

Sedative use of Dexmedetomidine vs. Propofol after Cardiac Surgery: A critical review and meta-analysis.

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Research Article

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Abstract

BACKGROUND: The efficacy and safety of dexmedetomidine in sedation for postoperative cardiac surgeries is controversial when compared to propofol.

METHODS: A computerized search of Medline, Cochrane and Google Scholar databases was performed through August 2018. Studies evaluating the efficacy of dexmedetomidine versus propofol in the sedation of postoperative cardiac surgery patients were searched. The main study outcomes were divided into time dependent (mechanical ventilation time; time to extubation; length of stay in the intensive care unit and in the hospital) and non-time dependent (delirium, bradycardia, and hypotension).

RESULTS: The final analysis included 15 trials with a total of 2488 patients. Time to extubation was significantly reduced in the dexmedetomidine group (Standardized Mean Difference (SMD) = -0.54, 95% Confidence Interval (CI): -0.89 to -0.18, $p=0.003$), as well as mechanical ventilation time (SMD= -0.71, 95% CI: -1.19 to -0.23, $p=0.004$). Moreover, the dexmedetomidine group showed a significant reduction in Intensive Care Unit length of stay (SMD= -0.38, 95% CI: -0.60 to -0.16, $p=0.001$) and hospital length of stay (SMD= -0.39, 95% CI: -0.60 to -0.19, $p<0.001$). However, these time dependent outcomes could have been affected by several confounding factors, thus limiting the value of these results. Incidence of delirium was reduced in the dexmedetomidine group (OR: 0.47, 95% CI: 0.29 to 0.76, $p=0.002$), while this group of patients had higher rates of bradycardia (OR: 2.52, 95% CI: 1.15 to 5.55, $p=0.021$). There was no significant difference in rates of hypotension between the two groups.

CONCLUSION: Despite the apparent time advantages afforded by dexmedetomidine over propofol, the former does not show particular overall improvements in postoperative care of cardiac surgery patients. Since time dependent outcomes seems to be affected by several confounding factors, more efforts are needed to analyze factors that could affect sedation in post-cardiac surgery patients and choose unbiased outcomes.

KEYWORDS: Dexmedetomidine; propofol; cardiac surgery; postoperative sedation.

Background

Cardiac surgery accounts for more than 2 million procedures performed each year worldwide [1] because of the prevalence of cardiovascular diseases (CVDs) in the world's population [2,3]. Coronary Arterial Bypass Grafting (CABG) and valvuloplasty represent a large percentage of the cardiac surgeries performed. Despite current advancements in surgical techniques, postoperative complications in cardiac surgery are a frequent event that affects up to 30% of patients [4-6].

After cardiac surgery, 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. However, these settings are associated with high incidences of pain, agitation, and delirium. These stressful conditions can lead to tachycardia, hypertension, immunosuppression, increased oxygen consumption,

and increased catecholamine production, potentially contributing to the development of myocardial ischemia [7,8].

Opioids and sedatives are administered to reduce the incidence of postoperative pain, agitation, and delirium in PACU or ICU [7]. In particular, opioids are the gold standard for pain control after cardiac surgery, and titrated sedatives provide the necessary level of hypnosis, amnesia, and anxiolysis. However, opioids have numerous side effects – such as nausea, vomiting, urinary retention, decreased gastric motility, pruritus, sedation and respiratory depression. High dosages of sedatives can lead to prolonged length of stay (LOS) and other drug-specific side effects. Hence, multimodal sedoanalgesia is currently preferred, allowing small doses of several analgesics and sedatives combined to achieve pain and agitation prevention, but at the same time reducing the side effects of any single drug used.

Several studies evaluating the use of dexmedetomidine versus propofol in postoperative sedation of cardiac surgery patients have been previously published, but with limited sample sizes. Propofol is a phenolic derivative, highly lipophilic, intravenous anesthetic agent with sedative and hypnotic properties. Its use after cardiac surgery is well known for its ease of administration, rapid onset, and short awakening time [9]. However, a frequent side effect of propofol 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 prior to and during surgical procedures [12].

We have reviewed current literature regarding this subject in order to define which strategy could improve quality of sedation and outcomes in post-cardiac surgery patients. With this manuscript, we provide a larger number of patients than the previous meta-analyses and also offer a critical review of the outcomes currently described in 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 studies 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 on 15 – 22 August 2018 on PubMed/Medline, Cochrane and Google Scholar, using the subsequent selected terms combined with the Boolean operator AND: “dexmedetomidine”, “propofol” and “cardiac”. No publication date restrictions were applied. Restrictions regarding the age (≥ 18) and

studies including humans were only applied to PubMed/Medline, being the only search engine that provided such filters. In Google Scholar, the terms were applied to title text only to exclude irrelevant contents. In order to include all possible studies, a further search on clinicaltrials.gov was performed.

Titles and abstracts of identified literature were independently screened by two authors (HA, EC). Literature not complying with the inclusion criteria was excluded. When disagreement occurred, the opinion of a third reviewer 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. Study selection process is described in the flow diagram below [Figure 1].

Inclusion and exclusion criteria

- Inclusion criteria (all of them):
 - randomized Clinical Trials or retrospective cohort or observational trials;
 - use of dexmedetomidine in comparison to propofol for sedation of postoperative surgeries;
 - any Cardiac surgery;
 - age > 18 years.

Exclusion criteria (at least one):

- - non – English language;
 - improper study design (e.g. abstract, commentary, editorials);
 - 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: first author, publication year, country, study design, number of participants, protocol used (dexmedetomidine or propofol) [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 3 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 lengths of stay are referred to 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]. 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.

Data and Quality analysis

In this manuscript, all statistical analyses were performed by Comprehensive Meta-Analysis (CMA) software (version 3.0; Biostat Inc., Englewood, NJ, USA). Mean and standard deviation (SD) 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 SD 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 significant 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, 5 of the outcomes had significant heterogeneity and those included TTE, MVT, LOS-ICU, LOS-H, and hypotension.

Results

Our final analysis included 15 studies: 8 RCTs, 6 retrospective studies, and 1 prospective descriptive study [Table 1]. These studies were published between 2003 and 2018, and included a total of 2488 patients. Of note, most of the studies were carried out in the USA (9 studies), and the smallest included only 28 patients for each arm [19]. The most assessed outcome was LOS-ICU (11/15), followed by LOS-H and TTE (9/15). None of the included studies assessed all the outcomes selected for this meta-analysis 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 2]. According to our analysis, TTE and MVT were significantly reduced in the dexmedetomidine group. (In 9/15 studies, SMD = -0.54, 95% CI: -0.89 to -0.18, $p = 0.003$ for TTE) [Figure 2-A]; (In 8/15 studies, SMD = -0.71, 95% CI: -1.19 to -0.23, $p = 0.004$ for MVT) [Figure 2-B]. Furthermore, dexmedetomidine significantly reduced LOS-ICU (in 11/15 studies; SMD = -0.38, 95% CI: -0.60 to -0.16, $p = 0.001$) [Figure 3-A] and LOS-H (in 9/15 studies; SMD = -0.39, 95% CI: -0.60 to -0.19, $p < 0.0001$) [Figure 3-B]. With regard to adverse events, delirium significantly affected less patients in the dexmedetomidine group (in 6/15 studies; OR 0.47, 95% CI: 0.29 to 0.76, $p = 0.002$) [Figure 4-A], while bradycardia was significantly more reported in the propofol group (in 6/15 studies; OR 2.52, 95% CI: 1.15 to 5.55, $p = 0.021$) [Figure 4-B]. No statistically significant difference between the two groups was found regarding hypotension (in 8/15 studies; OR 1.35, 95% CI: 0.84 to 2.18, $p = 0.215$) [Figure 4-C].

Discussion

This meta-analysis represents the largest number of papers and patients available about the use of dexmedetomidine versus propofol in the sedation following cardiac surgery, involving 15 studies and a total of 2488 patients. Three main reasons prompted this investigation. First, we wanted to perform a further and wider meta-analysis comparing dexmedetomidine and propofol, after similar previous

publications [1, 30, 31], to provide the reader with a more comprehensive statistical analysis of such a comparison. Our data increases the number of patients by more than 45%, and, to be more precise, the comparison was limited to dexmedetomidine and propofol only, in contrast with previous studies which compared sedatives to placebo [31]. Second, studies conducted on an international level, rather than those limited to the United States, were included to provide the reader with a wider perspective, a higher external validity and conclusions applicable to different healthcare systems. Third, we performed a critical analysis of the endpoints used so far in literature to emphasize the importance of confounding factors affecting the outcomes on which previous meta-analyses were based. In fact, despite the apparent time advantages afforded by dexmedetomidine over propofol, the former does not show particular overall improvements in postoperative care of cardiac surgery patients.

Time-dependent outcomes assessed in the included studies (TTE, MVT, LOS-ICU and LOS-H) showed great limitations for two reasons. First, many factors – such as patients' comorbidities, surgical complications and postoperative bleeding – are well known to influence the postoperative care of cardiac surgery patients [32]. In particular, the Society of Thoracic Surgeons (STS) listed in its database 6 acute postoperative complications of cardiac surgery (re-operation, deep sternal wound infection / mediastinitis, permanent stroke, renal failure, prolonged ventilation [> 24 hours], and new onset atrial fibrillation) [33], which can happen singularly or, in 4% of cases, in combination [34]. Each of those is therefore capable to alter the time-dependent endpoints used in the included studies. Second, local protocols and physician's evaluations can affect the decision to extubate the patient, thus altering both TTE and MVT and, accordingly, LOS in ICU and in the hospital.

With regard to TTE, our results are consistent with those of Liu X et al., [1] showing a reduction in TTE in the dexmedetomidine group [Figure 2-A]. Furthermore, MVT seems to be reduced for the dexmedetomidine – sedated patients in our analysis [Figure 2-B], while Chang et al., did not find a significant difference between the two groups [30] (probably because Chang et al., merged TTE and MVT into one outcome). However, 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 these endpoints. Moreover, there is no consensus about the time of extubation after cardiac surgery, and the actual ventilation time that leads to complications is not known [32].

As shown in Figure 3-A and B, dexmedetomidine seems to reduce both LOS-ICU and LOS-H. A prolonged LOS-ICU or LOS-H has several implications, ranging from the increased risk of infections to bad outcomes and growing financial issues [35]. Anyway, LOS-ICU and LOS-H are affected by the same factors that undermine the reliability of TTE and MVT, and indirectly by all the remaining postoperative complications of cardiac surgery [34]. 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 mechanical ventilation or pain. Furthermore, delirium is strongly associated with increased ICU mortality and post – ICU cognitive impairment, also establishing a vicious circle with LOS-ICU [7]. Our analysis found a significantly decreased incidence of delirium in the dexmedetomidine – sedated patients [Figure 4-A], as suggested by all the included studies except for the trial conducted by Wanat et al [23]. Nevertheless, a limitation of this study was its retrospective design [23].

Despite decades of experience with propofol in cardiac anesthesia, bradycardia and hypotension are serious concerns that can potentially cause organ hypoperfusion and dysfunction, such as brain damage [9]. Our analysis suggests a significant diminished incidence of bradycardia in the dexmedetomidine – sedated patients. No significance was found regarding hypotension, even if Anger et al., reported a reduction of hypotension in the dexmedetomidine group [19]. However, most of the patients included in their study recovered with fluid infusion and/or vasopressors [19]. Of note, the study of Torbic et al., was excluded from the analysis of the last two outcomes because the published percentages were not compatible with the number of patients provided [21].

Apart from the critic about time-dependent endpoints, several limitations were noted during our analysis. Firstly, analgesic therapy used to reduce pain during post – surgery (mainly opioids) showed a high variability in dosage and different starting and ending points of administration that were not clearly stated. This variability was noted also with regard to other sedatives (e.g.: benzodiazepines) used during the surgeries, without a standardized protocol for general anesthesia. Future trials should take into account these aspects and try to follow a standardized protocol for the administration of intraoperative general anesthesia and of postoperative analgesics.

Although our study intended to include all types of cardiac surgery, the search did not return any paper regarding cardiac transplant in the adult population. The post-cardiac transplant sedation has been covered only on pediatric population, in which dexmedetomidine showed a better prevention of opioid withdrawal syndrome [36]. However, more efforts are needed to evaluate sedation after this important subset of cardiac surgeries, with a particular attention to 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 [37], and are validated on sedatives in general but not specifically on dexmedetomidine (that has a specific alpha – 2 receptor agonism related sedation mechanism). Since the sedation of dexmedetomidine resembles natural sleep [38], future studies should better assess this particular aspect of sedation level evaluation.

Finally, the medical authorities globally, except for 2 countries, recommend to limit 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 [39].

Conclusions

This meta-analysis did not find particular advantages in the use of dexmedetomidine compared to propofol for the sedation of post – cardiac surgery patients. Only bradycardia showed a significant reduction in patients sedated with dexmedetomidine, and the results on the other endpoints are questionable. Time-dependent endpoints, widely used in previous trial in this field, are inaccurate due to several reasons and are not reliable for a proper evaluation of benefits of dexmedetomidine versus propofol.

More efforts are needed to find new reliable outcomes for this evaluation, to standardize sedation protocols in post cardiac surgery patients, and to assess mid- and long – term outcomes in the two groups.

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

Declarations

- Ethics approval and consent to participate
 - Not applicable as manuscript is a meta-analysis of existing literature
- Consent for publication
 - All listed authors agree with the submission of “Sedative use of Dexmedetomidine vs. Propofol after Cardiac Surgery: A critical review and meta-analysis” to BMC Anesthesiology
- Availability of data and material
 - All data generated or analysed during this study are included in this published article. For supplementary data please refer to the list of references in the works cited, restrictions may apply to the availability of supplementary data based on third party licensing.
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- Acknowledgements
 - None

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Tables

TABLE 1

Name of the study	Type of study/Country	Publication Year	No. of patients (Dex/propofol)	Mean Age (years) (Dex/propofol)	Male (%) (Dex/propofol)
Herr[15]	RCT/USA and Canada	2003	148/147	61.9/62.4	93/87
Corbett[16]	RCT/USA	2005	43/46	63.6/62.4	81.4/82.6
Barletta[17]	Retrospective cohort/ -	2009	50/50	63/61	76/76
Maldonado[18]	RCT/USA	2009	30/30	55/58	65/58
Anger[19]	Prospective descriptive/USA	2010	28/28	63.7/69	82.2/57.1
Curtis[20]	Retrospective/USA	2013	291/291	67.6/65.7	68.7/65.3
Torbic[21]	Retrospective/USA	2013	53/73	62.2/68.8	73.6/61.6
Thoma[22]	Retrospective cohort/USA	2014	42/42	64.1/64.2	90.5/90.5
Wanat[23]	Retrospective/USA	2014	33/319	63/68	75.8/70.5
Karaman[24]	RCT/Turkey	2015	31/33	62.5/63.9	83.8/87.9
Djaiani[25]	RCT/Canada	2016	91/92	72.7/72.4	74.7/76
Liu a[26]	RCT/China	2016	44/44	53/56.5	47.7/31.8
Liu b[27]	RCT/China	2016	29/32	53/55	34/47
Mogahd[28]	RCT/Egypt	2017	35/35	53.5/54.9	51.4/57
Chuich[29]	Retrospective/USA	2018	69/209	64/62	68/66
Total			1017/1471	(61.3/63.0)	(72.2/67.7)
(overall mean)					

RCT: Randomized Clinical Trial; **Dex:** dexmedetomidine. Country of the Barletta study was not clearly stated in the manuscript.

TABLE 2

Study (year)	Time dependent				Non-time dependent		
	TTE	MVT	LOS-ICU	LOS-H	Delirium	Bradycardia	Hypotension
Herr(2003)[15]	Y	Y	N	N	N	Y	Y
Corbett(2005)[16]	N	Y	Y	N	N	N	Y
Barletta(2009)[17]	N	Y	N	N	N	N	Y
Maldonado(2009)[18]	Y	N	Y	Y	Y	N	N
Anger (2010)[19]	N	Y	Y	Y	N	Y	Y
Curtis (2013)[20]	Y	N	Y	Y	N	N	N
Torbic (2013)[21]	N	Y	Y	Y	N	N	N
Thoma (2014)[22]	N	Y	Y	Y	N	Y	Y
Wanat (2014)[23]	N	Y	Y	Y	Y	N	N
Karaman (2015)[24]	Y	N	N	N	N	Y	Y
Djaiani (2016)[25]	Y	N	Y	Y	Y	N	N
Liu a (2016)[26]	Y	N	Y	Y	Y	Y	Y
Liu b (2016)[27]	Y	N	N	N	Y	Y	Y
Mogahd (2017)[28]	Y	Y	Y	N	N	N	N
Chuich (2018)[29]	Y	N	Y	Y	Y	N	N
No. of studies addressing the outcome (out of 15):	9	8	11	9	6	6	8

TTE: Time To Extubation; **MVT:** Mechanical Ventilation Time; **LOS-ICU:** Length Of Stay in Intensive Care Unit; **LOS-Hosp:** Length Of Stay in the hospital; **Y:** yes (assessed); **N:** no (not assessed).

Figures

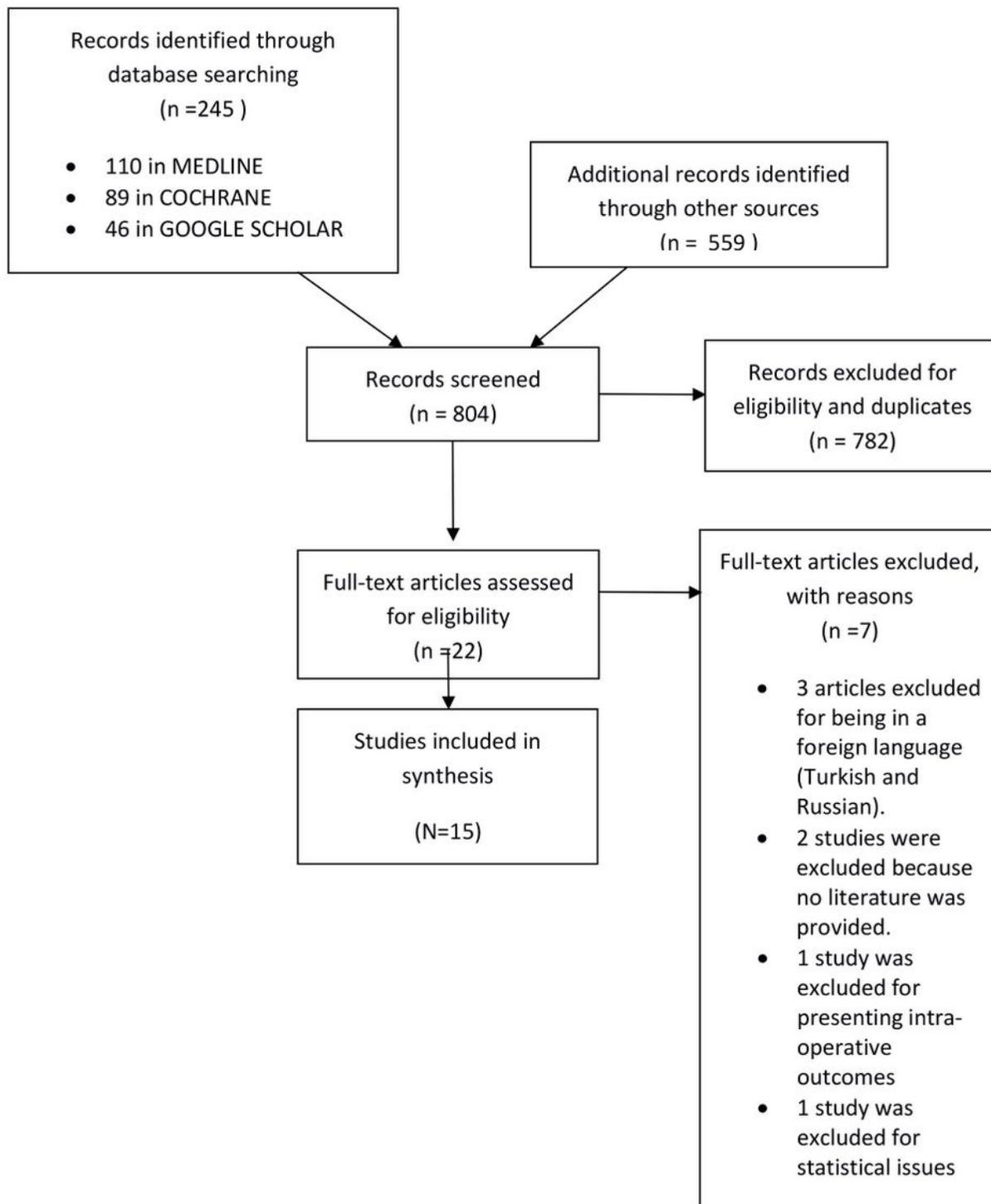


Figure 1

Study flow diagram.

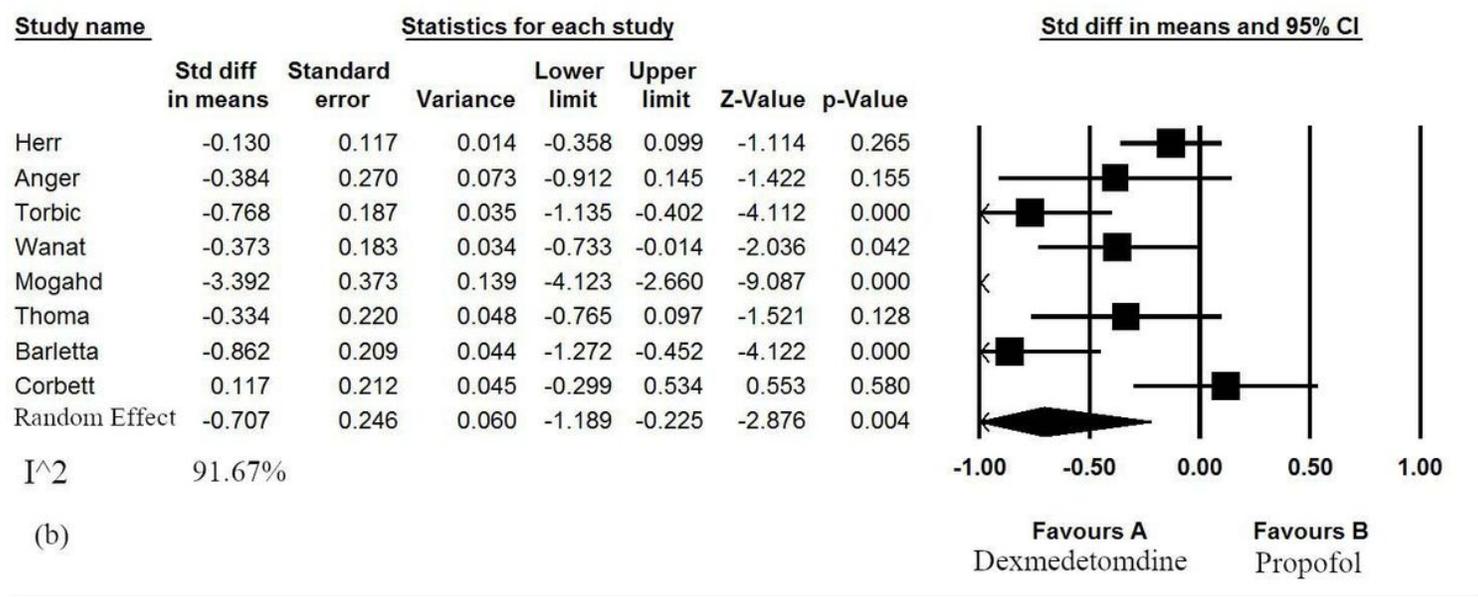
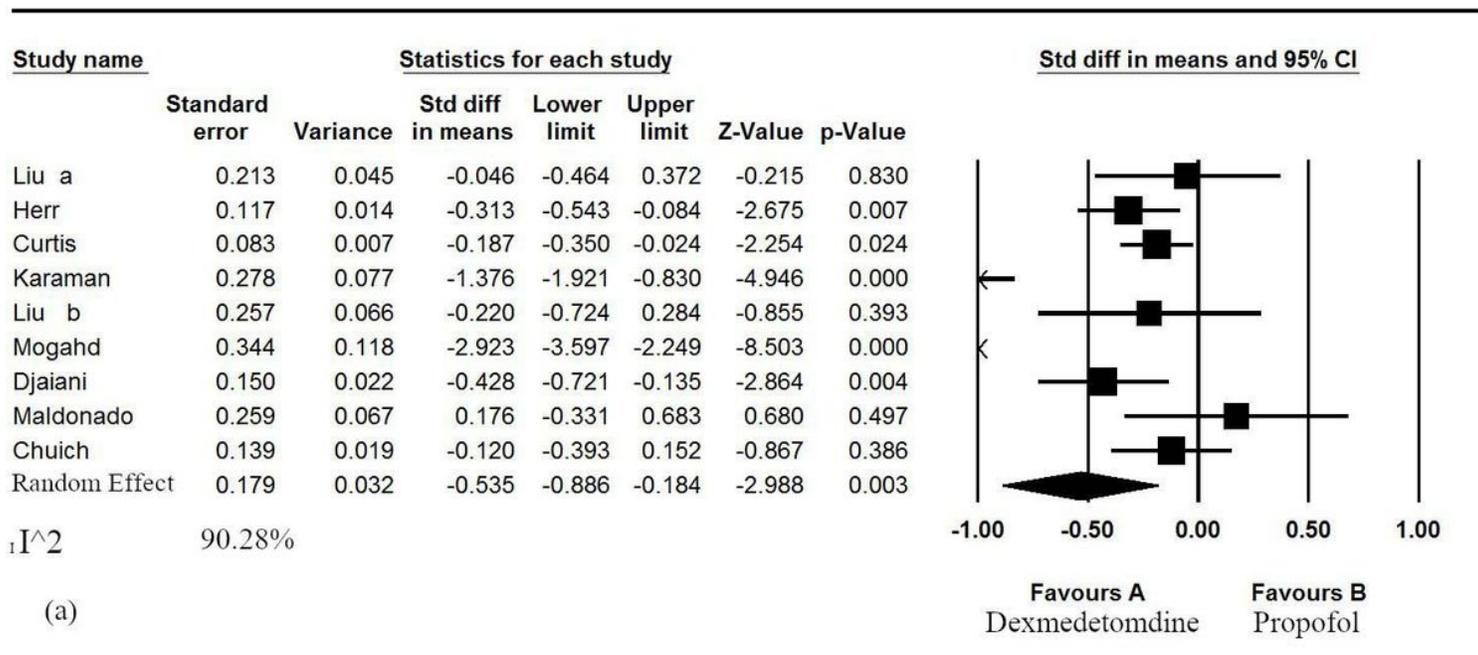


Figure 2

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.

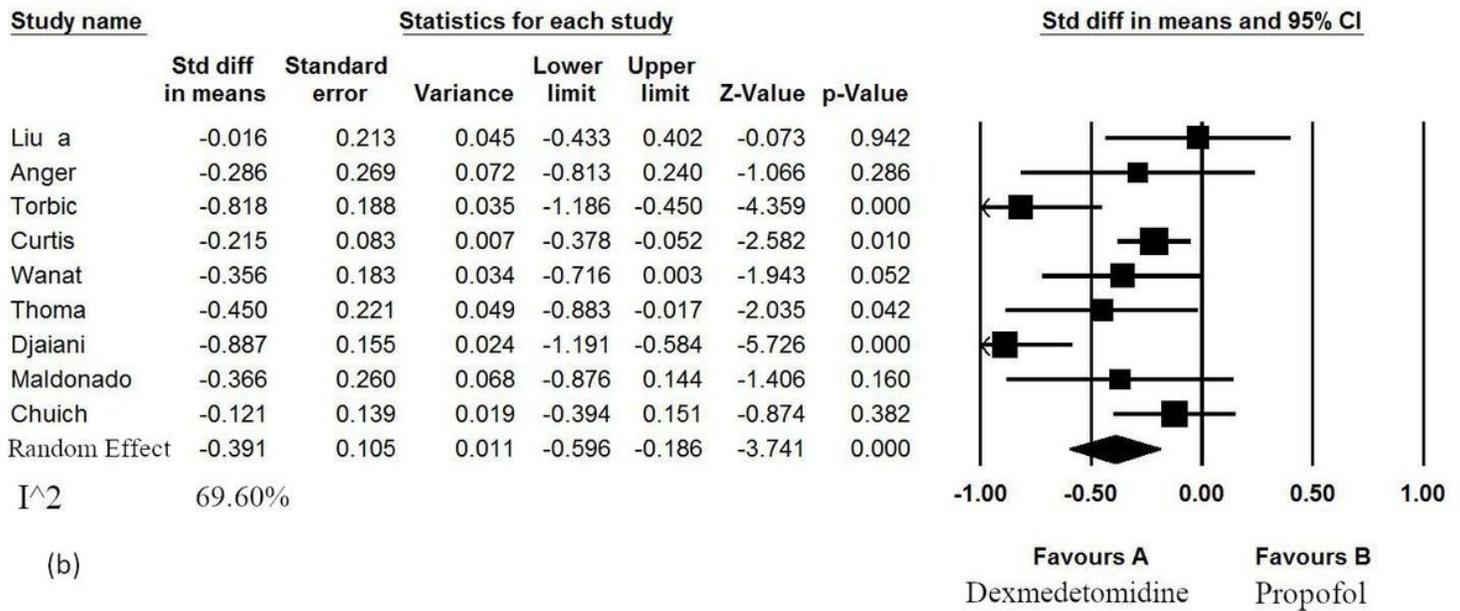
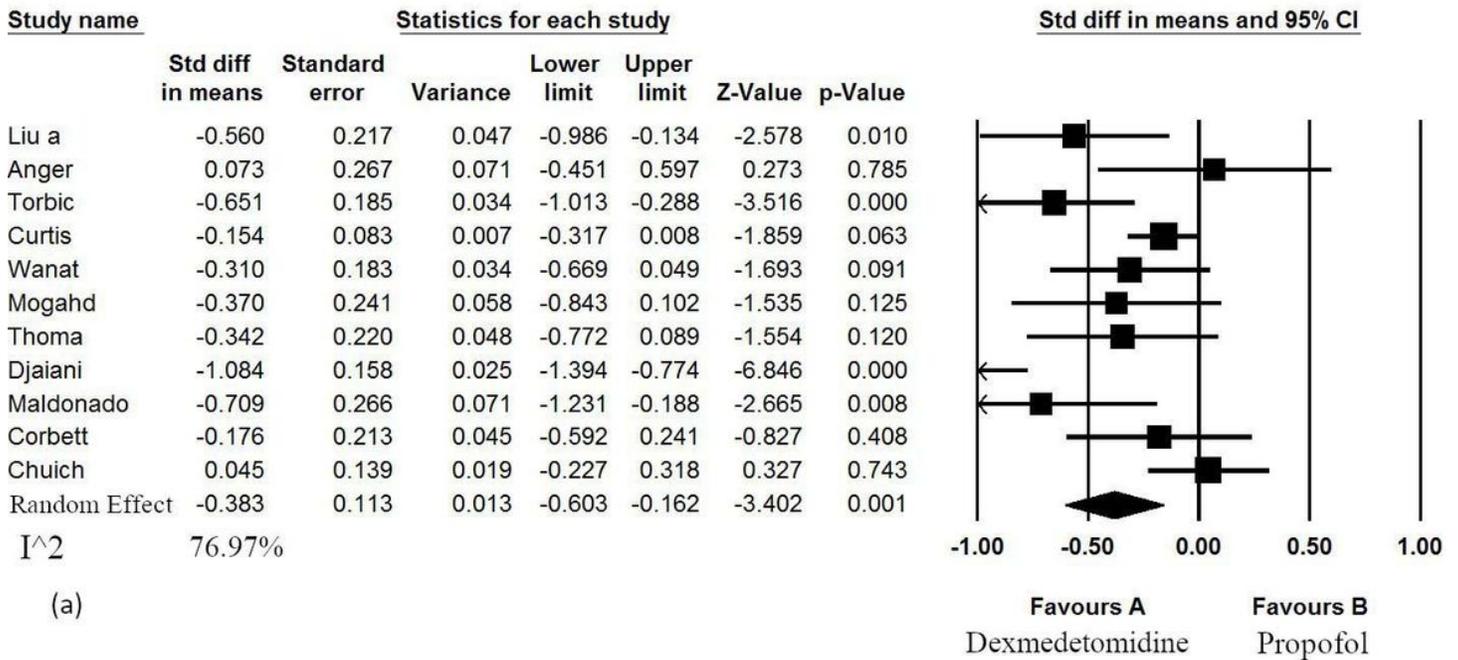


Figure 3

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.

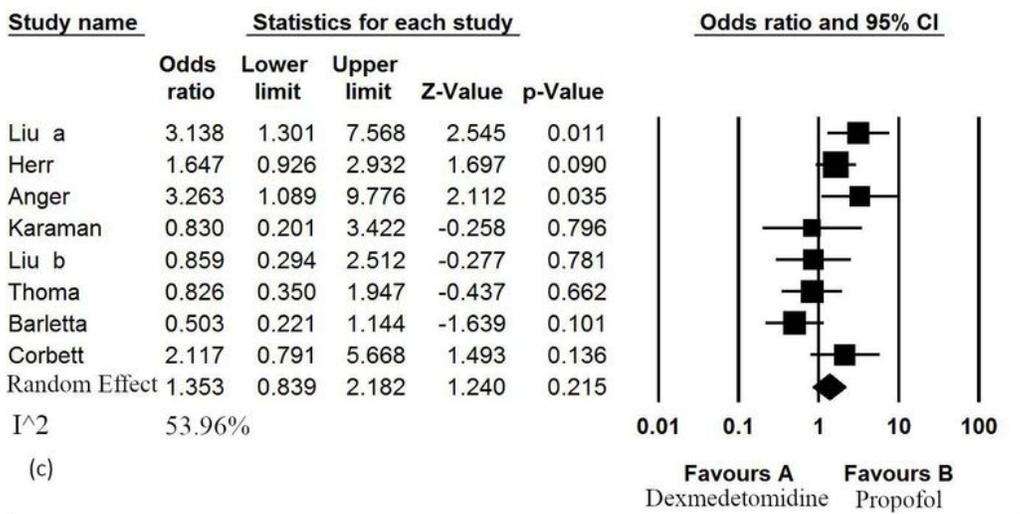
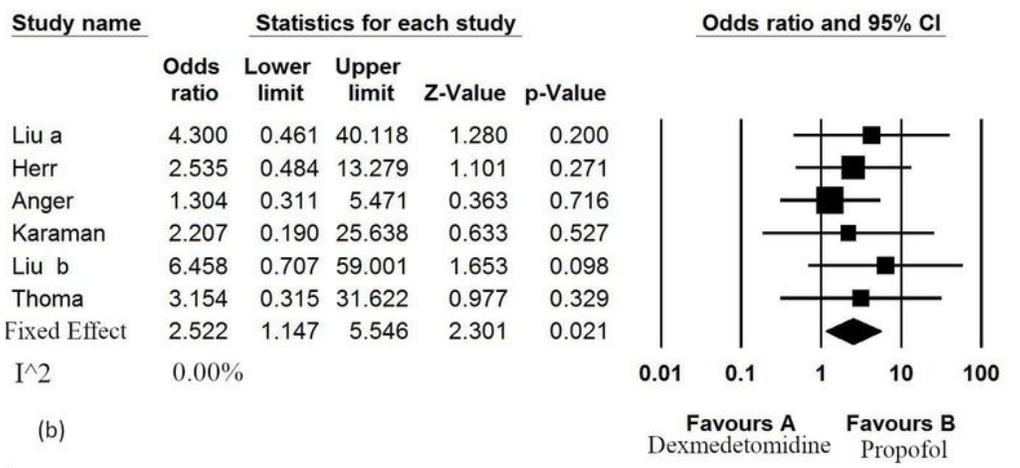
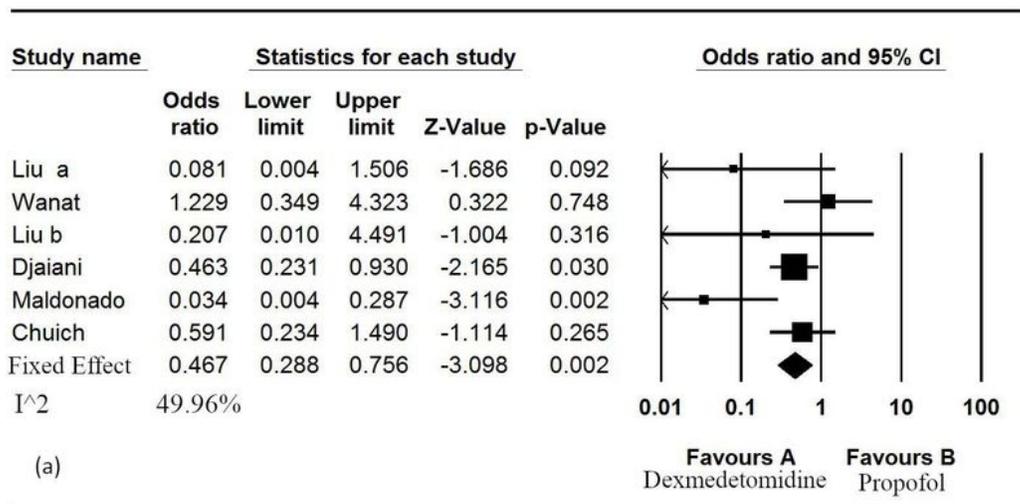


Figure 4

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.