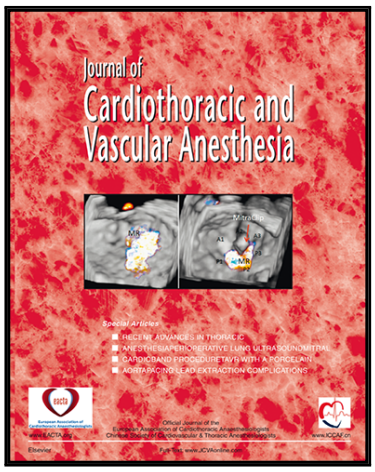

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Critical Review and Meta-Analysis of Postoperative Sedation after Adult Cardiac Surgery: Dexmedetomidine vs. Propofol

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Abstract

Objective

To evaluate reports from the published literature of all randomized clinical trials (RCT) comparing postoperative sedation with dexmedetomidine (Dex) versus propofol (Prop) in adult patients, after open cardiac surgery.

Design

A computerized search on Medline, EMBASE, Web of Science, and Agency for Healthcare Research and Quality databases was completed through June 2020. Meta-analysis of all published RCT comparing Dex versus Prop utilization in the postoperative phase, utilizing the standard PRISMA checklist.

Setting

Assemblage and critical discussion of eleven RCTs comparing postoperative sedation from standard published reports from 2003 to 2019.

Participants

The comparison of comprised 1184 patients and analyzed critical discussion of time-based parameters (time to extubation; intensive care unit length of stay; hospital length of stay) and non-time-dependent factors (delirium; bradycardia and hypotension).

Measurements and Main Results

Time to extubation was significantly reduced in the dexmedetomidine group (Standardized Mean Difference (SMD) = -0.70, 95% Confidence Interval (CI): -0.98 to -0.42, $p<0.001$), however no difference in mechanical ventilation time was observed (SMD= -0.72, 95% CI: -1.60 to 0.15, N.S.). Dexmedetomidine significantly reduced the Intensive Care Unit length of stay (SMD= 0.23, 95% CI: -1.06 to -0.16, $p=0.008$), but this did not translate into a reduced hospital length of stay (SMD= -1.13, 95% CI: -2.43 to 0.16, N.S). For non time-dependent factors: incidence of delirium was unaffected between groups (OR:0.68, 95% CI: 0.43 to 1.06, N.S).while higher rates of bradycardia (OR: 3.39, 95% CI: 1.20 to 9.55, $p=0.020$) and hypotension (OR: 1.68, 95%CI: 1.09 to 2.58, $p=0.017$) were reported with propofol.

Conclusions

Despite the ICU time advantages afforded by dexmedetomidine over propofol, the former does not seem to contribute to an overall reduction in hospital length of stay or improvement in postoperative outcomes of heart valve surgery and CABG patients.

Keywords

- dexmedetomidine
- propofol
- adult open cardiac surgery
- postoperative sedation

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List of Abbreviations

CVDs	Cardiovascular Diseases
CABG	Coronary Arterial Bypass Grafting
CI	Confidence Interval
CMA	Comprehensive Meta-Analysis
ICU	Intensive Care Unit
IQR	Inter Quartile Ranges
LOS	Length of Stay
LOS-H	Length of Stay in the Hospital
LOS-ICU	Length of Stay in Intensive Care Unit
MeSH	Medical Subject Headings
MVT	Mechanical Ventilation Time
OR	Odds Ratio
PACU	Post-anesthesia Care Unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SD	Standard Deviation
SMD	Standardized Mean Difference
TTE	Time to Extubation

BACKGROUND

Due to the prevalence of cardiovascular diseases (CVDs) in the world's population [1-,3], Coronary Arterial Bypass Grafting (CABG) and valvular surgery represent a large percentage of the cardiac surgeries performed. Despite current advancements in surgical techniques, postoperative complications in adult cardiac surgery can affect up to 30% of patients and include stroke, renal failure, deep sternal wound infection, and prolonged ventilation or length of stay [4-6].

Patients must be closely monitored during their stay in the post-anesthesia care unit (PACU) or intensive care unit (ICU) to ensure early detection of acute complications. In these settings, opioids and sedatives are administered to reduce the incidence of postoperative pain, agitation, and delirium [7,8]. However, high dosages of sedatives can lead to prolonged ventilation, prolonged stay (LOS), and other drug-specific side effects. To evaluate the best strategies, several studies investigated the use of dexmedetomidine versus propofol in postoperative sedation of cardiac surgery patients, but with limited sample sizes.

Propofol has been widely used after cardiac surgery for its ease of administration, rapid onset, and short awakening time [9]. However, a common side effect administration is hypotension, and its use as a sedative is limited by the depressant effect on respiration, which can be exacerbated with the administration of opioids [9,10]. In contrast, dexmedetomidine is a highly selective alpha-2 adrenergic agonist that provides sympatholytic, sedative, anxiolytic, and analgesic effects without causing respiratory depression [11]. Even if a risk of hypotension and bradycardia is present, its use is growing. Since 2007, dexmedetomidine has been approved for the sedation of non-intubated patients before and during surgical procedures [12].

Thus, here we have conducted a meta-analysis on published studies to assess which strategy could improve the quality of sedation and outcomes in post-cardiac surgery patients, along with a critical review of the outcomes described in the literature.

Methods

Search Strategy

Our study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [13] to identify all English language RCTs that evaluated the use of dexmedetomidine in comparison to propofol for sedation of postoperative cardiac surgery patients.

The controlled vocabulary of Medical Subject Headings (MeSH) from PubMed, including subheadings, publication types, and supplementary concepts, was used to define the research terms. The search was performed up to June 30, 2020, on PubMed/Medline, EMBASE, Web of Science, and Agency for Healthcare Research and Quality (AHRQ) using the following selected terms combined with the Boolean operator AND: "dexmedetomidine", "propofol", and "cardiac". Additional post-hoc filters were applied for searches returning more than 300 results. No publication date restrictions were applied. In order to include all possible studies, a further search for grey literature was performed from June 30, 2020 (see Supplementary Materials 1 for algorithm details).

Titles and abstracts of identified literature were independently screened by two authors (HA, GE). Literature not complying with the inclusion criteria was excluded. When disagreement occurred, the opinion of a third reviewer (MP) was sought. Records whose full text was unavailable were excluded in the inclusion stage. To further reduce the risk of overlooking

pertinent literature, a hand search of reference lists in the included literature and relevant meta-analyses was conducted. The study selection process is described in the flow diagram below [Figure 1].

Inclusion and exclusion criteria

- Inclusion criteria:
  - RCTs;
  - use of dexmedetomidine in comparison to propofol for sedation of postoperative surgeries;
  - any Cardiac surgery;
  - age > 18 years.

- Exclusion criteria:
  - non – English literature;
  - literature without an available abstract
  - literature without available data

Data extraction

Data extraction was performed by two investigators, according to PRISMA guidelines [13] (EA, GA). These basic features were obtained: primary author, publication year, study design, and country, along with the number, mean age, and gender of participants [Table 1]. Time to Extubation (TTE), Mechanical Ventilation Time (MVT), Length of Stay in Intensive Care Unit (LOS-ICU), and Length of Stay in the Hospital (LOS-H) were defined as time-dependent outcomes, while other three items (delirium, bradycardia, and hypotension) were defined as non-time-dependent [Table 2].

TTE was defined as the number of minutes from intubation in the operating room to extubation, and MVT as the number of minutes that the patient needed mechanical ventilatory support after the arrival in PACU. The two LOS outcomes are referred to as the period of stay in ICU and in the hospital, respectively. These outcomes were selected because they were frequently reported in this field, therefore increasing the external validity of our meta-analysis. For each outcome, the number of studies that addressed the item was specified [Table 2, last row]. Other possible associations depicted by the included studies on other possible outcomes or adverse effects were only discussed if a statistical analysis was considered unreliable.

Risk of Bias

Two authors (GE, MP) assessed the risk of bias of each included study independently. Disagreements were resolved by consultation with a third author (AE). Risk of bias was assessed using the following items, according to the Cochrane Collaboration's tool [15, 16]: random sequence generation (selection bias); allocation concealment (selection bias); blinding (performance bias and detection bias), blinding of participants and personnel assessed separately from blinding of outcome assessment; incomplete outcome data (attrition bias); selective reporting (reporting bias). The risk of bias was defined as 'low risk', 'high risk', or 'unclear risk', and individual bias items were evaluated as described in the Cochrane Handbook for Systematic Reviews of Interventions [15]. Reporting bias was assessed using funnel plots [17, 18]; briefly, variables were evaluated by plotting standard error (S.E.) against estimated effect size, SDM for time-dependent variables, and log of the odds ratio for non-time dependent variables. The Egger test was utilized as a regression test for funnel plot asymmetry in order to estimate the impact of small-study effects. A p-value of <0.05 was considered significant.

Data and Quality analysis

In this manuscript, all statistical analyses were performed using the Comprehensive Meta-Analysis (CMA) software (version 3.0; Biostat Inc., Englewood, NJ, USA). Mean, and standard deviation (S.D.) were used to report continuous variables. Age is only reported as a mean value. When only a median was available, Wan's formula was used to convert median and Inter Quartile Ranges (IQR) into mean and S.D. values, as it has been demonstrated to be more accurate than Hozo's method for sample sizes exceeding n = 25 [14]. Categorical variables were described using frequencies. For estimating the effect of each outcome, the Standardized Mean Difference (SMD) and Odds Ratio (OR) are reported at a 95% Confidence Interval (CI). The p values were two-tailed and considered statistically significant if less than 0.05. Heterogeneity was assessed using Cochran's Q test with $p<0.05$ for statistical significance and I^2 index>50% for substantial heterogeneity. Fixed Effect Model was used if no significant heterogeneity was present. However, if heterogeneity was significant, Random Effect Model was used. In the analysis of the outcomes, six of the outcomes had significant heterogeneity, and those included TTE, MVT, LOS-ICU, LOS-H, delirium, and hypotension.

RESULTS

Our final analysis included 11 RCTs [Table 1]. These studies were published between 2003 and 2019 and included a total of 1184 patients that underwent heart valve surgery or CABG. Of note, most of the RCTs were carried out in the USA and China (3 studies respectively), and the smallest trial included only 25 patients for each arm [27]. The most assessed outcomes were TTE and LOS-ICU (8/11), followed by delirium (6/11). None of the included trials assessed all the outcomes selected for this meta-analysis at the same time. The study conducted by Liu in 2016 [24] was the only one to assess most of the endpoints (all except MVT) [Table 2]. According to our analysis, TTE was significantly reduced in the dexmedetomidine group (in 8/8 studies, SMD = -0.70, 95% CI: -0.98 to -0.42, $p<0.001$) [Figure2-A]; however no difference in mechanical ventilation time was observed (SMD= -0.72, 95% CI:-1.60 to 0.15, N.S.) [Figure 2-B]. Furthermore, dexmedetomidine significantly reduced LOS-ICU (in 7/8 studies; SMD= 0.23, 95% CI: -1.06 to -0.16, p=0.008) [Figure 3-A] but this did not translate into a reduced LOS-H (SMD= -1.13, 95% CI: -2.43 to 0.16, N.S) [Figure 3-B]. With regard to non-time dependent events, no difference in the incidence of delirium was detected between groups (OR: 0.68, 95% CI: 0.43 to 1.06, N.S.) [Figure 4-A]. In contrast, bradycardia (4/4 studies; OR: 3.39, 95% CI: 1.20 to 9.55, p=0.020) [Figure 4-B] and hypotension (in 5/5 studies; OR: 1.68, 95%CI: 1.09 to 2.58, p=0.017) [Figure 4-C] were significantly more reported with dexmedetomidine.

As depicted in Table 3, the overall quality of the studies is moderate. Except for one study [28], none of the papers fully met the “blinding of participants and personnel” bias criterion (Table 3). No small-study effects were found as a result of funnel analysis (Supplementary Materials 2).

DISCUSSION

This work represents a meta-analysis of the largest number of RCTs about the use of dexmedetomidine versus propofol in the sedation following heart valve surgery and CABG currently available, involving 11 RCTs, totaling 1184 patients.

Our results are consistent with those of Liu X et al., [1] showing a reduction in TTE in the dexmedetomidine group [Figure 2-A]. Still, MVT seems to be unaffected by the type of sedation in our analysis [Figure 2-B], as previously found by Chang et al. [30]. Furthermore, dexmedetomidine is associated with a reduction in LOS-ICU, as shown in [Figure 3-A] but not LOS-H [Figure 3-B]. In any case, the reduction in LOS-ICU could translate in a proportional cut in costs or exposure to infections, and increase patients' turnover with more beds available. However, these four time-dependent outcomes showed significant limitations. Many factors, such as patients' comorbidities, surgical complications, and postoperative bleeding, are well known to influence the postoperative care of cardiac surgery patients [37, 38, 39]. Any postoperative complication can delay the timing of extubation directly (e.g., prolonged ventilation) or indirectly (e.g., re-operation) and alter the value of time-dependent endpoints. Moreover, there is no consensus about the time of extubation after cardiac surgery, mostly relying on local protocols and physician's evaluations, thus changing both TTE and MVT and, accordingly, LOS in ICU and the hospital [32]. A prolonged LOS-ICU or LOS-H has several implications, ranging from the increased risk of infections to adverse outcomes and growing financial issues [37]. Since the debate on the best "fast-track cardiac recovery" modality is still ongoing, the possible interference of this lack of consensus with results cannot be ruled out. Therefore, we think that these time-dependent outcomes are inaccurate in the evaluation of postoperative sedation. In future investigations, it might be possible to stratify patients in classes

of postoperative risk of complications and risk of prolonged LOS, and then assess other endpoints, such as the time elapsed between the decision to extubate and the actual extubation time.

Delirium incidence in adult ICU is related to several factors, such as age, mechanical ventilation, or pain. Furthermore, delirium is strongly associated with increased ICU mortality and post – ICU cognitive impairment, establishing a vicious circle with LOS-ICU [7]. Unlike previous meta-analyses [1, 32-33], ours did not find a statistically significant difference in the incidence of delirium between the two groups of patients [Figure 4-A]. A possible explanation for this result is that our analysis included a more recent trial that favored propofol over dexmedetomidine [29] and could have influenced the results.

Propofol has been used for decades in general anesthesia and cardiac surgery, despite its direct cardiovascular depressant effects [34]. However, our analysis suggests a significantly increased incidence of bradycardia and hypotension in dexmedetomidine sedated patients following heart valve surgery and CABG. Such adverse effects have already been reported using dexmedetomidine, but promptly resolved with fluid boluses. Also, in a previous review, Wu and coll. proposed a correlation between cardiovascular effects and dexmedetomidine infusion at high doses or started with a loading dose [33]. Therefore, close advanced monitoring with at least heart rhythm and non-invasive blood pressure should be used in this subset of patients, regardless of the agent used for sedation, and possibly avoiding boluses.

Several limitations were noted during our analysis. Firstly, analgesic therapy used during post-surgery showed high variability in dosage and duration, also not always stated. This variability was also observed with regard to other sedatives (e.g., benzodiazepines) used during the surgeries, without a standardized protocol for general anesthesia. Such variability could have

affected both time-dependent outcomes and especially delirium, which has several influencing factors precipitating this clinical condition. Future trials should take into account these aspects and try to follow a standardized protocol. Although our study intended to include all types of cardiac surgery, the search did not return any paper regarding cardiac transplants in the adult population. The post-cardiac transplant sedation has been covered only on the pediatric population, in which dexmedetomidine showed better prevention of opioid withdrawal syndrome [40]. However, more efforts are needed to evaluate sedation after this vital subset of cardiac surgeries, with particular attention to the sympatholytic effects of dexmedetomidine on a denervated transplanted heart.

Additionally, the sedation scales used in these studies (RASS and Ramsey scores) are often affected by incorrect evaluation by healthcare professionals [41] and are validated on sedatives in general but not specifically on dexmedetomidine (that has a specific alpha – 2 receptor agonism related sedation mechanism). Since dexmedetomidine sedation resembles natural sleep [43], future studies should carefully assess this particular aspect of sedation level evaluation. Finally, the medical authorities globally, except for two countries, recommend limiting the use of dexmedetomidine to 24 hours; this may limit the benefits seen from using such a sedative in the postoperative setting of cardiac surgery patients [42].

Conclusion

This meta-analysis did not find particular advantages in the use of dexmedetomidine than propofol for the sedation of post-cardiac surgery patients. Time-dependent parameters, widely used in previous trials in this field, are inaccurate due to several reasons and are not reliable for a proper evaluation of the benefits of dexmedetomidine versus propofol. More efforts are needed to find new, reliable outcomes, standardize sedation protocols in post-cardiac surgery patients, and assess mid- and long-term outcomes in the two groups.

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Figure/Table Legend

Figure 1: Study flow diagram.

Table 1: Baseline characteristics of the 11 included trials.

RCT: Randomized Clinical Trial; Dex: dexmedetomidine.

Table 2: Outcomes assessed and features of the 11 included trials. TTE: Time To Extubation; MVT: Mechanical Ventilation Time; LOS-ICU: Length Of Stay in Intensive Care Unit; LOS-H: Length Of Stay in the hospital. dex: dexmedetomidine; prop: propofol; NS: the difference is statistically not significant; S: the difference is statistically significant, n/a: not assessed. When significant, the symbol > means "is prolonged with / the incidence is increased with" the drug indicated. When non significant, the eventual direction of the trend is indicated.

TTE and LOS-ICU were the most assessed outcomes. None of the studies assessed all the outcomes at the same time. The study conducted by Liu in 2016 [26] was the only to assess most of the endpoints (all except MVT).

Table 3: Risk of Bias in the 11 included trials. The overall quality of the trials is moderate and all of them – except the study by Sheikh – lacked a proper blinding of participants and personnel.

Figure 2: Time to Extubation and Mechanical Ventilation Time Standardized Mean Differences.

(A): Time To Extubation; (B): Mechanical Ventilation Time. Heterogeneity was assessed using Cochran's Q test with $p<0.05$ for statistical significance and I^2 index>50% for significant heterogeneity.

Figure 3: Length of Stay in the Intensive Care Unit and Length of Stay in the hospital Standardized Mean Differences. (A): Length Of Stay in ICU; (B): Length of Stay in the hospital. Heterogeneity was assessed using Cochran's Q test with $p<0.05$ for statistical significance and I^2 index>50% for significant heterogeneity.

Figure 4: Delirium, Bradycardia and Hypotension Odds Ratios. (A): delirium; (B): bradycardia; (C): hypotension. Heterogeneity was assessed using Cochran's Q test with $p<0.05$ for statistical significance and I^2 index>50% for significant heterogeneity.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 1: baseline characteristics of the 11 included trials.

Primary Author	Publication Year	Type of Study/ Country of Origin	No of patients (Dex/ Propofol)	Mean Age (Dex Propofol)	%Male (Dex/ Propofol
Herr	2003	RCT/USA	148/147	61.9/62.4	93/87
Corbett	2005	RCT/USA	43/46	63/61	76/76
Maldonado	2009	RCT/USA	30/30	55/58	65/58
Karaman	2015	RCT/Turkey	31/33	62.5/63.9	83.8/87.9
Djaiani	2016	RCT/ Canada	91/92	72.7/72.4	74.7/76
Liu a	2016	RCT/China	44/44	53/56.5	47.7/31.8
Liu b	2016	RCT/China	29/32	53/55	34/47
Mogahd	2017	RCT/Egypt	35/35	53.5/54.9	51.4/57
Elgebaly	2018	RCT/Egypt	25/25	53.7/52.5	50/30
Sheikh	2018	RCT/India	30/30	33.6/35.6	60/40
Shi	2019	RCT/ China	84/80	74.7/74.4	75/70
P-value				N.S	N.S

RCT: Randomized Controlled Trial; Dex: dexmedetomidine.

Table 2: Outcomes assessed and features of the 11 included trials.

Study	Time Dependent				Non-time Dependent			Procedures	Neuroblockade post-op	Time of Dex protocol initiation	Protocol intra op
	TTE	MVT	LOS-ICU	LOS-H	Delirium	Bradycardia	Hypotension				
Herr (2003) [15]	NS (less time in Dex group)	NS	n/a	n/a	n/a	NS	NS (more pts. in Dex group)	OR heart surgeries	None	On sternal closure	Same between Dex and propofol groups
Corbett (2005) [16]	n/a	NS	NS	n/a	n/a	n/a	NS (more pts. in Dex group)	OR heart surgeries	None	Study initiated after bypass	Same between Dex and propofol groups
Maldonado (2009) [18]	NS	n/a	NS (more stay in propofol group)	NS (more stay in propofol group)	S (more pts. in propofol group)	n/a	n/a	OR heart surgeries	None	On sternal closure	Same between Dex and propofol groups
Karaman (2015) [24]	S (less time in Dex group)	n/a	n/a	n/a	n/a	NS	NS	OR heart surgeries	None	Upon arrival to ICU	Same between Dex and propofol groups
Djaiani (2016) [25]	S (>Dex)	n/a	NS (more stay in Dex group)	NS	S (more pts. in propofol group)	n/a	n/a	OR heart surgeries	None	Upon arrival to ICU	Same between Dex and propofol groups
Liu a (2016) [26]	NS	n/a	S (more stay in propofol group)	NS	NS (more pts. in Dex group)	NS(more pts. in Dex group)	S (more pts. in Dex group)	OR heart surgeries	None	Upon arrival to ICU	Same between Dex and propofol groups
Liu b (2016) [27]	NS	n/a	n/a	n/a	NS	NS (more pts. in Dex group)	NS	OR heart surgeries	None	Upon arrival to ICU	Same between Dex and propof

											ol groups
Mogahd (2017) [28]	S (less time in Dex group)	S (less time in Dex group)	NS	n/a	n/a	n/a	n/a	OR heart surgeries	None	Not mentioned	Same between Dex and propofol groups
Elgebaly (2018) [44]	n/a	NS	NS (more stay in propofol group)	n/a	n/a	n/a	n/a	OR heart surgeries	None	Upon arrival to ICU	Same between Dex and propofol groups
Sheikh (2018) [45]	n/a	S (less time in Dex group)	S (less time in Dex group)	n/a	S (more pts. in propofol group)	n/a	n/a	OR heart surgeries	None	Intra-op.	Same between Dex and propofol groups
Shi (2019) [46]	S (less time in Dex group)	n/a	NS (less time in Dex group)	NS (less time in Dex group)	NS (shorter in Dex group)	n/a	n/a	OR heart surgeries	None	Intra-op.	Same regimen
No. of studies addressing the outcome (out of 11)	8	5	8	4	6	4	5	-	-	-	-

Table 2: Outcomes assessed and features of the 11 included trials. TTE: Time To Extubation; MVT: Mechanical Ventilation Time; LOS-ICU: Length Of Stay in Intensive Care Unit; LOS-H: Length Of Stay in the hospital. Dex: dexmedetomidine; prop: propofol; NS: the difference is statistically not significant; S: the difference is statistically significant, n/a: not assessed. When

significant, the symbol > means “is prolonged with / the incidence is increased with” the drug indicated. When non-significant, the eventual direction of the trend is indicated. TTE and LOS-ICU were the most assessed outcomes. None of the studies assessed all the outcomes at the same time. The study conducted by Liu in 2016 [26] was the only to assess most of the endpoints (all except MVT).

Table 3: Risk of Bias in the 11 included trials.

Author / date	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Herr (2003)	Uncertain	Low Risk	High Risk	Uncertain	Low Risk	Uncertain	Low Risk
Corbett (2005)	Low Risk	Low Risk	High Risk	Uncertain	Low Risk	Uncertain	Low Risk
Maldonado (2009)	Low Risk	Uncertain	High Risk	Uncertain	Low Risk	Uncertain	Low Risk
Karaman (2015)	Uncertain	Low Risk	High Risk	Uncertain	Low Risk	Uncertain	Low Risk
Djaiani (2016)	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	Low Risk
Liu a (2016)	Low Risk	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Liu b	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	Low

(2016)							Risk
Mogahd (2017)	Uncertain	Uncertain	High Risk	Uncertain	Low Risk	Uncertain	Low Risk
Elgebaly (2018)	Uncertain	Uncertain	High Risk	Uncertain	Low Risk	Uncertain	Low Risk
Sheikh (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Uncertain	Low Risk
Shi (2019)	Low Risk	Uncertain	High Risk	Uncertain	Low Risk	High Risk	Low Risk

The overall quality of the trials is moderate and all of them – except the study by Sheikh – lacked a proper blinding of participants and personnel.

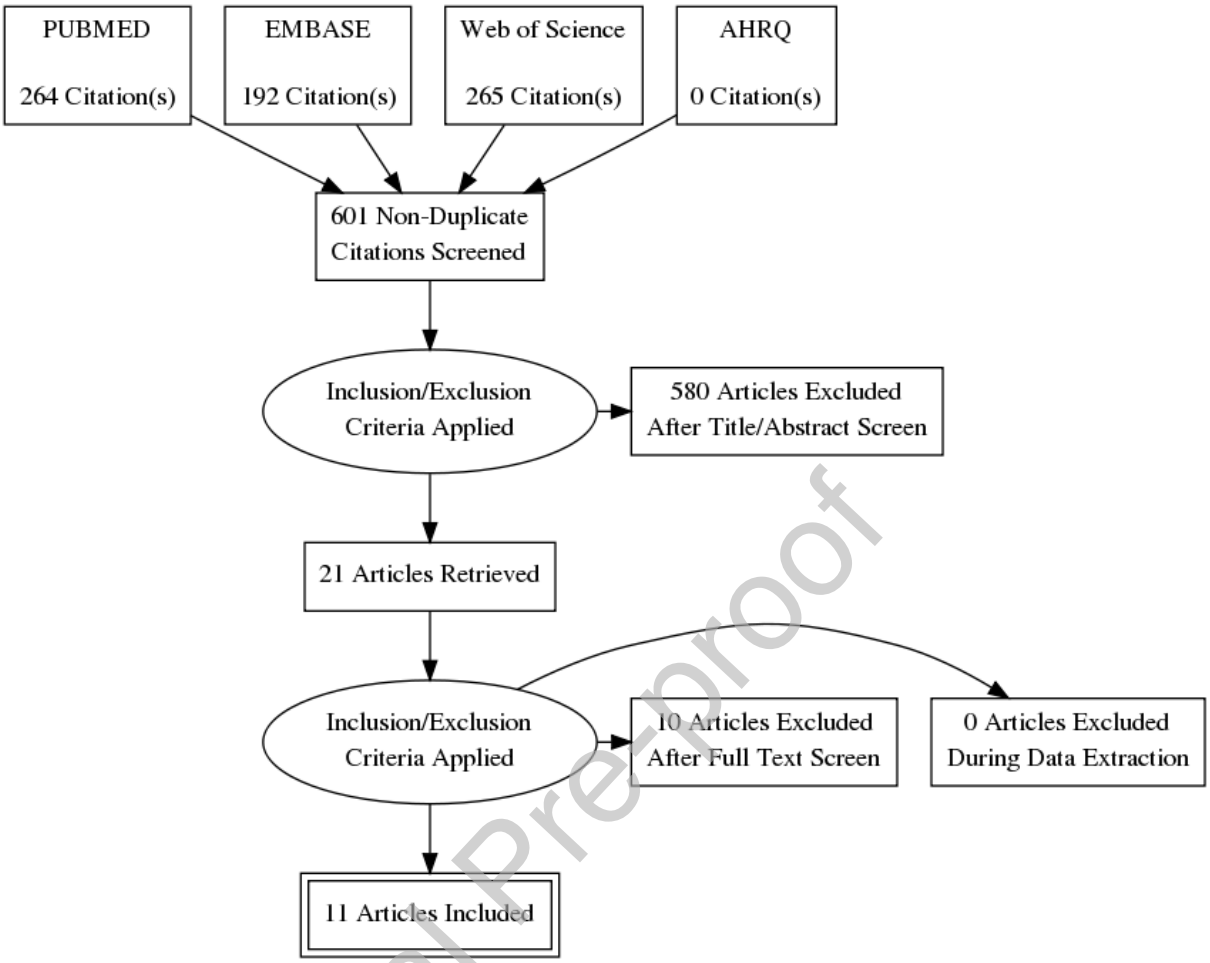
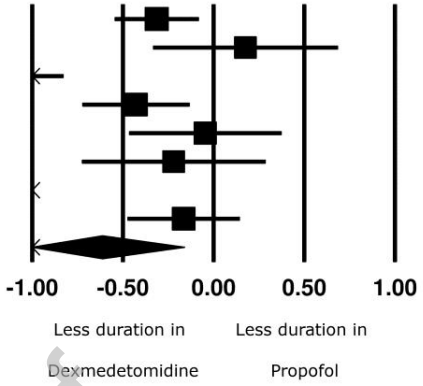


Figure 1

Time to extubation

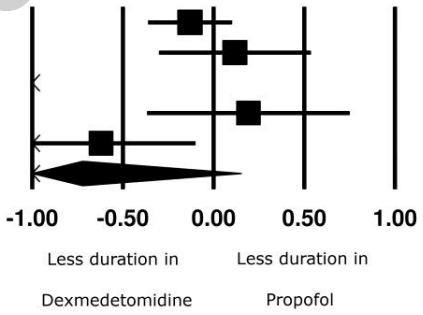
Study name	Standard error	Variance	Std diff in means	Lower limit	Upper limit	Z-Value	p-Value
Herr	0.117	0.014	-0.313	-0.543	-0.084	-2.675	0.007
Maldonado	0.259	0.067	0.176	-0.331	0.683	0.680	0.497
Karaman	0.278	0.077	-1.376	-1.921	-0.830	-4.946	0.000
Djaiani	0.150	0.022	-0.428	-0.721	-0.135	-2.864	0.004
Liu a	0.213	0.045	-0.046	-0.464	0.372	-0.215	0.830
Liu b	0.257	0.066	-0.220	-0.724	0.284	-0.855	0.393
Mogahd	0.344	0.118	-2.923	-3.597	-2.249	-8.503	0.000
Shi	0.156	0.024	-0.165	-0.472	0.142	-1.055	0.292
Random	0.231	0.053	-0.612	-1.064	-0.160	-2.655	0.008



(A)

Mechanical ventilation time

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Herr	-0.130	0.117	0.014	-0.358	0.099	-1.114	0.265
Corbett	0.117	0.212	0.045	-0.299	0.534	0.553	0.580
Mogahd	-3.392	0.373	0.139	-4.123	-2.660	-9.087	0.000
Elgebaly	0.192	0.283	0.080	-0.363	0.748	0.678	0.498
Sheikh	-0.621	0.264	0.070	-1.139	-0.102	-2.348	0.019
Random	-0.722	0.446	0.199	-1.597	0.152	-1.619	0.105

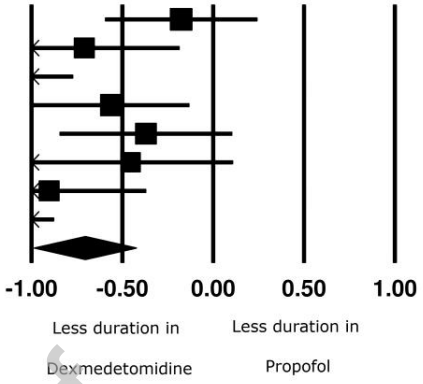


(B)

Figure 2

ICU length of stay

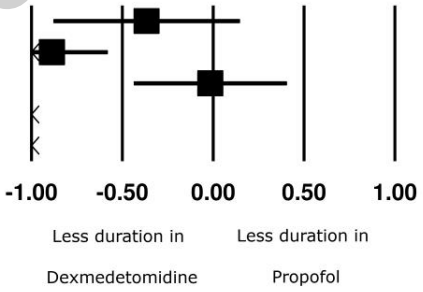
Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Corbett	-0.176	0.213	0.045	-0.592	0.241	-0.827	0.408
Maldonado	-0.709	0.266	0.071	-1.231	-0.188	-2.665	0.008
Djaiani	-1.084	0.158	0.025	-1.394	-0.774	-6.846	0.000
Liu a	-0.560	0.217	0.047	-0.986	-0.134	-2.578	0.010
Mogahd	-0.370	0.241	0.058	-0.843	0.102	-1.535	0.125
Elgebaly	-0.455	0.286	0.082	-1.016	0.107	-1.587	0.112
Sheikh	-0.903	0.271	0.073	-1.434	-0.371	-3.330	0.001
Shi	-1.211	0.170	0.029	-1.545	-0.878	-7.129	0.000
Random	-0.703	0.143	0.020	-0.983	-0.423	-4.919	0.000



(A)

Hospital length of stay

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Maldonado	-0.366	0.260	0.068	-0.876	0.144	-1.406	0.160
Djaiani	-0.887	0.155	0.024	-1.191	-0.584	-5.726	0.000
Liu a	-0.016	0.213	0.045	-0.433	0.402	-0.073	0.942
Shi	-3.269	0.239	0.057	-3.737	-2.801	-13.694	0.000
Random	-1.133	0.662	0.439	-2.431	0.166	-1.710	0.087

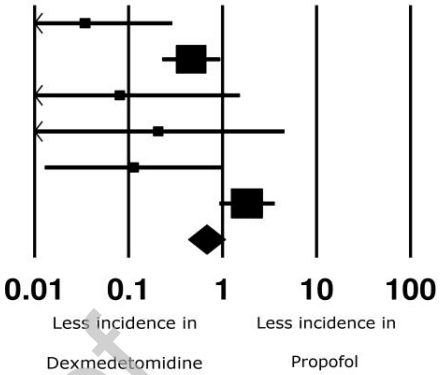


(B)

Figure 3

Delirium

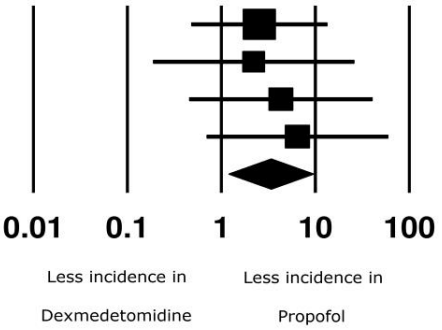
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Maldonado	0.034	0.004	0.287	-3.116	0.002
Djaiani	0.463	0.231	0.930	-2.165	0.030
Liu a	0.081	0.004	1.506	-1.686	0.092
Liu b	0.207	0.010	4.491	-1.004	0.316
Sheikh	0.113	0.013	0.988	-1.971	0.049
Shi	1.818	0.937	3.528	1.767	0.077
Random	0.683	0.437	1.069	-1.668	0.095



(A)

Bradycardia

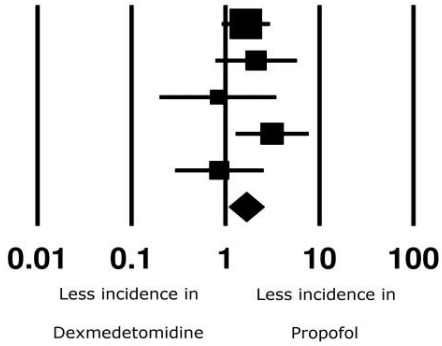
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Herr	2.535	0.484	13.279	1.101	0.271
Karaman	2.207	0.190	25.638	0.633	0.527
Liu a	4.300	0.461	40.118	1.280	0.200
Liu b	6.458	0.707	59.001	1.653	0.098
Fixed	3.397	1.208	9.552	2.319	0.020



(B)

Hypotension

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Herr	1.647	0.926	2.932	1.697	0.090
Corbett	2.117	0.791	5.668	1.493	0.136
Karaman	0.830	0.201	3.422	-0.258	0.796
Liu a	3.138	1.301	7.568	2.545	0.011
Liu b	0.859	0.294	2.512	-0.277	0.781
Random	1.682	1.096	2.580	2.380	0.017



(C)

Figure 4