was reported.[15]

Cognitive function

The RCT published by Mirski et al.[15] and Goodwin et al.[16] reported that dexmedetomidine was associated with statistically significantly better cognitive functions than propofol in the overall score as well as in the scores of the individual five domains of the adaptive cognitive exam.[16]

Bradycardia

Bradycardia was reported in three meta-analyses and three RCTs.[8-12,14] One meta-analysis reported a statistically significant higher incidence of bradycardia associated with the use of dexmedetomidine compared wtih comparators; the risk ratio was 2.08.[9] The other two meta-analyses showed that risk of bradycardia was not statistically different between dexmedetomidine and comparators.[8,10]

Three RCTs comparing dexmedetomidine versus midazolam reported inconsistent results of bradycardia.[11,12,14] Aydogan et al. reported higher incidence rate of bradycardia in the dexmedetomidine group (25%) versus 6.25% in the midazolam group; the statistical significance of these results were not reported, however.[11] MacLaren reported a numerically higher incidence of bradycardia with dexmedetomidine.[12] In contrast, Huang et al. reported statistically significant higher rate of bradycardia in the dexmedetomidine group (18.2%) compared with midazolam group (0%).[14]

Limitations

The included studies evaluated the use of dexmedetomidine for patient sedation in ICU or PICU settings; however, the medical conditions that cause patients to need ICU stay were not systematically considered in the analyses. Patients' medical condition may affect clinical outcomes such as the length of ICU stay and the length of mechanical ventilation; therefore, results of this review should be interpreted with caution because other factors might affect the some of the included outcomes than the sedative agents used.

Furthermore, most of the included trials did not consider factors associated with sedation management that could affect patients' outcomes. These factors include the sedative doses and the administration protocols.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This report aimed to evaluate effectiveness and safety of dexmedetomidine for sedation of patients in ICU/PICU. A total of four meta-analyses, one systematic review and five randomized-controlled trials were retrieved.

With respect to the effectiveness of dexmedetomidine, the reviewed evidence showed that dexmedetomidine might be associated with lower ICU stay when compared with traditional sedative agents. The included studies showed that dexmedetomidine was associated with a shorter period of mechanical ventilation than the compared groups.

Safety of dexmedetomidine was also reviewed in the included studies. The included evidence suggested that dexmedetomidine did not increase the risk of mortality, but it showed that dexmedetomidine was associated with decrease in the risk of delirium. Bradycardia was reported in higher rates in dexmedetomidine groups than comparators.

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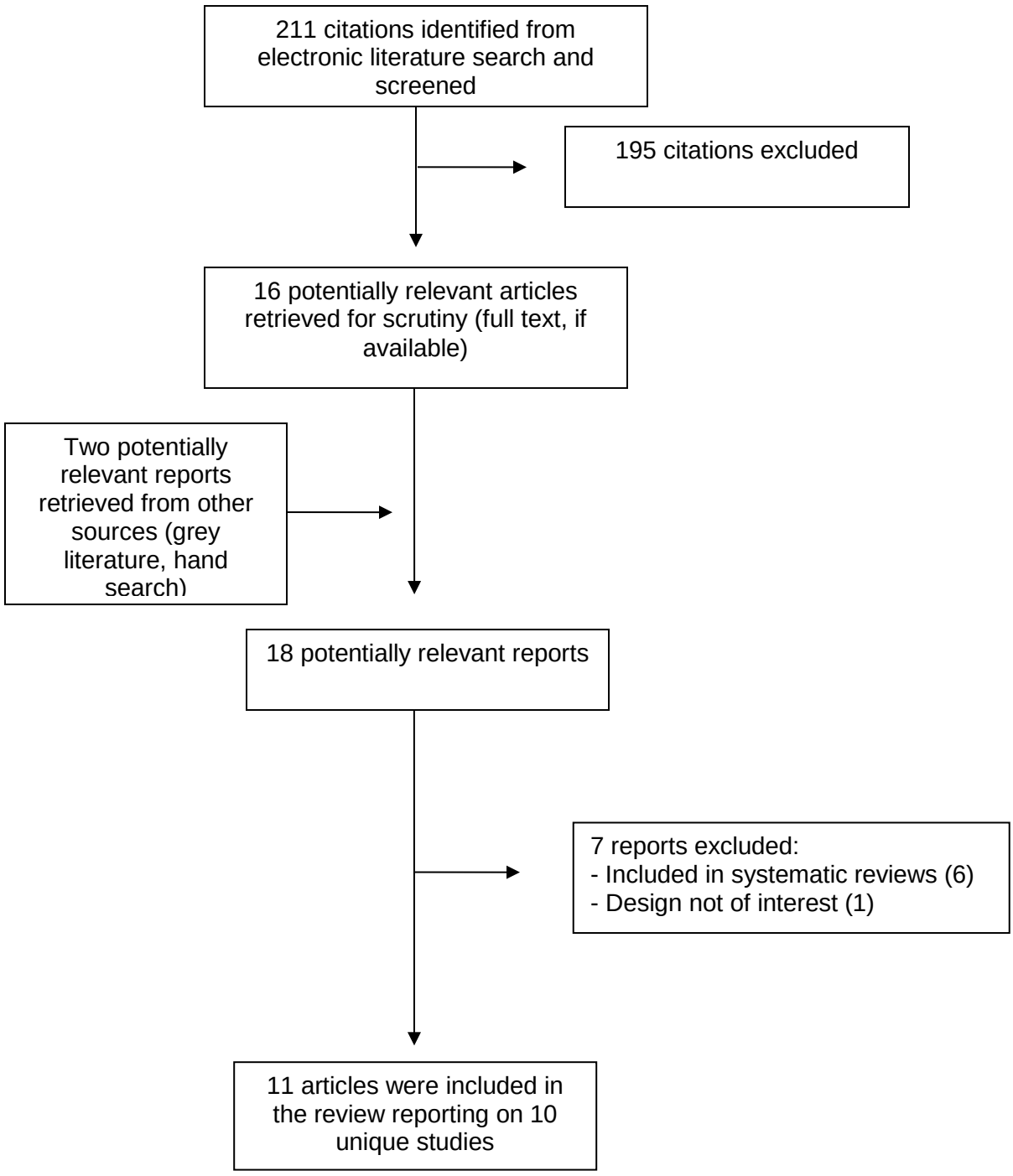
APPENDIX I: SELECTION OF INCLUDED STUDIES



APPENDIX II: CHARACTERISTICS OF THE INCLUDED STUDIES

Table 2. Characteristics of the Included Systematic Reviews and Meta-analyses

Objectives/Scope	Type of primary studies	Population/ Medical context	Intervention	Comparator	Outcomes	Notes
1/5. Frazer et al. 2013[7] – USA						
To evaluate the differences in clinical outcomes between benzodiazepine and non-benzodiazepine sedation in mechanically ventilated adult ICU patients. Systematic review and meta-analysis of randomized controlled trials	RCTs only • A total of 6 trials, were included in the review; of which, 4 trials evaluated dexmedetomidine • Trials were published between 1997 and 2012 • A total of 1,235 patients contributed to mortality analysis	The review included trials on adult medical or surgical ICU patients receiving invasive mechanical ventilation and administration of IV sedation. Studies on cardiac or critically ill patients were excluded	• Non-benzodiazepine: o Dexmedetomidine (4 trials) o 1% propofol (2 trials)	Benzodiazepine: • Midazolam (4 trials) • Lorazolam (2 trials)	• ICU length of stay • Duration of mechanical ventilation • Delirium prevalence • All-cause mortality	The review included two studies that are common with other systematic reviews (Ruokonen et al. 2013[17] and Jakob et al. 2012[18])
2/5. Mo et al. 2013[6] – UK						
To evaluate the role of dexmedetomidine in the prevention and treatment of delirium in ICU patients. Systematic review of clinical trials	The review included 8 studies • 5 double-blind RCTs • 2 open-label RCTs • 1 observational study • Studies were published between 2007 and 2012	The review included only studies that used dexmedetomidine continuously for sedation in mechanically ventilated patients for at least 6 hours. Three studies were conducted on cardiac surgery patients	• Dexmedetomidine (various doses and regimens)	• Lorazepam (1 study) • Propofol or midazolam (3 studies) • Midazolam (2 studies) • Haloperidol (1 study) • Morphine (1 study)	• Delirium (incidence and/or duration)	The review included six studies that are common with other systematic reviews (Ruokonen et al. 2013[17], Jakob et al. 2012[18], Yapici et al. 2011[19], Reade et al. 2009[20], and Shehabi et al. 2009[21]).
3/5. Xia et al. 2013[8] – China						
To evaluate the difference between dexmedetomidine	RCTs only • A total of ten trials were included	The review included studies conducted in ICU settings and	• Dexmedetomidine (various doses and regimens)	• Propofol	• ICU length of stay • Duration of mechanical	The review included one study that are common with other

Table 2. Characteristics of the Included Systematic Reviews and Meta-analyses

Objectives/Scope	Type of primary studies	Population/ Medical context	Intervention	Comparator	Outcomes	Notes
and propofol for adult ICU sedation. Systematic review and meta-analysis of randomized controlled trials	• Trials were published between 2003 and 2012 • A total of 1,202 patients contributed to mortality analysis	compared dexmedetomidine with propofol			ventilation • Delirium prevalence • All-cause mortality • Hypotension • Bradycardia • Hypertension	systematic reviews Jakob et al. 2012[18]
4/5. Lin et al. 2012[9] – China						
To evaluate the clinical safety and efficacy of dexmedetomidine for sedation in post-cardiac surgery patients. Systematic review and meta-analysis of controlled studies	The review included 11 studies • 4 double-blind RCTs • 1 open-label RCT • 2 prospective observational studies • 4 retrospective studies • Studies were published between 2003 and 2011	The review included studies conducted in ICU setting with cardiac surgery patients	• Dexmedetomidine (various doses and regimens)	• Propofol_5 trials • Propofol or midazolam_1 trial • Propofol, lorazepam, or midazolam_1 trial • Midazolam_1 trial • Morphine_2 trials • Propofol and midazolam_1 trial	• ICU length of stay • Hospital stay • Duration of mechanical ventilation • Delirium • Hospital mortality • Hypotension • Bradycardia • Hypertension	The review included two studies that are common with other systematic reviews (Abd Aziz et al. 2011,[22] and Shehabi et al. 2009[21]).
5/5. Tan et al. 2010[10] – Australia						
To evaluate the clinical outcome when using dexmedetomidine as a sedative and analgesic agent in adult ICU patient. Meta-analysis of RCTs	The review included 24 RCTs • 12 double-blinded • 1 single-blinded • 11 open-label • 1 blinding wasn't known	15 studies included high-risk elective surgery, and nine studies included non-elective critically ill patients	• Dexmedetomidine (various doses and regimens)	• Placebo_7 trials • Propofol_9 • Midazolam_5 • Lorazepam_3 • Morphine or haloperidol_2	• ICU length of stay • Hospital stay • Duration of mechanical ventilation • Delirium • Mortality • Hypotension • Bradycardia • Vomiting	The review included three studies that are common with other systematic reviews (Ruokonen et al. 2013,[17] Reade et al. 2009,[20] and Shehabi et al. 2009[21]).

Characteristics of the Included Randomized Controlled Trials

Study Objectives and Design	Inclusion Criteria, Sample Size, and Patient Characteristics	Intervention, Comparator, and Study Conduct	Clinical Outcomes
1/5. Aydogan et al. 2013[11] – Turkey			
To compare the sedation efficacy of dexmedetomidine versus midazolam. Parallel design RCT	• Pediatric patients between 12 and 18 years operated for scoliosis and admitted to the ICU • Patients were included if they required mechanical ventilation • Patient with history of delirium were excluded • A total of 32 patients were randomized	**Intervention:** • Dexmedetomidine (N =16) • 0.4 mcg/k/h **Comparator:** • Midazolam (N = 16) • 0.1 mg/kg/h	• Duration of ICU stay • Duration of mechanical ventilation • Pain • Fentanyl consumption
2/5. MacLaren et al. 2013[12] – USA			
To evaluate the efficacy of dexmedetomidine as transitioning agent from benzodiazepine when ICU patients are qualified for daily awakening. Parallel design RCT	• The trial included patients requiring mechanical ventilation and receiving a benzodiazepine infusion with an anticipated need of at least 12 additional hours of sedation. • Patient were qualified for daily awakenings • Exclusion criteria included: use of benzodiazepines for purposes other than sedation; use of neuromuscular blockers for more than 12 hours; use of epidural medications; active myocardial ischemia; second- or third-degree heart block; hemodynamic 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.	**Intervention:** • Dexmedetomidine (N = 11) • started at 0.15 mcg/kg/ h and adjusted by 0.15 mcg/kg/h to a maximum of 1.5 mcg/kg/h, **Comparator:** • Midazolam (N = 12) • started at 1 mg/h and adjusted by 1 mg/h to a maximum of 10 mg/h.	Evaluation after at least 72 hours after extubation or tracheostomy, but before hospital discharge: • Post-ICU anxiety • Post-ICU depression • Acute stress disorder manifestation

Characteristics of the Included Randomized Controlled Trials

Study Objectives and Design	Inclusion Criteria, Sample Size, and Patient Characteristics	Intervention, Comparator, and Study Conduct	Clinical Outcomes
3/5. Prasad et al. 2012[13] – India			
To compare the sedation with dexmedetomidine and fentanyl in post-operative pediatric cardiac surgical patients. Parallel design RCT	• Patients between one and fourteen years operated for congenital cardiac conditions were included. • The included patients had an anticipated overnight ventilation • Exclusion criteria prevented the participation of patients undergoing re-operation or surgeries done under deep hypothermia. Patients were excluded also if they had severe liver dysfunction, second and third degree heart block, and if they potentially needed ventilation for more than 24 hours.	**Intervention:** • Dexmedetomidine (N = 30) • 0.5 mcg/kg/ h **Comparator:** • Fentanyl (N = 30) • 1 mcg/kg/ h	• Time to extubation • Ramsay sedation score
4/5. Huang et al. 2012[14] – China			
To compare the use of dexmedetomidine with midazolam for the sedation of patient with acute cardiogenic pulmonary edema and hypoxemia. Parallel design RCT	• The trial included patient with acute cardiogenic pulmonary edema and hypoxemia. • Patients were treated with non-invasive ventilation • Exclusion criteria prevented the participation poor respiratory state requiring immediate intubation; a clear alternative primary diagnosis; severely altered consciousness; patients 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.	**Intervention:** • Dexmedetomidine (N = 33) • started at 0.2-0.7 mcg/kg/h **Comparator:** • Midazolam (N = 29) • started at 0.05 mg/kg/h and adjusted by 0.05-0.1 mg/kg/h	• Need for endotracheal intubation • Mean time to endotracheal intubation • Length of ICU stay • ICU mortality
5/5. Mirski et al. 2010[15] and Goodwin et al. 2013[16] – USA			
To compare the sedative efficacy of dexmedetomidine and propofol in ICU patients Cross-over design	• The trial included ICU patients who were awake, able to follow commands, and displaying restlessness or agitation. • Patients were included if they required new implementation of continuous i.v. sedation or an increase in opioid above analgesic dosing	**Intervention:** • Dexmedetomidine • Titrated to 0.2-0.7 mcg/kg/h **Comparator:** • Propofol • Titrated to 20-70 mcg/kg/min	• Change in the cognitive functions • Incidence of delirium • Need for adjunctive fentanyl

APPENDIX III: CRITICAL APPRAISAL OF THE INCLUDED STUDIES

Strengths	Limitations
Frazer et al. 2013[7] – USA; Systematic review and meta-analysis 1/5	
• Literature selection and data extraction were conducted by two reviewers independently. • The risk of bias and the methodological quality were evaluated systematically by the two reviewers using the Cochrane risk of bias tool.	• The review excluded trials on cardiac and critically ill ICU patients; the results of the review may not be generalizable to these two categories of patients. • The meta-analysis evaluated heterogeneity using statistical methods only; the clinical heterogeneity (e.g. the use of different sedation regimens and protocols) were not taken into consideration. • The exclusion criteria in each of the included studies were not reported; therefore, the generalizability of the study finding could not be ascertained.
Mo et al. 2013[6] – UK; Systematic review 2/5	
• The review included studies that evaluated delirium using objective monitoring tools; this was done to minimize bias in the outcome evaluation	• The article did not report who conducted the literature search and data selection; double selection and extraction could not verified. • The quality of the included studies was not evaluated. • The exclusion criteria in each of the included studies were not reported; therefore, the generalizability of the study finding could not be ascertained.
Xia et al. 2013[8] – China; Systematic review and meta-analysis 3/5	
• Literature selection and data extraction were conducted by two reviewers independently. • The article reported that the methodological quality was evaluated using the Cochrane Collaboration tool; however, the results of this evaluation wasn't reported.	• The meta-analysis evaluated heterogeneity using statistical methods only; the clinical heterogeneity (e.g. the use of different sedation regimens and protocols) were not taken into consideration. • The exclusion criteria in each of the included studies were not reported; therefore, the generalizability of the study finding could not be ascertained.
Lin et al. 2012[9] – China; Systematic review and meta-analysis 4/5	
• Literature selection and data extraction were conducted by two reviewers independently. • The risk of bias and the methodological quality were evaluated systematically by the two reviewers using the Newcastle-Ottawa scale.	• The meta-analysis evaluated heterogeneity using statistical methods only; the clinical heterogeneity (e.g. the infusion rate) were not taken into consideration. • The exclusion criteria in each of the included studies were not reported; therefore, the generalizability of the study finding could not be ascertained.
Tan et al. 2010[10] – Australia; Systematic review and meta-analysis 5/5	
• Literature selection and data extraction were conducted by two reviewers independently. • The methodological quality of the included studies were evaluated and reported; the article did not specify the method used or who conducted this evaluation • The review conducted subgroup analysis for studies that included elective surgery, and those that included	• The meta-analysis included studies that allowed rescue medications; the analysis did not consider the differences in the used rescue medications or their amount, dosage and regimens.

Strengths	Limitations
non-elective critically ill patients; this was done as complement for the statistical heterogeneity assessment	
• Literature selection and data extraction were conducted by two reviewers independently. • The methodological quality of the included studies were evaluated and reported; the article did not specify the method used or who conducted this evaluation • The review conducted subgroup analysis for studies that included elective surgery, and those that included non-elective critically ill patients; this was done as complement for the statistical heterogeneity assessment	• The meta-analysis included studies that allowed rescue medications; the analysis did not consider the differences in the used rescue medications or their amount, dosage and regimens.
Aydogan et al. 2013[11] – Turkey; Randomized-controlled trial 1/5	
• The study was double blinded • The sample size was estimated based on power calculation. The trial was powered to detect 30% difference in fentanyl consumption. • All randomized patients completed the study	• Randomization method and allocation concealment were not described. • The article did not precise if the analysis was based on the intention to treat or per-protocol dataset. • The trial excluded several medical condition that may affect the reaction to sedative agents. Therefore, the finding form this study might not be generalizable to the excluded patients.
MacLaren et al. 2013[12] – USA; Randomized-controlled trial 2/5	
• The study was double blinded • Allocation concealment was assured by indistinguishable infusion bags and same dose adjustment increments (2 mL/h) • The sample size was based on power calculation to detect 30% difference in the occurrence of anxiety, depression and ASD manifestations. However, the study was stopped before including the estimated sample size.	• Primary outcome was reported for 70% of the randomized patients • The article did not precise if the analysis was based on the intention to treat or per-protocol dataset. • Exclusion criteria were extensive and eliminated several medical condition that cause patients' admission to ICU. Therefore, the finding form this study might not be generalizable to the excluded patients.
Prasad et al. 2012[13] – India; Randomized-controlled trial 3/5	
• The study was double blinded • The sample size was based on power calculation to detect 180 minutes difference in time to extubation; another calculation was based on power estimation to detect 0.6 RSS difference.	• Methods used for allocation concealment were not described in the report • The article did not precise if the analysis was based on the intention to treat or per-protocol dataset. • The study excluded several medication conditions that require ICU admission; results might not be generalizable to other than the included patients.

Strengths	Limitations
Huang et al. 2012[14] – China; Randomized-controlled trial 4/5	
• The study was double blinded • All randomized patients completed the study and were included in outcome analysis	• The sample size was based on convenience rather than power analysis • The article did not precise if the analysis was based on the intention to treat or per-protocol dataset. • Concealment of treatment allocation was not clear. The trial interventions could be adjusted; the adjustment rates are different. And therefore, the allocated treatment could be unconcealed. • The trial excluded many clinical conditions that require patients' admission to ICU. The trial findings could not be applied to the excluded patients.
Mirski et al. 2010[15] and Goodwin et al. 2013[16] – USA ; Randomized-controlled trial 5/5	
• The study was double blinded • Sample size was based on power calculation	• The article did not precise if the analysis was based on the intention to treat or per-protocol dataset. • Of the 35 randomized patients, 33 received at least one treatment, and 30 patients completed the trial. • Concealment of treatment allocation was not clear. Treatment allocation could be breached by the differences in solution texture and the titration regimens of the compared interventions. • The article did not report any exclusion criteria, and it did not specify that there weren't any.

APPENDIX IV: RESULTS OF THE INCLUDED STUDIES

Table 3. Summary of Findings from the included studies

<table>
<tr><th colspan="3">Main Study Findings</th><th>Conclusions</th></tr>
<tr><td colspan="4">Frazer et al. 2013[7] – USA; Systematic review and meta-analysis 1/5</td></tr>
<tr><td colspan="3">The meta-analysis included six trials; two of which evaluated propofol instead of dexmedetomidine. The published results grouped both dexmedetomidine and propofol as one group. CADTH reviewer meta-analyzed dexmedetomidine studies separately. The two sets of results are reported in the table below</td><td rowspan="11">The authors concluded that adult ICU sedation with dexmedetomidine or propofol may reduce ICU length of stay and duration of mechanical ventilation.</td></tr>
<tr><td></td><td>Participants (studies)</td><td>Non-benzodiazepine (or dexmedetomidine)</td></tr>
<tr><td colspan="3">ICU length of stay (days); mean difference (95% CI)</td></tr>
<tr><td>• Non-benzodiazepine versus benzodiazepine</td><td>1,235 (6)</td><td>-1.64 (-2.57, -0.70)</td></tr>
<tr><td>• Dexmedetomidine versus benzodiazepine[a]</td><td>1,026 (4)</td><td>-1.54 (-2.54, -0.54)</td></tr>
<tr><td colspan="3">Duration of mechanical ventilation (days); mean difference (95% CI)</td></tr>
<tr><td>• Non-benzodiazepine versus benzodiazepine</td><td>1,101 (4)</td><td>-1.87 (-2.51, -1.22)</td></tr>
<tr><td>• Dexmedetomidine versus benzodiazepine[a]</td><td>969 (3)</td><td>-1.80 (-2.47, -1.12)</td></tr>
<tr><td colspan="3">Delirium; risk ratio (95% CI)</td></tr>
<tr><td>• Dexmedetomidine versus benzodiazepine</td><td>296 (2)</td><td>0.82 (0.61, 1.11)</td></tr>
<tr><td colspan="3">All-cause mortality; risk ratio (95% CI)</td></tr>
<tr><td>• Non-benzodiazepine versus benzodiazepine</td><td>1,101 (4)</td><td>1.01 (0.78, 1.30)</td></tr>
<tr><td>• Dexmedetomidine versus benzodiazepine[a]</td><td>969 (3)</td><td>0.99 (0.68, 1.43)</td></tr>
<tr><td colspan="3">Studies evaluating dexmedetomidine versus benzodiazepine were meta-analyzed by CADTH reviewer based on the data provided in the reviewed article by Frazer et al.[7]</td></tr>
<tr><td colspan="4">Mo et al. 2013[6] – UK; ; Systematic review 2/5</td></tr>
<tr><td colspan="3"></td><td rowspan="10">The authors concluded that the available evidence showed that dexmedetomidine is useful in the prevention and treatment of delirium in ICU patients.</td></tr>
<tr><td>Study</td><td>Delirium evaluation</td><td>Dexmedetomidine vs. comparator</td></tr>
<tr><td rowspan="2">Jakob 2012</td><td rowspan="3">Incidence of positive CAM-ICU</td><td>Vs. midazolam: difference NS</td></tr>
<tr><td>Vs. propofol: difference NS</td></tr>
<tr><td>Yapici 2011</td><td>No events</td></tr>
<tr><td>Reade 2009</td><td>ICDSC score</td><td>Vs. haloperidol: difference NS</td></tr>
<tr><td>Riker 2009</td><td rowspan="2">Incidence of positive CAM-ICU</td><td>Vs. midazolam: difference NS</td></tr>
<tr><td>Ruokonen 2009</td><td>Vs. midazolam or propofol: difference NS</td></tr>
<tr><td>Shehabi 2009</td><td>CAM-ICU (incidence of delirium)</td><td>Vs. morphine: difference NS</td></tr>
<tr><td>Maldonado 2009</td><td>DSM-IV-TR (incidence of delirium)</td><td>Vs. midazolam or propofol: difference P<0.001</td></tr>
<tr><td>Pandharipande 2007</td><td>CAM-ICU (delirium free days)</td><td>Vs. lorazepam: difference NS</td></tr>
</table>

Table 3. Summary of Findings from the included studies

<table>
<tr><th colspan="3">Main Study Findings</th><th>Conclusions</th></tr>
<tr><td colspan="3">CAM-ICU = Confusion Assessment Method for the ICU; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders; ICDSC = Intensive Care Delirium Screening Checklist</td><td></td></tr>
<tr><td colspan="4">Xia et al. 2013[8] – China; Systematic review and meta-analysis 3/5</td></tr>
<tr><td></td><td>Participants (studies)</td><td>Dexmedetomidine vs. propofol</td><td rowspan="12">The authors concluded that the use of dexmedetomidine for ICU patients' sedation shortened the length of ICU stay and decreased the incidence of delirium; the author also pointed out that dexmedetomidine was associated with increased incidence of hypertension.</td></tr>
<tr><td>ICU length of stay (days);</td><td></td><td></td></tr>
<tr><td>• mean difference (95% CI)</td><td>655 (5)</td><td>-0.81 (-1.48, -0.15)</td></tr>
<tr><td>Duration of mechanical ventilation (days);</td><td></td><td></td></tr>
<tr><td>• mean difference (95% CI)</td><td>895 (5)</td><td>0.53 (-2.66, 3.72)</td></tr>
<tr><td>Delirium;</td><td></td><td></td></tr>
<tr><td>• risk ratio (95% CI)</td><td>658 (3)</td><td>0.40 (0.22, 0.74)</td></tr>
<tr><td>All-cause mortality;</td><td></td><td></td></tr>
<tr><td>• risk ratio (95% CI)</td><td>267 (5)</td><td>0.83 (0.32, 2.12)</td></tr>
<tr><td>Hypotension</td><td></td><td></td></tr>
<tr><td>• risk ratio (95% CI)</td><td>1015 (6)</td><td>1.12 (0.86, 1.47)</td></tr>
<tr><td>Bradycardia</td><td></td><td></td></tr>
<tr><td>• risk ratio (95% CI)</td><td>788 (2)</td><td>1.36 (0.85, 2.18)</td></tr>
<tr><td>Hypertension</td><td></td><td></td></tr>
<tr><td>• risk ratio (95% CI)</td><td>846 (3)</td><td>1.56 (1.11, 2.20)</td></tr>
<tr><td colspan="4">Lin et al. 2012[9] – China; Systematic review and meta-analysis 4/5</td></tr>
<tr><td></td><td>Participants (studies)</td><td>Dexmedetomidine vs. comparator</td><td rowspan="12">The authors concluded that dexmedetomidine was associated with shorter length of mechanical ventilation and fewer incidence of delirium compared with other sedatives; however, dexmedetomidine was associated with a significantly higher incidence of bradycardia.</td></tr>
<tr><td>ICU length of stay (days);</td><td></td><td></td></tr>
<tr><td>• mean difference (95% CI)</td><td>NR</td><td>-3.44 (-11.40, 4.52)</td></tr>
<tr><td>Duration of mechanical ventilation (hours);</td><td></td><td></td></tr>
<tr><td>• mean difference (95% CI)</td><td>16613 (9)</td><td>-2.70 (-5.05, -0.35)</td></tr>
<tr><td>Delirium;</td><td></td><td></td></tr>
<tr><td>• risk ratio (95% CI)</td><td>10830 (4)</td><td>0.36 (0.21, 0.64)</td></tr>
<tr><td>Hospital mortality;</td><td></td><td></td></tr>
<tr><td>• risk ratio (95% CI)</td><td>NR</td><td>0.72 (0.37, 1.39)</td></tr>
<tr><td>Hypotension</td><td></td><td></td></tr>
<tr><td>• risk ratio (95% CI)</td><td>839 (5)</td><td>0.99 (0.72, 1.36)</td></tr>
<tr><td>Bradycardia</td><td></td><td></td></tr>
<tr><td>• risk ratio (95% CI)</td><td>650 (3)</td><td>2.08 (1.16, 3.74)</td></tr>
<tr><td colspan="4">Tan et al. 2010[10] – Australia; Systematic review and meta-analysis 5/5</td></tr>
<tr><td></td><td>Participants (studies)</td><td>Dexmedetomidine vs. comparator</td><td rowspan="8">The authors concluded that the included studies had significant heterogeneity and provided limited evidence that dexmedetomidine might reduce the length of ICU stay. However, it was associated with higher risk of bradycardia.</td></tr>
<tr><td colspan="3">ICU length of stay (days); mean difference (95% CI)</td></tr>
<tr><td>• Overall</td><td>1264 (12)</td><td>-0.48 (0.78, -0.18)</td></tr>
<tr><td>• elective postoperative</td><td>586 (5)</td><td>-0.11 (-0.28, 0.07)</td></tr>
<tr><td>• non-elective critically-ills</td><td>678 (7)</td><td>-1.41 (-2.94, 0.12)</td></tr>
<tr><td colspan="3">Duration of mechanical ventilation (days); mean difference (95% CI)</td></tr>
<tr><td>• Overall</td><td>1901 (12)</td><td>-0.51 (-1.75, 0.73)</td></tr>
<tr><td>• elective postoperative</td><td>1410 (9)</td><td>-0.43 (-1.15, 0.29)</td></tr>
</table>

Table 3. Summary of Findings from the included studies

Main Study Findings			Conclusions
• non-elective critically-ills	491 (3)	-16.96 (-70.55, 36.63)	
Delirium; risk ratio (95% CI)			
• Overall	1754 (8)	0.79 (0.56, 1.11)	
• elective postoperative	1200 (5)	0.54 (0.24, 1.22)	
• non-elective critically-ills	554 (3)	0.95 (0.67, 1.34)	
Mortality; risk ratio (95% CI)			
• Overall	1839 (16)	0.85 (0.64, 1.13)	
• elective postoperative	1145 (9)	0.75 (0.32, 1.76)	
• non-elective critically-ills	694 (7)	0.86 (0.64, 1.17)	
Hypotension; risk ratio (95% CI)			
• Overall	1545 (12)	1.43 (0.78, 2.60)	
• elective postoperative	955 (8)	1.23 (0.50, 2.98)	
• non-elective critically-ills	590 (4)	2.73 (0.40, 18.39)	
Bradycardia[a]; risk ratio (95% CI)			
• Overall	1164 (10)	1.82 (0.66, 5.03)	
• elective postoperative	574 (6)	0.95 (0.39, 2.34)	
• non-elective critically-ills	590 (4)	7.30 (1.73, 30.81)	
Nausea and vomiting; risk ratio (95% CI)			
• Overall	NR	1.03 (0.66, 1.59)	
[a] bradycardia requiring intervention			

Aydogan et al. 2013[11] – Turkey; Randomized-controlled trial 1/5

	Dexmedetomidine (N = 16)	Midazolam (N = 16)	Difference (P-value)	The authors concluded that dexmedetomidine may be beneficial for managing sedation in adolescents who have undergone scoliosis surgery.
ICU length of stay				
• Days	2	2	(0.421)	
Duration of mechanical ventilation				
• Minutes	107	225	(0.035)	
Delirium;				
• Incidence rate	12.5%	31.3%	(<0.05)	
Use of fentanyl				
• µg (at 24 hours)	124.1	165.8	(0.002)	
Bradycardia;				
• Incidence rate	25%	6.25%	NR	

MacLaren et al. 2013[12] – USA; Randomized-controlled trial 2/5

	Dexmedetomidine (N = 11)	Midazolam (N = 12)	Difference (P-value)	The authors concluded that dexmedetomidine didn't reduce the mechanical ventilation time, and it was associated with more hypotension, less delirium and greater recall of the ICU experience.
HADS, mean score (SD)				
• Anxiety	6 (7.6), n=8	3 (3.1), n=8	NS	
• Depression	4 (5.3) , n=8	6 (6.7) , n=8	NS	
ASD; mean score (SD)				
• Intrusion	16 (6.3), n=8	4 (5.2), n=8	(0.007)	
• Avoidance	18 (4), n=8	6 (7), n=8	(0.066)	
• Hyperarousal	6 (2.3), n=8	3 (1.6), n=8	(0.013)	
• Cumulative	36 (12), n=8	13 (12), n=8	(0.029)	
Delirium;				
• Incidence rate	36.4%	66.7%	(0.07)	
Tachycardia;				
• Incidence rate	63.6%	41.7%	NS	
Hypotension;				
• Incidence rate	90.9%	50%	(0.069)	

Table 3. Summary of Findings from the included studies

Main Study Findings				Conclusions
Bradycardia; risk ratio (95% CI)				
• Incidence rate	63.6%	58.3%	NS	
HADS = hospital anxiety and depression scale; NS = not significant				
Prasad et al. 2012[13] – India; Randomized-controlled trial 3/5				
	Dexmedetomidine (N = 30)	**Fentanyl (N = 30)**	**Difference (P-value)**	The authors concluded that dexmedetomidine was associated with earlier extubation than fentanyl, and it was associated with minimal depression of respiratory drive.
Time to extubation;				
• Mean minutes (SD)	131 (51.06)	373 (121.4)	(<0.001)	
Ramsay sedation score				
• Mean	NR	NR	NS	
NR = not reported; NS = not significant				
Huang et al. 2012[14] – China; Randomized-controlled trial 4/5				
	Dexmedetomidine (N = 33)	**Midazolam (N = 29)**	**Difference (P-value)**	The authors concluded that dexmedetomidine reduced the failure of non-invasive ventilation in patients with acute cardiogenic pulmonary edema.
Endotracheal intubation;				
• Incidence rate	21.2%	44.8%	(0.043)	
Time to intubation				
• Mean time (hours)	27.6	17.8	(0.024)	
ICU length of stay				
• Mean (days)	4.9	8.5	(0.042)	
ICU mortality;				
• Incidence rate	6.1%	10.3%	(0.658)	
Delirium;				
• Incidence rate	3.0%	13.8%	0.089	
Hypotension;				
• Incidence rate	12.1%	17.2%	0.772	
Bradycardia; risk ratio (95% CI)				
• Incidence rate	18.2%	0	0.016	
Mirski et al. 2010[15] and Goodwin et al. 2013[16] – USA ; Randomized-controlled trial 5/5				
	Dexmedetomidine	**Propofol**	**Difference (P-value)**	The authors concluded that dexmedetomidine ameliorate the cognitive functions when used for sedation of selected ICU patients.
Cognitive function (Adaptive cognitive exam: Overall)				
• Change from baseline	6.81	-12.38	19.19 (0.001)	
Cognitive function (Adaptive cognitive exam: Orientation)				
• Change from baseline	1.15	-3.04	4.19 (0.002)	
Cognitive function (Adaptive cognitive exam: Language)				
• Change from baseline	-0.23	-3.4	3.17 (0.007)	
Cognitive function (Adaptive cognitive exam: Registration)				
• Change from baseline	0.46	-1.11	1.58 (<0.001)	
Cognitive function (Adaptive cognitive exam: Attention/calculation)				

Table 3. Summary of Findings from the included studies

Main Study Findings				Conclusions
• Change from baseline	3.55	-1.97	5.52 (<0.001)	
Cognitive function (Adaptive cognitive exam: Recall)				
• Change from baseline	2.02	-2.86	4.87 (<0.001)	
Delirium; risk ratio (95% CI)				
• Number of cases	1		NR	