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Title: Preoperative Dexmedetomidine and intraoperative bradycardia in laparoscopic cholecystectomy: meta-analysis with trial sequential analysis

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Running title: Dexmedetomidine and cholecystectomy

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assessed each of the included studies. ADC performed the statistical analysis. The manuscript has been read and approved by all the authors. All the authors believe that the present manuscript represents honest work.

Approval: the review protocol was preregistered in PROSPERO (CRD42021249799) on April 18, 2021.

Preoperative Dexmedetomidine and intraoperative bradycardia in laparoscopic cholecystectomy: meta-analysis with trial sequential analysis

Running title: Dexmedetomidine and laparoscopic surgery

Abstract

Background: Laparoscopic surgical procedures have various advantages over traditional open techniques, however, the artificial pneumoperitoneum is associated with severe bradycardia and also with cardiac arrest. Dexmedetomidine is an imidazole derivative that highly selectively binds to α2-receptors. It has sedative and analgesic properties, however it could cause hypotension and bradycardia. Our primary aim was to assess the association of dexmedetomidine use with intraoperative bradycardia during laparoscopic cholecystectomy.

Methods: We performed a systematic review with meta-analysis and trial sequential analysis of the medical literature using the following PICOS: adult patients undergoing endotracheal intubation for laparoscopic cholecystectomy (P); intravenous dexmedetomidine before tracheal intubation (I); no intervention or any placebo administration (C); intraoperative bradycardia (primary outcome), intraoperative hypotension, SBP at intubation, MAP at intubation, HR at intubation, dose of anesthetic needed for induction of anesthesia, total anesthetics (both ipnotics and opioids) requirement throughout the operative procedure, percentage of patients requiring postoperative analgesics, PONV and postoperative shivering occurrence (O); randomized controlled trials (S).

Results: Fifteen studies were included in the meta-analysis (980 patients). Patients receiving dexmedetomidine compared to patients not receiving it had a higher risk of developing intraoperative bradycardia (RR 2.81 (1.34 - 5.91)) and hypotension (RR 1.66 (0.92 - 2.98)), however they need lower dose of intraoperative anesthetics and had a lower incidence of PONV. In the TSA for bradycardia, the cumulative z-score crossed the monitoring boundary for harm at the tenth trial.

Conclusions: Patients undergoing laparoscopic cholecystectomy receiving dexmedetomidine at tracheal intubation are more likely to develop intraoperative bradycardia and hypotension.

Keywords: Dexmedetomidine; Laparoscopic surgery; Bradycardia; Meta-analysis; Trial sequential analysis; Review.

Introduction

Laparoscopic surgical procedures present various advantages over traditional open techniques, in particular early ambulation, lower analgesic needs, and reduced hospital stay [1]. However, pneumoperitoneum induction is associated with the release of vasopressin and catecholamines, the subsequent increase in heart rate (HR), systemic vascular resistance, and mean arterial pressure (MAP) [2]. Furthermore, artificial abdominal gas insufflation during laparoscopy might cause severe bradycardia and cardiac arrest, related to an uncontrolled increase in vagal tone due to peritoneal stretch [3].

Several strategies have been employed to control the sympathetic response to pneumoperitoneum, among them dexmedetomidine showed promising results [4].

Dexmedetomidine, an imidazole derivative, highly selectively binds to α2-receptors, thus inhibits norepinephrine release at the level of sympathetic terminals, determining hypotension and bradycardia, and promotes analgesia in spinal cord receptors [5].

Given the above, we may infer that although dexmedetomidine could be useful to control the sympathetic stimulation, its administration associated with peritoneal insufflation could lead to severe intraoperative bradycardia.

It is known that dexmedetomidine for tracheal intubation, compared with no dexmedetomidine or placebo, is at increased risk for intraoperative bradycardia in the general surgical population [6]. However, no information on patients undergoing laparoscopic procedures was reported. Therefore, we decided to perform a meta-analysis of randomized controlled trials (RCTs) comparing dexmedetomidine versus placebo or no intervention in patients undergoing laparoscopic cholecystectomy with respect to the occurrence of intraoperative bradycardia. In order to avoid bias related to surgical procedures, we decided to focus our investigation only on laparoscopic cholecystectomies.

The secondary aim was to assess the association of dexmedetomidine use with hemodynamics at intubation (HR, MAP, systolic blood pressure [SBP]), the occurrence of intraoperative hypotension, intraoperative hypnotics and opioids consumption, and the occurrence of postoperative side effects (nausea and vomiting [PONV], shivering, analgesic requirement).

Material and Methods

We followed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) Statement Guidelines to prepare this manuscript [7].

The review protocol was preregistered in PROSPERO (CRD42021249799) on April 18, 2021.

Search strategy

We performed a systematic research of the medical literature for the identification, screening, and inclusion of articles. The search was performed in the following databases from inception until April 18, 2021 with no language restrictions: Pubmed, Scopus, the Cochrane Central Register of Controlled Trials, EMBASE, and Google Scholar. The reference lists of included studies were also examined. The search strategy is available as Online Resource 1. Search strategy was developed in order to include all RCTs employing dexmedetomidine in general surgery.

Study selection

Two researchers (ADC and FG) independently screened the titles and abstracts of the identified papers to select relevant and not-relevant articles. Each citation was reviewed with full-text retrieval of any citation considered potentially relevant. All studies meeting the following PICOS criteria were included in our analysis: adult (aged 18 years or older) patients undergoing endotracheal intubation for laparoscopic cholecystectomy (P); intravenous dexmedetomidine before tracheal intubation (I); no intervention or any placebo administration (C); intraoperative bradycardia (primary outcome), intraoperative hypotension, SBP at intubation, MAP at intubation, HR at intubation, dose of anesthetic needed for induction of anesthesia, total anesthetics (both ipnotics and opioids) requirement throughout the operative procedure, percentage of patients requiring

postoperative analgesics, PONV and postoperative shivering occurrence (O); randomized controlled trials (S)

Data extraction and data retrieval

After identifying those studies meeting inclusion criteria, two members of our team (MI, GZ) independently reviewed and assessed each of the included studies. Any disagreement on both study selection and data extraction was planned to be solved by discussion with a further author (ADC). The following information was collected: first author, year of the study, total number of patients per group, occurrence of intraoperative bradycardia (% of patients) and hypotension (% of patients), SBP, MAP, and HR at tracheal intubation, induction and intraoperative anesthetic type and dosage , analgesic requirement in the first 24 h , PONV and shivering (% of patients).

If data were missing, a request was sent by e-mail to the corresponding author of the study. If no response was received after our initial request, a second request was sent seven days later. A third and last request was sent one week after the second one.

Quality assessment and certainty of evidence assessment

Two researchers (EP and NR) independently evaluated the quality of included RCTs by using the Risk of Bias (RoB) 2 Tool [8]. Disagreements were resolved by discussion with a third researcher (AB).

We used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence related to each of the key outcomes [9].

We defined the following as key outcomes: intraoperative bradycardia, intraoperative hypotension, HR, SBP and MAP at tracheal intubation. Starting from “high quality” of evidence, the certainty of evidence for each outcome was downgraded by one level for serious, or by two levels for very

serious study limitations, such as risk of bias, indirectness of evidence, inconsistency, imprecision of effect estimates or other considerations. 'Other considerations' include publication bias, large effect, plausible confounding, and dose response gradient.

Statistical methods

Meta-analysis of data was performed using RevMan version 5.3 (The Cochrane Collaboration, 2020) .

The treatment effect for continuous outcomes was expressed as standardized mean difference (SMD) with 95% confidence interval (CI), when the outcome was expressed with different measurement techniques, or mean difference (MD) with 95% CI, when the outcome was derived from the same measurement technique. The treatment effect for dichotomous outcomes was expressed as risk ratio (RR) with 95% CI.

Zero events were treated by applying a continuity correction adding one to each value.

Heterogeneity and publication bias analysis

For assessment of study heterogeneity, the Chi-squared test and I^2-statistic were used (considering I^2 values as follows: low heterogeneity: < 25%, moderate heterogeneity: 25% to 50%, and high heterogeneity: > 50%) [10]. A random-effects model was preferred when I^2 > 25%. Publication bias was evaluated by a visual inspection of funnel plots . Egger test (p-value < 0.05 indicating a possible publication bias) will be used for outcome with more than ten studies included [11].

Subgroup and sensitivity analysis

We performed the following pre-planned subgroup analyses on the main outcome:

i) Dexmedetomidine dose

We arbitrarily subdivided the dose of dexmedetomidine in a high dose (>=0.70 mcg/kg), medium dose (0.40-0.69 mcg/kg), and low dose (<0.40 mcg/kg) and evaluated the effects of these different dosing regimens on intraoperative bradycardia.

ii) Intraoperative dexmedetomidine infusion

iii) Anticholinergic premedication

To investigate the robustness of our findings, we planned to perform the following sensitivity analyses: analyzing only low risk of bias studies, analyzing outcomes with a low heterogeneity (from 0 to 25%) with a random-effect model and by removing continuity correction.

Trial Sequential Analysis

A pre-specified Trial Sequential Analysis (TSA) [12] was performed on the main outcome with the Trial Sequential Analysis software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen). We estimated the required sample size on the calculated minimal intervention effect, considering a type I error of 5% and a power of 90%. Values of $p < 0.05$ were considered to be statistically significant in all analyses.

Results

Study selection and data retrieval

The search results are summarized in the PRISMA diagram (Fig. 1). We retrieved a total of 3841 studies. Among them, only 15 studies (980 patients) were included in the qualitative and quantitative analysis [4, 13-26].

Study characteristics

The 15 included studies randomized 519 patients to the dexmedetomidine group and 461 to the no intervention or placebo group.

One study [16] included patients older than 65 years with all the remaining including only younger patients. All studies included patients with an ASA-PS of I-II and only one study [26] included ASA-PS III patients. One study [20] reported no information regarding both ASA-PS and the age of the included patients.

Dexmedetomidine bolus used for tracheal intubation ranged from 1 mcg/Kg [4, 17, 19, 21, 22] to 0.01 mcg/Kg [15]. Five studies used a bolus dose higher than 0.7 mcg/Kg (137 patients to dexmedetomidine and 139 patients to placebo/no intervention)[4, 17, 19, 21, 22], five studies used a dose between 0.7 mcg/Kg and 0.4 mcg/Kg (177 patients to dexmedetomidine and 177 patients to placebo/no intervention)[13,14,20,24,26], four studies used a dose below 0.4 mcg/Kg (115 patients to dexmedetomidine and 115 patients to placebo/no intervention)[15,16,18 ,23] while one study [25] used both medium and high bolus dose of dexmedetomidine(90 patients to dexmedetomidine and 30 patients to placebo/no intervention).

The characteristics of included studies are available for consultation as Online Resource 2.

Two studies [17, 25] were evaluated to be at low risk of bias, while all the remaining were judged to raise some concerns. No study was evaluated to be at high risk of bias (Fig 2). The motivations that guided us while assigning the risk of bias judgements are available as Online Resource 3.

Outcomes

Primary and secondary outcomes are summarized in Table 1. All the forest plots and funnel plots are available as supplementary material (Online Resource 4 and 5).

Primary outcome

Ten studies described the occurrence of intraoperative bradycardia. Patients receiving dexmedetomidine had a higher risk of developing intraoperative bradycardia [RR 2.81 (95% CI 1.34 to 5.91, p-value 0.006, I^2 0%)] (Fig. 3). We calculated a number needed to harm (NNH) of 17.4 (95% CI 11.7 to 33.4), meaning that one patient every 17 will develop bradycardia because of the intervention.

In the TSA, the cumulative z-score crossed the monitoring boundary for harm at the tenth trial yielding an effect that is both statistically and clinically significant (Fig 4).

The certainty of evidence was evaluated as moderate (Online Resource 6)

To note, neither cardiac arrest or myocardial ischemia have been reported in any patient.

Secondary outcomes

i) Intraoperative hypotension

Nine studies reported the incidence of intraoperative hypotension. This complication happened more frequently in patients receiving dexmedetomidine compared to patients receiving placebo or no intervention (Table 1). The calculated number needed to harm is 24 (95% CI 13.3 to 107.1).

The certainty of evidence was evaluated as moderate (Online Resource 6)

ii) Hemodynamic at intubation

MAP, SBP, and HR were reported by 11, 5, and 13 studies respectively. Patients receiving dexmedetomidine at intubation had lower MAP,SBP, and HR (Table 1). The certainty of evidence for these three outcomes was evaluated as very low because of the high heterogeneity (Online Resource 4)

iii) Anesthetics

Six studies reported anesthetics requirements at anesthesia induction. The use of dexmedetomidine, as an adjuvant, allowed the use of a lower total dose of anesthetics for intubation (Table 1).

Few studies described the intraoperative requirements of opioids (2 studies [20, 23]) and hypnotics (1 study [23]) and a meta-analysis was not performed. Both studies employed a continuous infusion of dexmedetomidine during surgery and found a significant association between dexmedetomidine use and lower opioid and hypnotic intraoperative consumption.

iv) Postoperative analgesics and side-effects

Meta-analysis of five studies evaluating PONV revealed a lowered risk for patients receiving dexmedetomidine (Table 1). Two studies evaluated shivering and both found a statistically significant difference in favour of dexmedetomidine (0% vs 12.5% in Chilkoti et al paper [18], and 3.3% vs 13.2% in Bielka et al paper [16]).

Postoperative rescue analgesics were evaluated in two studies with different results. Park et al [23] found no differences in the use of analgesic, while Khanduja et al [20] reported a lower need for analgesics in the postoperative period.

Sensitivity Analysis

Excluding the continuity correction did not change the effect estimation for all the outcomes where the correction was applied (intraoperative bradycardia RR 5.70, 95% CI 1.84 to 17.76, p-value 0.003, I^2 0%; intraoperative hypotension RR 1.96 , 95% CI 0.99 to 3.86, p-value 0.05, I^2 21%).

Given that no meta-analysis was found with low heterogeneity and only two studies were at low risk of bias, the other two preplanned sensitivity analyses were not performed.

Publication bias

Egger test was performed for intraoperative bradycardia HR and MAP outcomes, both with at least ten studies included. There was no publication bias for all the examined outcomes: intraoperative bradycardia (p-value 0.755), MAP at intubation showed no publication bias (p- value 0.635), HR outcome revealed a possible publication bias (p-value 0.124). For the other outcomes, notwithstanding the lack of clear asymmetry at visual inspection, a definite interpretation of the funnel plots is not possible consequent to the paucity of studies (Online Resource 5).

Subgroup analysis

Subgroup analysis forest plots are available as supplementary material (Online Resource 7).

i) Dexmedetomidine dose

Five studies used a dose >= 0.70 mcg/Kg, study used a dose between 0.70 and 0.40 mcg/Kg, and three studies used a low dose regimen (<0.40 mcg/Kg), while one study [25] used all three the regimens. There was no difference in the occurrence of intraoperative bradycardia when considering the three different dose regimens (p-value for subgroup differences 0.47, I^2 0%)

ii) Intraoperative dexmedetomidine infusion

All studies but two [19, 25] used a dexmedetomidine continuous infusion protocol during the surgery. There was no statistical difference among the subgroups caused by the intraoperative dexmedetomidine infusion (p-value for subgroup differences 0.23, I^2 29.6%)

iii) Anticholinergic premedication

Patient receiving an anticholinergic drug at anesthesia induction did not develop bradycardia (RR 1.86, 95% CI 0.52 to 6.66, p-value 0.34, I^2 0%), however the difference was not statistically significant among the groups (p-value 0.46)

Discussion

Our meta-analysis shows that premedication with dexmedetomidine for endotracheal intubation during laparoscopic cholecystectomy is associated with higher risk of intraoperative bradycardia as compared to placebo or no intervention. Moreover, patients receiving dexmedetomidine, despite requiring less anesthetics at anesthesia induction, developed lower blood pressure and HR at tracheal intubation, and experienced more frequent intraoperative hypotension, but less frequent PONV.

Although laparoscopy is commonly considered a minimally invasive surgical approach, pneumoperitoneum is responsible for extensive perturbations of patient's physiology, due to the increased intra-abdominal pressure, the cephalic displacement of the diaphragm with alterations of intrathoracic pressure, the carbon dioxide accumulation, and the marked hemodynamic response [27]. On the one hand, laparoscopic surgery is associated with a profound sympathetic stimulus with an increase in HR and blood pressure due to catecholamine release [27], while, on the other hand, peritoneal stretch secondary to intra-abdominal gas insufflation may lead to an increase in the vagal tone with subsequent bradycardia [3].

Given its potential impact on postoperative outcome, sympathetic stimulus control during anesthesia is of paramount importance. Particularly, an uncontrolled intraoperative tachycardia is associated with an increased risk of perioperative myocardial infarction [28] and mortality [29].

Dexmedetomidine is employed for sedation in different settings of care and, even at low concentration, was shown to reduce the plasmatic levels of catecholamines [30].

Our meta-analysis suggests that the administration of dexmedetomidine before endotracheal intubation may be associated with lower HR and blood pressure as compared to no dexmedetomidine or placebo. These findings confirm the results of a previous meta-analysis, which

showed dexmedetomidine use associated with a reduction in the adrenergic response at induction, surgical incision, and extubation [6].

However, the blunting of the adrenergic response should be weighted against potential perioperative complications such as bradycardia and hypotension. Our work suggests that dexmedetomidine administration may be associated with the occurrence of these hemodynamic alterations in about 5 every 100 patients.

Two previous meta-analyses evaluated the effect of dexmedetomidine administered at tracheal intubation [5, 6].

Our group [6] investigated the effect of dexmedetomidine during all surgical procedures (laparoscopic, robotic, and open surgeries). We found that the risk of bradycardia is relevant (one patient every 12 patients treated with dexmedetomidine) and its use during daily practice should be cautiously evaluated for each patient.

Demiri et al [5] recently studied the incidence of perioperative adverse events after the administration of alpha-2-agonist with 31% patients receiving clonidine. In their work they highlight that patients receiving dexmedetomidine but not clonidine were at a higher risk for intraoperative bradycardia compared to the patients receiving both medications.

In keeping with the aforementioned papers, based on all surgical procedures either open or laparoscopic [5, 6], the present study, focused only on laparoscopic cholecystectomy, cautions about routine dexmedetomidine use also during laparoscopic surgery. Indeed, our study suggests that dexmedetomidine should not be used as first drug choice in patients undergoing cholecystectomy given the above discussed hemodynamic alterations. Its use should be reserved and considered with a risk-benefit analysis performed in patients with a strict need of sympathetic response control, even if data regarding this specific population is still insufficient to express strong

recommendations. If dexmedetomidine is chosen, a dose of 0.5 mcg/kg is preferable than a higher dose (ie 1.0 mcg/kg) because the lower incidence of bradycardia in the general population [6]

The present study confirms the potential benefit of dexmedetomidine in the reduction of PONV [6].

Our work has the following limitations.

First, although we focused on laparoscopic cholecystectomy, thus decreasing clinical heterogeneity, we recognize that the heterogeneity in different anesthesia protocols and cut-off values for identifying some complications limits our conclusions.

Second, in order not to increase type I error we did not consider other potentially interesting outcomes (such as intraoperative hemodynamics).

CONCLUSIONS

Patients undergoing laparoscopic cholecystectomy receiving dexmedetomidine at tracheal intubation are more likely to develop intraoperative bradycardia and hypotension. This effect may be attenuated by administration of an anticholinergic agent.

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TABLE 1 - Outcomes

	N Study	Mean(95%CI)	p-value	I^2
Intraoperative Bradycardia	10	RR 2.81 (1.34 to 5.91)	0.006	0%
Intraoperative Hypotension	9	RR 1.66 (0.92 to 2.98)	0.09	0%
SBP	5	MD -18.54 (-34.01 to -3.08)	0.02	98%
MAP	11	MD -9.42 (-14.30 to-4.55)	<0.001	95%
Heart Rate	13	MD -16.30 (-21.48 to -11.13)	<0.001	95%
Induction Agents	6	SMD -2.68 (-4.06 to -1.30)	<0.001	96%
Postoperative Nausea/Vomiting	5	RR 0.55 (0.38 to 0.79)	0.001	21%

SBP: Systolic Blood Pressure, MAP: Mean Arterial Pressure; RR: Relative Risk; MD: Mean Difference; SMD: Standardized Mean Difference

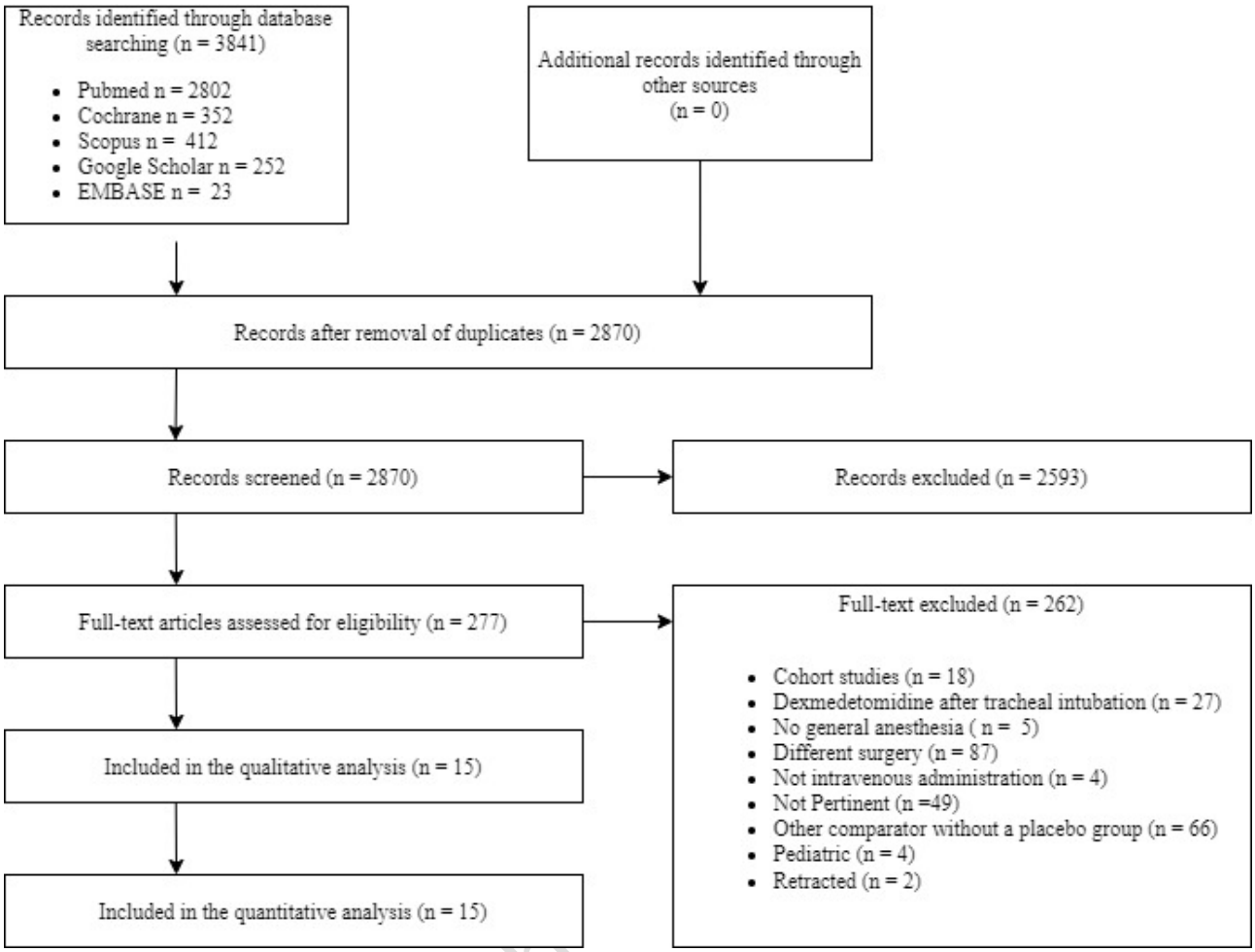

Figure 1 PRISMA flowchart.

Flowchart of the study.

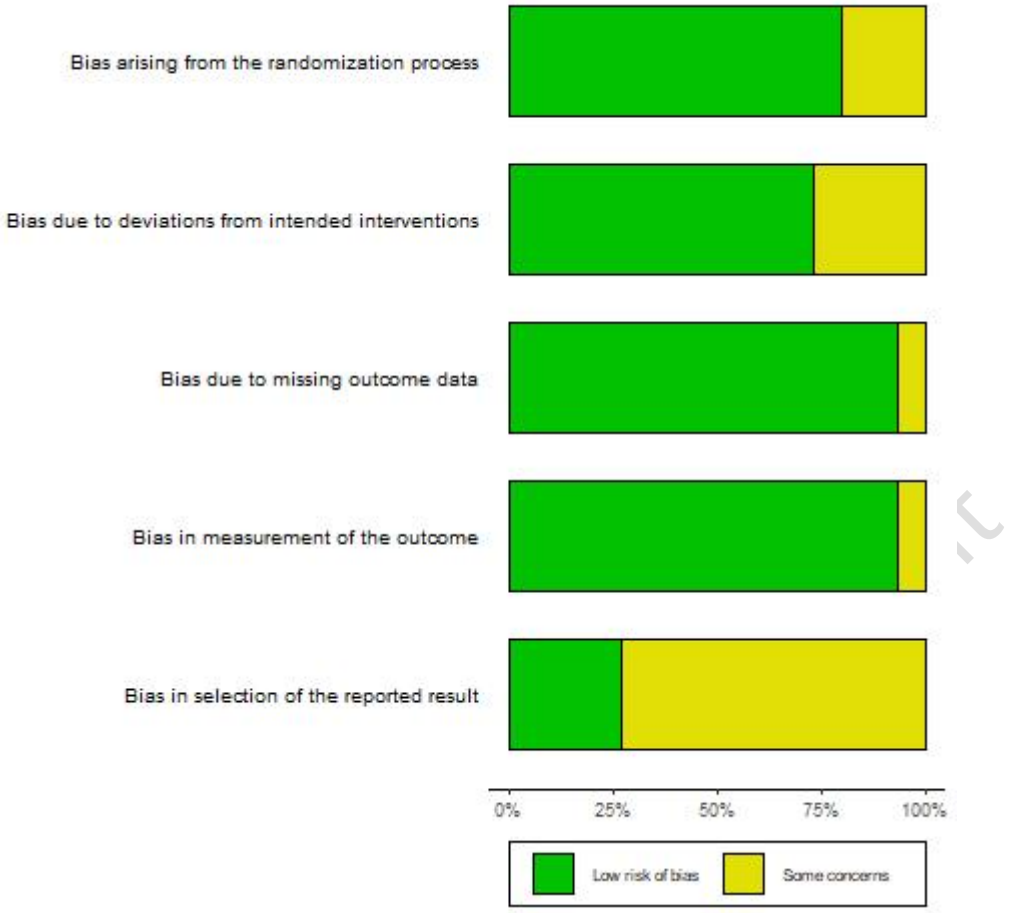

Figure 2 Bias assessment.

Overview of the ROB2 assessment.

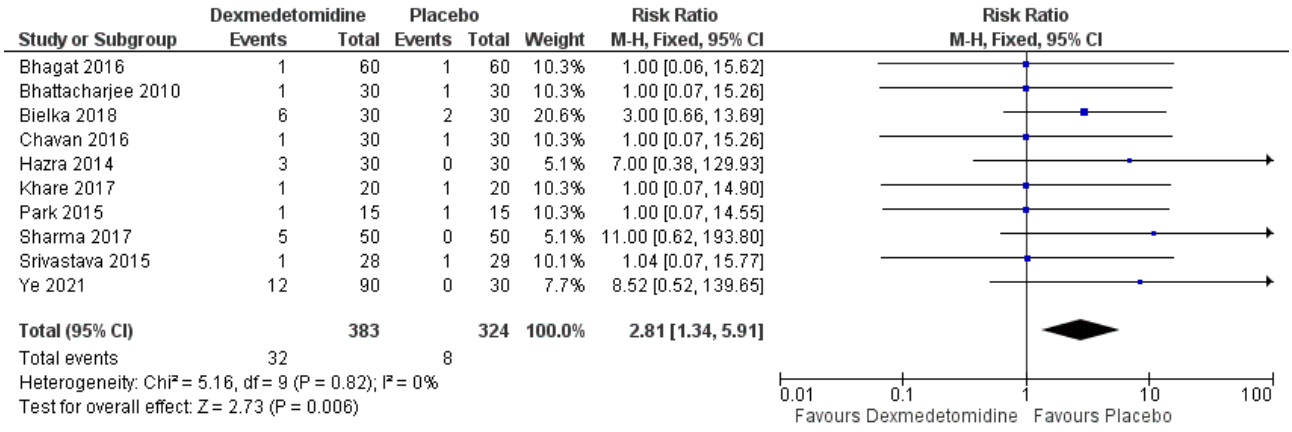

Figure 3 Intraoperative bradycardia forest plot.

Forest plot of intraoperative bradycardia.

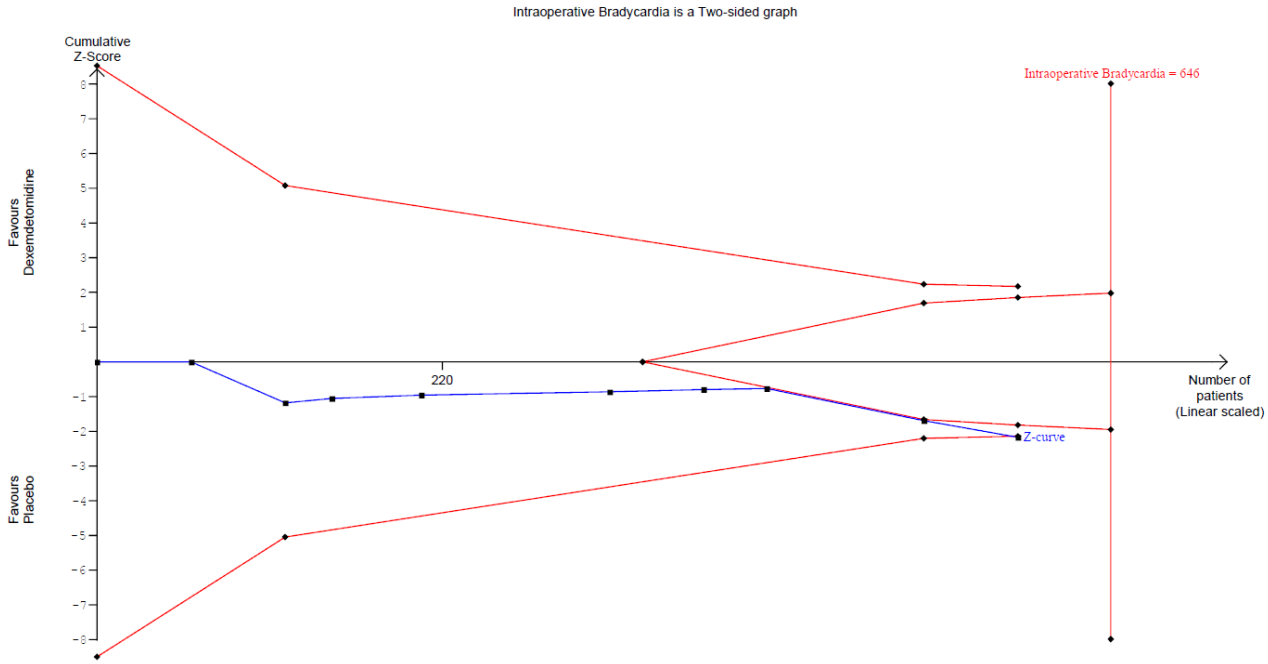

Figure 4 Intraoperative bradycardia Trial Sequential Analysis

Trial Sequential Analysis of intraoperative bradycardia.

Blue line represents cumulative evidence.

Red horizontal lines represents:

- monitoring boundaries for benefit (upper line);
- monitoring boundaries for harm (lower line);
- futility boundaries (middle lines).

The red vertical line corresponds to the required sample size.