Dexmedetomidine as a Sedative Agent in Critically Ill Patients: A Meta-Analysis of Randomized Controlled Trials

Laura Pasin1, Teresa Greco1, Paolo Feltracco2, Annalisa Vittorio1, Caetano Nigro Neto1, Luca Cabrini1, Giovanni Landoni1,3*, Gabriele Finco4, Alberto Zangrillo1

1 Anesthesia and Intensive Care Department, San Raffaele Scientific Institute, Milan, Italy, 2 Department of Pharmacology and Anesthesiology, University Hospital of Padua, Padua, Italy, 3 Outcomes Research Consortium, Cleveland, Ohio, United States of America, 4 Department of Medical Sciences “M. Aresu”, Cagliari University, Cagliari, Italy

Abstract

Introduction: The effect of dexmedetomidine on length of intensive care unit (ICU) stay and time to extubation is still unclear.

Materials and Methods: Pertinent studies were independently searched in BioMedCentral, PubMed, Embase, and the Cochrane Central Register of clinical trials (updated February first 2013). Randomized studies (dexmedetomidine versus any comparator) were included if including patients mechanically ventilated in an intensive care unit (ICU). Co-primary endpoints were the length of ICU stay (days) and time to extubation (hours). Secondary endpoint was mortality rate at the longest follow-up available.

Results: The 27 included manuscripts (28 trials) randomized 3,648 patients (1,870 to dexmedetomidine and 1,778 to control). Overall analysis showed that the use of dexmedetomidine was associated with a significant reduction in length of ICU stay (weighted mean difference (WMD) = −0.79 [−1.17 to −0.40] days, p for effect <0.001) and of time to extubation (WMD = −2.74 [−3.80 to −1.65] hours, p for effect <0.001). Mortality was not different between dexmedetomidine and controls (risk ratio = 1.00 [0.84 to 1.21], p for effect = 0.9). High heterogeneity between included studies was found.

Conclusions: This meta-analysis of randomized controlled studies suggests that dexmedetomidine could help to reduce ICU stay and time to extubation, in critically ill patients even if high heterogeneity between studies might confound the interpretation of these results.

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* E-mail: landoni.giovanni@hsr.it

Introduction

Dexmedetomidine was approved by the Food and Drug Administration (FDA) at the end of 1999 as a short-term medication (<24 hours) for analgesia and sedation in mechanical ventilated intensive care unit (ICU) patients. In 2008, the FDA approved a new indication in non intubated patients requiring sedation before and/or during surgical and non-surgical procedures. Dexmedetomidine is a highly selective α2-adrenergic receptor agonist, which binds to transmembrane G protein-binding adrenoreceptors in the periphery (α2A), brain and spinal cord (α2B, α2C) tissues [1]. In contrast to other sedative agents, dexmedetomidine, by acting on α2 receptors in the locus caeruleus [2], has potential analgesic effects [3] without respiratory depression [4,5]. Only one meta-analysis of randomized controlled trials (RCTs) [6] was published so far: Tan and Ho reported a reduction in length of ICU stay, but not in duration of time to extubation when dexmedetomidine was compared with alternative sedative agents.

Since several RCTs [7–14], including two large ones [8], were recently published, and one further RCT [15] was not included in the previous meta-analysis [6] we decided to perform an updated meta-analysis of all the RCTs ever performed on dexmedetomide versus any comparator in the ICU setting to evaluate time to extubation, ICU stay and survival.

Materials and Methods

Search Strategy

Pertinent studies were independently searched in BioMedCentral, PubMed, Embase, and the Cochrane Central Register of clinical trials (updated February 1st 2013) by four trained investigators. The full PubMed search strategy aimed to include any RCTs ever performed in humans with dexmedetomidine in...
Table 1. Description of the 28 trials included in the meta-analysis.

| First author | Year | Setting               | Dex patients | Control patients | Comparator | Comparator dose | Follow-up                  |
|--------------|------|-----------------------|--------------|------------------|------------|----------------|----------------------------|
| Aziz AN [7]  | 2011 | Cardiac surgery       | 14           | 14               | Morphine   | 4.6–46 μg/kg/h | 24 hours                  |
| Corbett SM [21] | 2005 | Cardiac surgery   | 43           | 46               | Propofol   | 0.2–0.7 μg/kg/h or 5–75 μg/kg/min | ICU stay               |
| Elbaradie S [22] | 2004 | Major surgeries   | 30           | 30               | Propofol   | Bolus dose of 1 mg/kg followed by an infusion of 0.5–1 mg/kg/h | 24 hours after commencement of sedative infusions |
| Esmaoglu A [23] | 2009 | Post caesarean eclampsia | 20           | 20               | Midazolam  | Loading dose of 0.05 mg/kg followed by an infusion of 0.1 mg/kg/h | ICU stay |
| Herr DL [24]  | 2003 | Cardiac surgery       | 148          | 147              | Propofol   | NA            | 24 hours after discharge from ICU |
| Jakob SM MIDEX [8] | 2012 | ICU                   | 249          | 251              | Midazolam  | 0.03–0.2 mg/kg/h | 45 days |
| Jakob SM PRODEX [8] | 2012 | ICU                   | 251          | 247              | Propofol   | 0.3–4.0 mg/kg/h | 45 days |
| Khalil MA [14] | 2012 | Cardiac surgery       | 25           | 25               | Placebo    | Loading dose 1 μg/kg over 10 minutes followed by a maintenance infusion of 0.5 μg/kg/h | Hospital stay |
| Leino K [9]   | 2011 | Cardiac surgery       | 44           | 43               | Placebo    | 39 ml/h for 20 min, 24.5 ml/h for 40 minutes, 14 ml/h for 60 min, 10.5 ml/h for 120 min and then 7 ml/h | 48 hours after catheter insertion |
| Maldonado JR [25] | 2009 | Cardiac surgery       | 40           | 38               | Propofol, midazolam | Propofol: 25–50 μg/kg/min; Midazolam: 0.5–2 mg/h | Hospital stay |
| Martin E [26] | 2003 | ICU                   | 203          | 198              | Placebo    | 1 μg/kg for 10 min (loading dose) and then 0.4 μg/kg/h. The latter rate could be adjusted within the range of 0.2 to 0.7 μg/kg/h | 24 hours from infusion end |
| Memis D [27]  | 2006 | ICU                   | 12           | 12               | Propofol   | 2 mg/kg/h over 5 h infusion | ICU stay |
| Memis D [28]  | 2007 | ICU                   | 20           | 20               | Midazolam  | Loading dose of 0.2 mg/kg over 10 min followed by 0.1–0.5 mg/kg/h infusion | ICU stay |
| Memis D [29]  | 2009 | ICU                   | 20           | 20               | Propofol   | 1 mg/kg over 15 min followed by a maintenance dose of 1 to 3 mg/kg per hour | ICU stay |
| MendaF [10]   | 2010 | Cardiac surgery       | 15           | 15               | Placebo    | 1 μg/kg in 15 min | ICU stay |
| Ozkan N [30]  | 2007 | Cardiac surgery       | 20           | 20               | Midazolam  | 0.05–0.07 mg/kg/h | 24 hours post extubation |
| Pandharipande PP [31] | 2007 | ICU                   | 52           | 51               | Lorazepam  | Maximum 10 mg/hr | 12 months |
| Reade MC [32] | 2009 | ICU                   | 10           | 10               | Haloperidol | 0.5–2 mg/hour preceded by a loading dose of 2.5 mg if desired | Hospital stay |
| Riker RR [33] | 2009 | ICU                   | 244          | 122              | Midazolam  | Loading dose 0.05 mg/kg then infusion rate 0.02–0.1 mg/kg/h | 30 days |
| Ruokonen E [34] | 2009 | ICU                   | 41           | 44               | Propofol Midazolam | Propofol: 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; Midazolam: boluses (1–2 mg), starting at 3 boluses per hour for 1 h, and thereafter 1–4 boluses per h, and if not sufficient as continuous infusion | 45 days |
| Sahin N [15]  | 2005 | Cardiac surgery       | 15           | 15               | Midazolam  | 0.1 mg/kg/h intraoperative; 0.5–1 μg/kg/min ICU | 12 hours postoperative |
| Shehabi Y [35] | 2009 | Cardiac surgery       | 154          | 152              | Morphine   | 10–70 μg/kg/ml | Hospital stay |
| Tasdogan M [36] | 2009 | Abdominal surgery     | 20           | 20               | Propofol   | 1 mg/kg over 15 minutes followed by a maintenance dose of 1–3 mg/kg/h | 25 days |
any clinical setting and is presented in the supplemental material (Text S1). In addition, we employed backward snowballing (i.e., scanning of references of retrieved articles and pertinent reviews) and contacted international experts for further studies with no language restriction.

**Study Selection**

References were first independently examined at a title/abstract level by four investigators, with divergences resolved by consensus, and then, if potentially pertinent, retrieved as complete articles. The following inclusion criteria were used for potentially relevant studies: random allocation to treatment (dexmedetomidine versus any comparator with no restrictions on dose or time of administration); studies involving patients who required mechanical ventilation in an ICU. The exclusion criteria were duplicate publications (in this case we referred to the first article published while retrieved data from the article with the longest follow-up available), non-adult patients and lack of data on all of the following: ICU stay, time to extubation and mortality. Two investigators independently assessed compliance to selection criteria and selected studies for the final analysis, with divergences resolved by consensus.

**Data Abstraction and Study**

Baseline, procedural, and outcome data were independently abstracted by four trained investigators (table 1 and table 2). If a trial reported multiple comparisons [25,34], the comparators were aggregated as a single control group. At least two separate attempts at contacting original authors were made in cases of missing data. The co-primary endpoints of the present review were the length of ICU stay (days) and time to extubation (hours from randomization to extubation).

The secondary endpoint was mortality rate at the longest follow-up available. Adverse effects (hypotension and bradycardia as per author definition) were also analysed. Further endpoints included the number of patients requiring rescue doses of analgesic (opioids) or sedative (propofol, benzodiazepines, or any antipsychotics) drugs and the number of patients completely comfortable during ICU stay.

The internal validity and risk of bias of included trials was appraised by two independent reviewers according to the latest version of the “Risk of bias assessment tool” developed by The Cochrane collaboration [16], with divergences resolved by consensus. Publication bias was assessed by visually inspecting funnel plots and scatter plots and by analytical appraisal based on the Egger’s linear regression test and on the Peters’ test for asymmetry. According to the Egger [17] or Peters [18] methods for publication bias evaluation, a two-sided p value of 0.10 or less was regarded as significant.

**Data Analysis and Synthesis**

Computations were performed with Stata release 11, College Station, TX) and SAS 2002–08 program (release 9.2, SAS Institute, Inc, Cary, NC). Hypothesis of statistical heterogeneity was tested by means of Cochran Q test, with statistical significance set at the two-tailed 0.10 level, whereas extent of statistical consistency was measured with I², defined as 100% \times (Q-df)/Q, where Q is Cochran’s heterogeneity statistic and df the degrees of freedom. Binary outcomes from individual studies were analysed to compute individual and pooled risk ratio (RR) with pertinent 95% confidence interval (CI), by means of inverse variance method and with a fixed-effect model in case of low statistical inconsistency (I²<25%) or with random-effect model (which better accommodates clinical and statistical variations) in case of
| First author | Study endpoint | Dexmedetomidine dose | Start study drug | Stop study drug |
|--------------|----------------|----------------------|------------------|-----------------|
| Aziz NA [7]  | Sedation quality | 0.03–0.25 μg/kg/h  | ICU arrival     | After 24 hours  |
| Corbett SM [17] | Sedation quality | Loading dose of 1 μg/kg in 10 minutes followed by 0.2–0.5 μg/kg/h infusion | During surgery, after CPB | Propofol was discontinued before extubation while dexmedetomidine was continued for up to 1 hour after extubation |
| Elbaradie S [22] | Sedation quality | Loading dose of 2.5 μg/kg in 10 min followed by a 0.2–0.5 μg/kg/h infusion | ICU arrival | Before extubation |
| Esmaoglu A [23] | Sedation quality | Loading dose of 1 μg/kg in 10 minutes followed by a 0.2 μg/kg/h infusion | ICU arrival | NA |
| Herr DL [24] | Sedation quality | Loading dose of 1 μg/kg in 10 minutes followed by a 0.1–0.6 μg/kg/h infusion | Sternal closure | 6–24 hours after extubation |
| Jakob SM MIDEX [8] | Sedation quality | Loading dose of 0.2–1.4 μg/kg/h | Within 72 hours after ICU admission | Extubation, 14 days maximum |
| Jakob SM PRODEX [8] | Sedation quality | Loading dose of 0.2–1.4 μg/kg/h | Within 72 hours after ICU admission | Extubation, 14 days maximum |
| Khalil MA [14] | Sedation quality | Loading dose of 1 μg/kg in 10 minutes followed by a 0.5 μg/kg/h infusion | After induction of general anaesthesia | After stabilization of haemodynamics in the ICU |
| Leino K [9] | Renal effects | Five-step infusion of 4 μg/ml with the following decreasing infusion rate: 39 μl/h for 20 min, 24.3 μl/h for 40 min, 14 μl/h for 60 min, 10.3 μl/h for 120 min and then 7 μl/h (rates needed to achieve a pseudo steady-state plasma concentration of 0.60 μg/ml) | Immediately after anaesthesia induction | 4 h after ICU arrival |
| Maldonado JR [25] | Sedation quality | Loading dose of 0.4 μg/kg/h followed by 0.2–0.7 μg/kg/h | After CPB weaning | Maximum 24 h |
| Martin E [26] | Sedation quality | Loading dose of 1 μg/kg in 10 min followed by 0.4 μg/kg/h. The latter rate could be adjusted within the range of 0.2–0.7 μg/kg/h | Within 1 hour after ICU admission | For a minimum of 6 hours post extubation; total time was <24 hours |
| Memis D [27] | Gastric emptying | Loading dose of 2.5 μg/kg in 10 min followed by 0.2 μg/kg/h over 5 h infusion | Within 4 hours after ICU admission | 5 hours |
| Memis D [28] | Inflammatory responses and gastric intramucosal pH | Loading dose of 1 μg/kg in 10 min followed by 0.2–2.5 μg/kg over 24 h infusion | ICU | NA |
| Memis D [29] | Indocarbonyl green elimination | Loading dose of 1 μg/kg in 10 min followed by a maintenance of 0.2–2.5 μg/kg/h | NA | 24 hours |
| Menda F [10] | Haemodynamic response to endotracheal intubation | 1 μg/kg in 15 min | Anaesthesia induction | NA |
| Ozkan N [30] | Haemodynamics and mixed venous oxygen saturation | Loading dose of 1 μg/kg followed by 0.2–0.4 μg/kg/h | Anaesthesia induction | NA |
| Pandharipande PP [31] | Sedation quality | Maximum 1.5 μg/kg/hr | ICU | Until extubation, for maximum 120 hours |
| Reade MC [32] | Sedation quality | Loading dose of 1.0 μg/kg in 20 min if desired followed by 0.2–0.7 μg/kg/hour | ICU | As long as clinically indicated, including following extubation if required |
| Riker RR [33] | Sedation quality | Loading dose of 1 μg/kg followed by 0.2–1.4 μg/kg/h | Within 96 hours after intubation | Extubation, 30 days maximum |
| Ruokonen E [34] | Sedation quality | 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 | Within 72 hours after ICU admission | Maximum 14 days |
| Sahin N [15] | Sedation quality and haemodynamics | 0.4 μg/kg/h intraoperative; 0.2–0.4 μg/kg/h in ICU | Anesthesia induction | 45 hours after extubation |
| Shehabi Y [35] | Sedation quality | 0.1–0.7 μg/kg/ml | Within 1 hour after ICU admission | Removal of chest drains, maximum 48 hours |
| Tasdogan M [36] | Inflammatory responses and intra-abdominal pressure | Loading dose of 1 μg/kg in 10 min followed by 0.2–2.5 μg/kg/h | ICU arrival | 24 hours |
| Terao Y [11] | Sedation quality | Loading dose of 0.1 μg/kg/min in 10 minutes followed by 0.4 μg/kg/h | ICU arrival | First postoperative morning |

**Table 2.** Doses, sedation scales and target sedation levels.
moderate or high statistical inconsistency ($I^2>25\%$). Standardized mean differences (SMD), or weighted mean difference (WMD), and 95% confidence intervals were computed for continuous variables using the same models as just described. To evaluate if the small study effect had an influence on the treatment effect estimate, in case of evidence of between-study heterogeneity ($I^2>25\%$), we compared the results of both fixed and random effect models. Sensitivity analyses were performed by sequentially removing each study and reanalysing the remaining dataset (producing a new analysis for each study removed) and by analysing only data from blinded studies and studies with low risk of bias.

Statistical significance was set at the two-tailed 0.05 level for hypothesis testing. Unadjusted $p$ values are reported throughout. This study was performed in compliance with The Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [16,19,20] (Checklist S1).

**Results**

**Study Characteristics**

Database searches, snowballing, and contacts with experts yielded a total of 573 articles. The flow chart to select the final 27 manuscripts (28 trials) [7–15,21–38] is detailed in figure 1, with major exclusions available in the supplemental material (Texts S2 and S3).

The 27 included manuscripts randomized 3,648 patients (1,870 to dexmedetomidine and 1,778 to control) (tables 1 and 2). Clinical heterogeneity was mostly due to setting, control treatment, and follow-up duration. Indeed, 13 trials used dexmedetomidine in a general ICU setting [8,12,13,26–29,31–34,37], ten in cardiac surgery ICU patients [7,9,10,14,15,21,24,25,30,35], four in major non-cardiac surgery ICU patients [11,22,36,38] and one after caesarean section-eclampsia admitted to ICU [23]. Different techniques of dexmedetomidine administration were used: in 18 trials the continuous infusion was preceded by a loading dose that was often 1 mcg/kg [13,14,17,23,24,26–28,30,32,33,36] but that varied between 0.1 to 6 mcg/kg in other trials [11,22,25,27,30,34,37,38]. In other 6 trials only continuous infusion was used and ranged between 0.1 to 2.5 mcg/kg/h [7–9,15,31,35] while in one trial only the loading dose was used [10] and one trial gave no details [12]. Study quality appraisal indicated that trials were of medium quality (Table S1); in particular 12 of them had a low risk of bias.

Six different comparators were identified: propofol in 11 study arms [8,11,17,22,24,25,27,29,34,36,38], midazolam in 10 arms [8,12,13,15,21,24,25,30,33,34], placebo in 5 arms [9,10,14,26,37], morphine in 2 arms [7,35], haloperidol [32] and lorazepam [31] in one study.

**Table 2. Cont.**

| First author       | Study endpoint | Dexmedetomidine dose | Start study drug | Stop study drug |
|--------------------|----------------|----------------------|-----------------|-----------------|
| Triltsch AE [37]   | Sedation quality | Loading dose of 6 µg/kg/h in 10 min followed by 0.1–0.7 µg/kg/h | Within 1 hour after ICU admission | 6–7 hours after extubation, maximum overall 72 h |
| Venn RM [38]       | Sedation quality | Loading dose of 2.5 µg/kg/h followed by 0.2–2.5 µg/kg/h | ICU arrival | Extubation |
| Wan LJ [12]        | Sedation quality | Loading dose of 1 µg/kg in 10 min followed by 0.2–0.7 µg/kg/h | NA | NA |
| Yao L [13]         | Sedation quality | Loading dose of 6 µg/kg/h in 10 min followed by 0.1–0.7 µg/kg/h | NA | NA |

ICU: Intensive Care Unit; CPB: cardiopulmonary bypass; NA: not available.

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**Figure 1. Flow diagram.** The flow chart to select the final 27 manuscripts (28 trials).
doi:10.1371/journal.pone.0082913.g001

**Quantitative Data Synthesis**

**Effect of dexmedetomidine on ICU stay and time to extubation.** Overall analysis (figure 2; figure S1) showed that the use of dexmedetomidine was associated with a significant reduction in length of ICU stay (WMD = $-0.79$ [−1.17 to −0.40] days, $p$ for effect $<0.001$, $p$ for heterogeneity $<0.001$, I$^2$ = 93%, SMD = $-0.48$ [−0.78 to −0.18], $p$ for effect = 0.002, $p$ for heterogeneity $<0.001$, I$^2$ = 91%; with 17 studies and 2,424 patients included) with results confirmed when subanalyses were performed on studies including patients undergoing elective surgery (SMD = $-0.60$ [−1.05 to −0.13], $p$ for effect = 0.008 with 8 studies included), in those including patients undergoing short term sedation (SMD = $-0.45$ [−0.81 to −0.09], $p$ for effect = 0.02 with 11 studies included), in those including patients undergoing...
receiving a loading dose (SMD = -0.58 [-1.03 to -0.13], p for effect = 0.01 with 11 studies included) and in those receiving low (<0.7 μg kg⁻¹ h⁻¹) maintenance dose of dexmedetomidine (SMD = -0.62 [-1.04 to -0.20], p for effect = 0.004 with 10 studies included) as detailed in table 3.

The use of dexmedetomidine was also associated (figure 3; figure S2) with a significant reduction of time to extubation (WMD = -2.74 [-3.80 to -1.65] hours, p for effect <0.001, p for heterogeneity <0.001, I² = 91%, SMD = -0.39 [-0.66 to -0.11], p for effect = 0.005, p for heterogeneity <0.001, I² = 93% with 24 studies and 3,478 patients included). Further subanalyses, detailed in table 3, confirmed these findings in patients receiving short term sedation (SMD = -0.28 [-0.49 to -0.07], p for effect = 0.009 with 18 studies included); in those receiving a low (<0.7 μg kg⁻¹ h⁻¹) maintenance dose (SMD = -0.30 [-0.53 to -0.07], p for effect = 0.009 with 16 studies included) and in those undergoing elective surgery (SMD = -0.31 [-0.52 to -0.09], p for effect = 0.005 with 17 studies included); with most of the positive finding coming from the cardiac surgery setting (SMD = -0.42 [-0.75 to -0.10], p for effect = 0.01 with 10 studies included). The largest study [8] included in this meta-analysis was also the only one to report both median and mean values for mechanical ventilation. Since these data were skewed, we repeated the analyses including median instead of mean values and didn’t find differences in pooled estimate results (SMD = -0.39, 95% CI -0.66 to -0.12, I² = 93%).

Further subanalyses with the different comparators (propofol, midazolam, placebo and morphine) are detailed in supplemental material (Table S2, Table S3, Table S4 and Table S5) but were not informative with respect to ICU stay or time to extubation due to the paucity of trials included.

Visual inspection of funnel and scatter plots (figures 4 and 5; figures S3 and S4) did not identify a skewed or asymmetrical shape for the co-primary endpoints. Quantitative evaluation did not suggest a presence of publication bias, as measured by the Egger’s test (p = 0.4 for the length of ICU stay and p = 0.5 for time to extubation) and Peters’ test (p = 0.6 for the length of ICU stay and p = 0.9 for time to extubation). Since the funnel plots identified three outlier studies [14,32,33] we repeated the analyses removing
### Table 3. Sensitivity analyses of intensive care unit stay and time to extubation.

| Outcome | Number of included patients | Dex patients | Control patients | SMD | 95% CI | P for effect | P for heterogeneity | I² (%) |
|---------|----------------------------|--------------|-----------------|-----|--------|-------------|-------------------|--------|
| ICU stay | 28 trials (27 manuscripts) | 1,870 patients | 1,778 patients | -0.48 | -0.78 to -0.18 | 0.002 | <0.001 | 86 |
| Postoperative elective surgery patients | 6 | 373 patients | 372 patients | 0.37 | 0.10 to 0.54 | 0.008 | <0.001 | 99 |
| Cardiac surgery | 6 | 336 patients | 336 patients | 0.27 | -0.11 to 0.13 | 0.04 | <0.001 | 98 |
| Non-Cardiac surgery | 2 | 36 patients | 36 patients | 0.38 | -0.10 to 0.27 | 0.02 | <0.001 | 92 |
| Long-term sedation | 13 | 1,548 patients | 1,447 patients | 0.41 | 0.29 to 0.52 | 0.005 | <0.001 | 93 |
| No loading dose | 6 | 281 patients | 282 patients | 0.04 | -0.26 to 0.34 | 0.93 | <0.001 | 99 |
| Loading dose | 10 | 281 patients | 282 patients | 0.44 | 0.28 to 0.60 | 0.004 | <0.001 | 94 |
| Low maintenance dose (<0.7 μg kg⁻¹ h⁻¹) | 7 | 395 patients | 394 patients | 0.14 | -0.25 to 0.53 | 0.25 | <0.001 | 95 |
| High maintenance dose | 7 | 859 patients | 737 patients | 0.42 | 0.13 to 0.71 | 0.01 | <0.001 | 83 |
| Loading dose and high maintenance dose | 2 | 142 patients | 40 patients | 0.09 | -0.79 to 0.96 | 0.81 | 0.12 | 60 |
| Sensitivity analyses (including only blinded studies) | 8 | 891 patients | 768 patients | 0.56 | 0.04 to 1.09 | 0.04 | <0.001 | 95 |
| Sensitivity analyses (including only low risk of bias studies) | 10 | 1,065 patients | 940 patients | 0.44 | 0.02 to 0.86 | 0.04 | <0.001 | 94 |

Time to extubation

| Outcome | Number of included patients | Dex patients | Control patients | SMD | 95% CI | P for effect | P for heterogeneity | I² (%) |
|---------|----------------------------|--------------|-----------------|-----|--------|-------------|-------------------|--------|
| Time to extubation | 24 | 1,804 patients | 1,674 patients | -0.39 | -0.66 to -0.11 | 0.005 | <0.001 | 93 |
| Postoperative elective surgery patients | 7 | 310 patients | 311 patients | 0.59 | 0.10 to 0.10 | 0.01 | <0.001 | 89 |
| Cardiac surgery | 7 | 310 patients | 311 patients | 0.42 | 0.07 to 0.77 | 0.03 | <0.001 | 95 |
| Non-Cardiac surgery (3 studies did not specify the operative setting) | 4 | 76 patients | 76 patients | 0.15 | -0.01 to 0.27 | 0.04 | <0.001 | 76 |
| Sensitivity analyses (including only low risk of bias studies) | 10 | 1,055 patients | 940 patients | 0.44 | 0.02 to 0.86 | 0.04 | <0.001 | 94 |

Sensitivity analyses of intensive care unit stay and time to extubation.

- **Overall trials**: 28 trials (27 manuscripts) 1,870 patients 1,778 patients
- **ICU stay**: 17 trials 1,274 patients 1,150 patients
- **Postoperative elective surgery patients**: 6 trials 373 patients 372 patients
- **Cardiac surgery**: 6 trials 336 patients 336 patients
- **Non-Cardiac surgery**: 2 trials 36 patients 36 patients
- **Long-term sedation**: 13 trials 1,548 patients 1,447 patients
- **No loading dose**: 6 trials 281 patients 282 patients
- **Loading dose**: 10 trials 281 patients 282 patients
- **Low maintenance dose (<0.7 μg kg⁻¹ h⁻¹)**: 7 trials 395 patients 394 patients
- **High maintenance dose**: 7 trials 859 patients 737 patients
- **Loading dose and high maintenance dose**: 2 trials 140 patients 40 patients
- **Sensitivity analyses (including only blinded studies)**: 8 trials 891 patients 768 patients
- **Sensitivity analyses (including only low risk of bias studies)**: 10 trials 1,065 patients 940 patients

*Note: All SMDs are significant at the 0.05 level.*
### Table 3. Cont.

| Outcome                  | SMD       | 95% CI     | P for effect | P for heterogeneity | I² (%)
|--------------------------|-----------|------------|--------------|--------------------|--------
| **Rescue doses of analgesic drugs** |           |            |              |                    |        
| Overall trials           | 1.778     | 0.66       | 0.001        | <0.001             | 279/1,266 [22%]
| No loading dose          | 1.112     | -0.72      | 0.38         | <0.001             | 24/1,404 [12%]
| Loading dose and high maintenance dose | 1.904     | -0.31      | 0.31         | <0.001             | 3/320 [1%]
| Sensitivity (removing 1 study at time) All 95% CIs of SMD, 0, and p<0.05 |           |            |              |                    |        
| Overall trials           | 0.38      | 0.04       | 0.04         | <0.001             | 279/1,266 [22%]
| No loading dose          | 0.56      | -0.38      | 0.38         | <0.001             | 24/1,404 [12%]
| Loading dose and high maintenance dose | 1.34      | -0.74      | 0.34         | <0.001             | 3/320 [1%]
| Sensitivity (removing 1 study at time) All 95% CIs of SMD, 0, and p<0.05 |           |            |              |                    |        
| Overall trials           | 0.38      | 0.04       | 0.04         | <0.001             | 279/1,266 [22%]
| No loading dose          | 0.56      | -0.38      | 0.38         | <0.001             | 24/1,404 [12%]
| Loading dose and high maintenance dose | 1.34      | -0.74      | 0.34         | <0.001             | 3/320 [1%]

The overall analyses using weighted mean differences showed a reduction in intensive care unit stay of -2.741 (95% CI: -3.80 to -1.65) hours in the dexmedetomidine group. It should be noted that the standard mean differences used in this table is not expressed in days or hours.

Dex: dexmedetomidine; CABG: coronary artery bypass grafting.

| 200/1,499 [13%] in the dexmedetomidine group versus 353/564 [63%] in the control group, RR = 0.80 [0.66 to 0.98], p = 0.03; with no differences in the number of patients requiring rescue doses of sedative drugs (271/532 [51%] in the dexmedetomidine group versus 353/564 [63%] in the control group, p = 0.3) (Table 4).

Dexmedetomidine was associated with an increased rate of bradycardia [220/1,374 (16%) in the dexmedetomidine group versus 64/1,246 [5%] in the control group, RR = 2.43 [1.38 to 3.14], p < 0.001, p for heterogeneity = 0.9, I² = 0% with 17 studies included] and with a trend towards an increased rate of hypotension [424/1,389 (31%) in the dexmedetomidine group versus 279/1,266 [22%] in the control group, RR = 1.27 [1.00 to 1.61], p for effect 0.052, p for heterogeneity <0.001, I² = 62% with 19 studies included) (Table 4).

No difference in mortality was recorded at the longest follow-up available [200/1,499 [13%] in the dexmedetomidine group versus 173/1,409 [12%] in the control group, RR = 1.00 [0.84 to 1.21], p for effect = 0.9 with 20 studies included]. The univariate meta-regression of average follow-up against log-risk mortality showed no significant effects for time on mortality (n = 20, slope coefficient = -0.001 [-0.003 to 0.001], p = 0.31) (Table 4).

**Sensitivity analyses**

Estimate results from both random and fixed effect models were extremely similar (table 3); hence we excluded a considerable small study effect. Sensitivity analyses performed by sequentially removing each study and reanalysing the remaining dataset (producing a new analysis for each study removed), did not determine major changes in direction or magnitude of statistical findings, confirming the pooled effect of each co-primary endpoints (all SMD<1) and the statistical significance (all p of effect <0.05). Sensitivity analyses carried out with studies with low risk of bias confirmed the overall results of our work showing a reduction in length of ICU stay in dexmedetomidine versus control group (SMD = 0.44 [-0.86 to -0.02] p for effect = 0.04, p for heterogeneity <0.001, I² = 94% with 10 studies and 2,005 patients included) and in time to extubation (SMD = -0.72 [-1.34 to -0.10], p for effect = 0.02, p for heterogeneity <0.001, I² = 97% with 3 studies and 1,922 patients included). Sensitivity analyses carried out with blinded studies confirmed the overall results of our work showing a reduction in length of ICU stay in dexmedetomidine versus control group (SMD = -0.56 [-1.09 to -0.04], p for effect = 0.04, p for heterogeneity <0.001, I² = 95% with 8 studies and 1,659 patients included) and a reduction in time to extubation (SMD = -0.56 [-1.06 to 0.05], p for effect = 0.03, p for heterogeneity <0.001, I² = 97% with 10 studies and 2,353 patients included).
Our meta-analysis confirmed that dexmedetomidine is associated with a reduction in ICU stay and suggested that it might reduce the time of extubation when compared to other sedative or hypnotic agent. Even if dexmedetomidine is associated with an increase in the risk of bradycardia and with a trend toward an increased risk of hypotension, no detrimental effects on mortality were detected.

The ideal sedative agent should provide anticipated, predictable effects, rapid onset, and quick recovery. It should be easy to administer with no adverse events, no interaction with other drugs, no accumulation of metabolites and no withdrawal effects at the end of infusion. Unluckily an ideal sedative agent that can suit the need of all patients does not yet exist.

Dexmedetomidine is one of the most recently released intravenous agents for sedation in the ICU, though the drug started to be investigated more than 20 years ago. It was introduced in clinical practice in the United States in 1999 while the European Medicine Agency authorised its use for all 27 European member states in September 2011. It is an alpha2-agonist and produces sedation acknowledged as “cooperative” or “arousable”, which is different from the sedation “clouding of consciousness” induced by drugs acting on GABA receptors, such as midazolam or propofol [39]. Tan and Ho, in a previous meta-analysis updated on December 2009 [6] reported that when dexmedetomidine was compared with alternative sedative agents it was associated with a statistically significant reduction in length of ICU stay, but not in duration of mechanical ventilation. We updated their findings on February 2013 identifying eight recently published manuscripts [7–14] and one trial that was not identified in their systematic search [15], thus increasing the number of patients by 50% (up to 3,648 overall randomized patients included) and providing more robust safety data. By

**Figure 3. Forest plot for the time to extubation.** Overall analysis showed that the use of dexmedetomidine was associated with a significant reduction of time to extubation (SMD = -0.39 [-0.66 to -0.11], p for effect = 0.005, p for heterogeneity <0.001, I² = 93% with 24 studies and 3,478 patients included). CI = confidence interval; SMD = standardized mean difference; N = number; SD = standard deviation; Dex = dexmedetomidine. doi:10.1371/journal.pone.0082913.g003

**Discussion**

Our meta-analysis confirmed that dexmedetomidine is associated with a reduction in ICU stay and suggested that it might reduce the time of extubation when compared to other sedative or hypnotic agent. Even if dexmedetomidine is associated with an increase in the risk of bradycardia and with a trend toward an increased risk of hypotension, no detrimental effects on mortality were detected.

The ideal sedative agent should provide anticipated, predictable effects, rapid onset, and quick recovery. It should be easy to administer with no adverse events, no interaction with other drugs, no accumulation of metabolites and no withdrawal effects at the end of infusion. Unluckily an ideal sedative agent that can suit the need of all patients does not yet exist.

Dexmedetomidine is one of the most recently released intravenous agents for sedation in the ICU, though the drug
adding more patients data we were able to show, for the first time in a meta-analysis, that dexmedetomidine increases the rate of bradycardia when all trials are pooled together and also shows a trend towards an increase rate of hypotension. However, these side effects were not associated with differences in mortality [200/1499 (13%) in the dexmedetomidine group vs 173/1409 (12%) in the control group, p = 0.9 with 20 studies included). 

Dexmedetomidine decreases sympathetic nervous system activity and is therefore associated with an increase in cardiovascular adverse events. These effects may be most pronounced in patients with decreased autonomic nervous system response such as the elderly, diabetic patients, patients with chronic hypertension or severe cardiac disease such as valve stenosis or regurgitation, advanced heart block, severe coronary artery disease, or in patients who are already hypotensive and/or hypovolemic [40]. Therefore, in patients who depend on a high level of sympathetic tone or in patients with reduced myocardial function who cannot tolerate the decrease in sympathetic tone, loading doses of

Figure 4. Funnel plot for the length of ICU stay. Visual inspection of funnel plots did not identify a skewed or asymmetrical shape for the co-primary endpoints. Quantitative evaluation did not suggest a presence of publication bias, as measured by the Egger’s test (p = 0.4) and Peters’ test (p = 0.6). ICU = intensive care unit; SE = standard error; SMD = standardized mean difference.
doi:10.1371/journal.pone.0082913.g004

Figure 5. Funnel plot for the time to extubation. Visual inspection of funnel plots did not identify a skewed or asymmetrical shape for the co-primary endpoints. Quantitative evaluation did not suggest a presence of publication bias, as measured by the Egger’s test (p = 0.5) and Peters’ test (p = 0.9). SE = standard error; SMD = standardized mean difference.
doi:10.1371/journal.pone.0082913.g005
Dexmedetomidine should be avoided. On the other side, the characteristics of dexmedetomidine to provide an ongoing sedation and sympathetic block could be beneficial in reducing early postoperative ischemic events in high-risk patients [41–42].

Intravenous administration of dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with an half-life (\(t_{1/2}a\)) of 6 min, a terminal elimination half-life (\(t_{1/2}b\)) of 2 hours, and a steady-state volume of distribution (\(V_{ss}\)) of 118 litres. It presents linear kinetics when infused in the range of 0.2–0.7 mg/kg/h for no more than 24 hours and undergoes almost complete biotransformation through direct glucuronidation and cytochrome P450 metabolism. Consequently it can accumulate in patients who are on P450 enzyme inhibitors, some of which are commonly used in ICU. Metabolites of biotransformation are excreted in the urine (95%) and faeces [43].

**Limitations**

We acknowledge that this study has several limitations. The quality of the included studies is not high since only 13 of them were blind. Moreover we noted high heterogeneity between the included studies. The heterogeneity remained when sensitivity analyses on studies with low risk of bias where performed. It was abolished only removing three outliers studies cited above. Nonetheless we excluded the possible influence of small-study effects on the results of our meta-analysis comparing the fixed- and random-effects estimates of the treatment effect (table 3). The overall reduction in ICU stay and time to extubation may appear clinically modest, but it should be acknowledged that the largest study [8] had very conservative imputation rules (to worst outcome) and this might have softened our results.

**Conclusions**

Dexmedetomidine for sedation in mechanically ventilated critically ill adult patients seems to help to reduce time to extubation and ICU stay. The known side effects (increased incidence of bradycardia and a trend toward an increased risk of hypotension) had no effect on the overall mortality in this meta-analysis of all the RCTs published so far.

Larger, multicentre, randomized clinical trials, especially in long term sedated patients requiring mechanical ventilation, would be welcome to confirm these findings.

**Supporting Information**

**Checklist S1 PRISMA checklist.**

(DoC)

**Figure S1 Forest plot for the length of ICU stay using standard mean difference (days) instead of weighted mean difference (absolute value with no units of measurement).** Overall analysis showed that the use of dexmedetomidine was associated with a significant reduction in length of ICU stay (SMD = −0.48 [−0.78 to −0.18]), p for effect = 0.002, p for heterogeneity <0.001, I² = 91% with 17 studies and 2,424 patients included. ICU = intensive care unit; CI = confidence interval; SMD = standardized mean difference; N = number; SD = standard deviation.

(DoC)

**Figure S2 Forest plot for the time to extubation using standard mean difference (days) instead of weighted mean difference (absolute value with no units of measurement).** Overall analysis showed that the use of dexmedetomidine was associated with a significant reduction of time to extubation (SMD = −0.39 [−0.66 to −0.11]), p for
effect = 0.005, p for heterogeneity < 0.001, I² = 93% with 24 studies and 3,478 patients included. CI = confidence interval; SMD = standardized mean difference; N = number; SD = standard deviation

Figure S3 Scatter plot for ICU stay

Figure S4 Scatter plot for time to extubation

Table S1 Methodological quality summary: review

Table S2 Subanalysis with propofol as comparator drug (DOCX)

Table S3 Subanalysis with midazolam as comparator drug (DOCX)

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Table S4 Subanalysis with morphine as comparator drug (DOCX)

Table S5 Subanalysis with placebo as comparator drug (DOCX)

Text S1 Full PubMed search strategy (DOCX)

Text S2 Major exclusions (DOCX)

Text S3 References of the excluded studies (DOCX)

Author Contributions

Conceived and designed the experiments: LP TG AV CNN LC GL GF AZ. Performed the experiments: LP TG PF AV CNN LC GL GF AZ. Analyzed the data: LP TG PF AV CNN LC GL GF AZ. Contributed reagents/materials/analysis tools: LP TG PF AV CNN LC GL GF AZ. Wrote the paper: LP TG PF AV CNN LC GL GF AZ.
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