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

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Background: While laparoscopic surgical procedures have various advantages over traditional open techniques, artificial pneumoperitoneum is associated with severe bradycardia and cardiac arrest. Dexmedetomidine, an imidazole derivative that selectively binds to α^2-receptors and has sedative and analgesic properties, can cause hypotension and bradycardia. Our primary aim was to assess the association between dexmedetomidine use and intraoperative bradycardia during laparoscopic cholecystectomy.

Methods: We performed a systematic review with a meta-analysis and trial sequential analysis using the following PICOS: adult patients undergoing endotracheal intubation for laparoscopic cholecystectomy (P); intravenous dexmedetomidine before tracheal intubation (I); no intervention or placebo administration (C); intraoperative bradycardia (primary outcome), intraoperative hypotension, hemodynamics at intubation (systolic blood pressure, mean arterial pressure, heart rate), dose needed for induction of anesthesia, total anesthesia requirements (both hypnotics and opioids) throughout the procedure, and percentage of patients requiring postoperative analgesics and experiencing postoperative nausea and vomiting and/or shivering (O); randomized controlled trials (S).

Results: Fifteen studies were included in the meta-analysis (980 patients). Compared to patients that did not receive dexmedetomidine, those who did had a higher risk of developing intraoperative bradycardia (RR: 2.81, 95% CI [1.34, 5.91]) and hypotension (1.66 [0.92, 2.98]); however, they required a lower dose of intraoperative anesthetics and had a lower incidence of postoperative nausea and vomiting. In the trial sequential analysis for bradycardia, the cumulative z-score crossed the monitoring boundary for harm at the tenth trial.

Conclusions: Patients undergoing laparoscopic cholecystectomy who receive dexmedetomidine during tracheal intubation are more likely to develop intraoperative bradycardia and hypotension.

Keywords: Bradycardia; Cholecystecomy; Dexmedetomidine; Laparoscopy; Meta-analysis; Review.

Introduction

Laparoscopic surgical procedures have various advantages over traditional open techniques, particularly in terms of early ambulation, decreased need for analgesia, and reduced hospital stay [1]. However, pneumoperitoneum induction is associated with the release of vasopressin and catecholamines and a 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 the uncontrolled increase in vagal tone caused by peritoneal stretch [3].

Several strategies have been employed to control this sympathetic response to pneumoperitoneum; among them, dexmedetomidine has shown promising results [4]. Dexmedetomidine is an imidazole derivative that highly selectively binds to α^2-receptors, thus inhibiting norepinephrine release at the level of sympathetic terminals, leading to hypotension and bradycardia and promoting analgesia in spinal cord receptors [5].

Therefore, we may infer that although dexmedetomidine could be useful for controlling sympathetic stimulation, administering it along with peritoneal insufflation could lead to severe intraoperative bradycardia.

It has been shown that compared with no dexmedetomidine or placebo, the use of dexmedetomidine for tracheal intubation is associated with an increased risk for intraoperative bradycardia in the general surgical population [6]. However, no information on patients undergoing laparoscopic procedures has been reported. Therefore, we performed 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. To prevent bias related to different surgical procedures, we focused our investigation on laparoscopic cholecystectomies only.

The secondary objectives of this study were to assess the association between dexmedetomidine use and hemodynamics at intubation (HR, MAP, systolic blood pressure [SBP]), the occurrence of intraoperative hypotension, intraoperative hypnotics and opioid consumption, and the occurrence of postoperative side effects (postoperative nausea and vomiting [PONV], shivering, and analgesic requirements).

Materials and Methods

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement guidelines to prepare this manuscript [7]. The review protocol was registered in PROSPERO (CRD42021249799) on April 18, 2021.

Search strategy

We performed a systematic review of the medical literature to screen for relevant 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 the included studies were also examined. Details regarding the search strategy are available in Supplemental Data S1. The search strategy was developed to include all RCTs employing dexmedetomidine in general surgery.

Study selection

Two researchers (A.D.C. and F.G.) independently screened the titles and abstracts of the identified studies for inclusion. Each citation was reviewed, and the full text of any potentially relevant study was retrieved. All studies meeting the following PICOS (Population, Intervention, Comparison, Outcome) criteria were included in our analysis: adult (aged ≥ 18 years) patients undergoing endotracheal intubation for laparoscopic cholecystectomy (P); who received intravenous dexmedetomidine before tracheal intubation (I); compared to no intervention or any placebo (C); with data on the following: intraoperative bradycardia (primary outcome), intraoperative hypotension, hemodynamics at intubation (SBP, MAP, HR), dose needed for induction of anesthesia, total anesthesia requirements (both hypnotics and opioids) throughout the procedure, percentage of patients requiring postoperative analgesics, and percentage of patients experiencing PONV and postoperative shivering (O); and only RCTs were included (S).

Data extraction and data retrieval

After identifying those studies that met the inclusion criteria, two members of our team (M.I. and G.Z.) independently reviewed and assessed each of the included studies. Any disagreement regarding study selection or data extraction was resolved by discussion with a third author (A.D.C.). The following information was collected: first author; year; total number of patients per group; occurrence of intraoperative bradycardia (percent of patients) and hypotension (percent of patients); SBP, MAP, and HR at tracheal intubation; induction and intraoperative anesthetic type and dosage; analgesic requirement in the first 24 h; and

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PONV and shivering (percent 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 request.

Quality assessment and certainty of evidence assessment

Two researchers (E.P. and N.R.) independently evaluated the quality of the included RCTs using the Risk of Bias (RoB) 2 Tool [8]. Disagreements were resolved by discussion with a third researcher (A.B.). 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; and HR, SBP, and MAP at tracheal intubation. Starting from a high quality of evidence, the certainty of evidence quality for each outcome is downgraded by one level for serious or by two levels for very serious study limitations, such as risk of bias, indirectness of evidence, inconsistencies, imprecision of effect estimates or other considerations (which include publication bias, large effect, plausible confounders, and dose response gradient).

Statistical methods

A meta-analysis of the data was performed using RevMan version 5.3 (The Cochrane Collaboration, 2020). The treatment effect for continuous outcomes is expressed as standardized mean difference (SMD) with 95% CIs when the outcome was expressed with different measurement techniques, or mean difference (MD) with 95% CIs when the outcome was derived from the same measurement technique. The treatment effect for dichotomous outcomes was expressed as risk ratios (RRs) with 95% CIs. Zero events were treated by applying a continuity correction adding one to each value.

Heterogeneity and publication bias analysis

To assess 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 was > 25%. Publication bias was evaluated by visual inspection of the funnel plots. The Egger test ($P < 0.05$ indicating a possible publication bias) was used for outcomes based on more than ten studies [11].

Subgroup and sensitivity analysis

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

Dexmedetomidine dose

We arbitrarily subdivided the dose of dexmedetomidine into a high dose (≥ 0.70 μg/kg), medium dose (0.40–0.69 μg/kg), and low dose (< 0.40 μg/kg) and evaluated the effects of these different dosing regimens on intraoperative bradycardia.

Intraoperative dexmedetomidine infusion

We evaluated whether the intraoperative use of dexmedetomidine continuous infusion affects the primary outcome.

Anticholinergic premedication

We evaluated the effects of anticholinergic premedication on intraoperative bradycardia.

To investigate the robustness of our findings, we planned to perform the following sensitivity analyses: 1) only low risk of bias studies and 2) 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 using TSA software (Copenhagen Trial Unit, Center 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%. Statistical significance was set at $P < 0.05$ for all analyses.

Results

Study selection and data retrieval

The search results are summarized in the PRISMA diagram (Fig. 1). We retrieved a total of 3,841 studies, 15 of which (980 patients) were included in the qualitative and quantitative analyses [4,13–26].

Study characteristics

The 15 included studies had a total of 519 patients randomized to the dexmedetomidine group and 461 randomized to the no in-

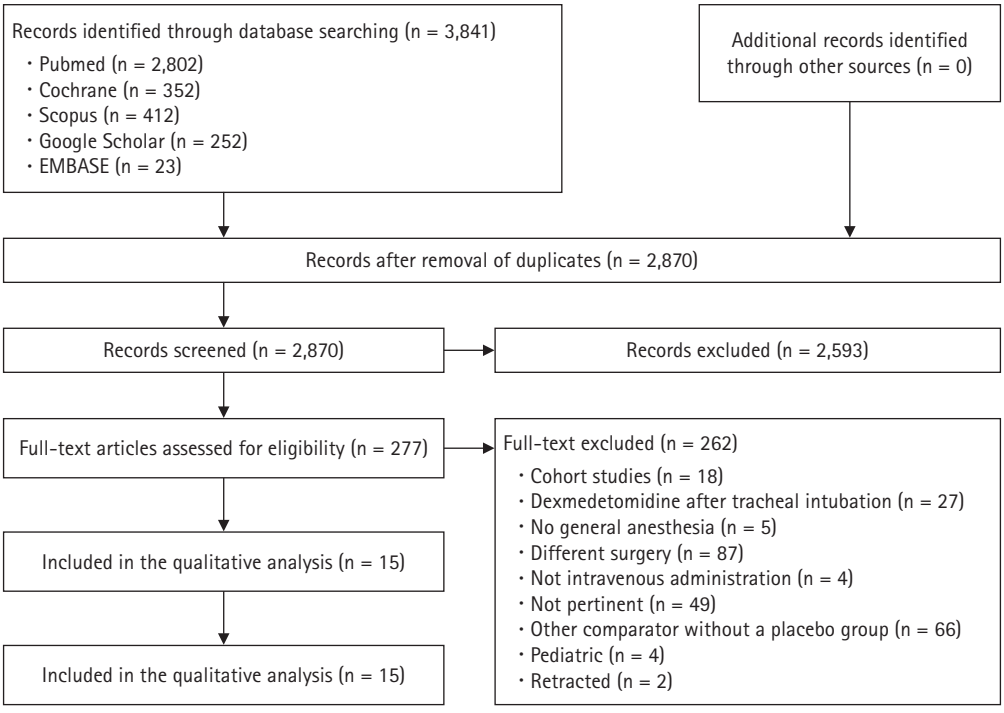

Fig. 1. PRISMA flowchart of the study.

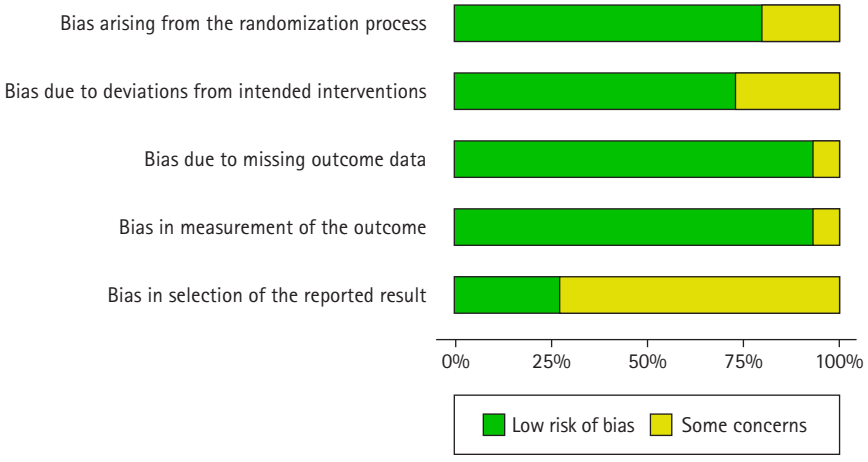

Fig. 2. Risk of bias assessment. Overview of risk of bias assessment using RoB2 Tool.

tervention or placebo group. One study [16] included patients aged > 65 years, while all the other studies included only younger patients. All the studies included patients with an American Society of Anesthesiologists Physical Status (ASA-PS) I-II, while only one study [26] included patients with an ASA-PS of III. One study [20] did not include any information regarding either the ASA-PS or the age of the included patients.

The dexmedetomidine bolus administered for tracheal intubation ranged from 1 μg/kg [4,17,19,21,22] to 0.01 μg/kg [15]. Five studies used a bolus dose > 0.7 μg/kg (dexmedetomidine group: 137 patients; placebo/no intervention group: 139 patients) [4,17,19,21,22], five studies used a dose between 0.7 μg/kg and 0.4 μg/kg (dexmedetomidine and placebo/no intervention groups: 177 patients each) [13,14,20,24,26], four studies used a dose < 0.4 μg/kg (dexmedetomidine and placebo/no intervention groups: 115 patients each) [15,16,18,23], and one study [25] used both medium and high bolus doses of dexmedetomidine (dexmedetomidine group: 90 patients; placebo/no intervention group: 30 patients). The characteristics of the included studies are available in Supplemental Data S2.

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Two studies [17,25] were evaluated as having a low risk of bias, while all the remaining studies had some potential risk of bias. However, no study was evaluated as having a high risk of bias (Fig. 2). Further details regarding the risk of bias assessments are available in Supplemental Data S3.

The primary and secondary outcomes are summarized in Table 1. All forest plots and funnel plots are available as supplementary materials (Supplemental Data S4 and S5).

Primary outcome

Ten studies described the occurrence of intraoperative bradycardia [4,14–17,19,21,23–25],. Patients receiving dexmedetomidine had a higher risk of developing intraoperative bradycardia (RR: 2.81, 95% CI [1.34, 5.91], P = 0.006, I^2 = 0%) (Fig. 3). We calculated a number needed to harm (NNH) of 17.4 (95% CI [11.7, 33.4]), meaning that one in every 17 patients develop bradycardia as a result of the intervention.

In the TSA, the cumulative z-score crossed the monitoring boundary for harm at the tenth trial, yielding an effect that was both statistically and clinically significant (Fig. 4). The certainty of evidence was evaluated as moderate (Supplemental Data S6). Notably, no patient included in this study experienced either cardiac arrest or myocardial ischemia.

Secondary outcomes

Intraoperative hypotension

Nine studies reported the incidence of intraoperative hypotension [4,14–19,23,25]. This complication occurred more frequently in patients receiving dexmedetomidine than in those receiving placebo or no intervention (Table 1). The calculated NNH was 24 (95% CI [13.3, 107.1]). The certainty of evidence was evaluated as moderate (Supplemental Data S6).

Hemodynamics at intubation

The MAP, SBP, and HR were reported in 11 [4,13–19,21,22,26], 5 [4,19,22,24,25], and 13 [4,13,19,21,22,24–26] studies, respectively. Patients who received dexmedetomidine at intubation had lower MAP, SBP, and HR values (Table 1). The certainty of evidence for these three outcomes was evaluated as very low due to high heterogeneity (Supplemental Data S4).

Table 1. Primary and Secondary Outcomes of the Studies Involved

Outcomes	N study	Mean (95% CI)	P value	I^2
Intraoperative bradycardia	10	RR 2.81 (1.34, 5.91)	0.006	0%
Intraoperative hypotension	9	RR 1.66 (0.92, 2.98)	0.09	0%
SBP	5	MD −18.54 (−34.01, −3.08)	0.02	98%
MAP	11	MD −9.42 (−14.30, −4.55)	< 0.001	95%
HR	13	MD −16.30 (−21.48, −11.13)	< 0.001	95%
Induction agents	6	SMD −2.68 (−4.06, −1.30)	< 0.001	96%
Postoperative nausea/vomiting	5	RR 0.55 (0.38, 0.79)	0.001	21%

SBP: systolic blood pressure, MAP: mean arterial pressure, HR: heart rate. RR: relative risk, MD: mean difference, SMD: standardized mean difference.

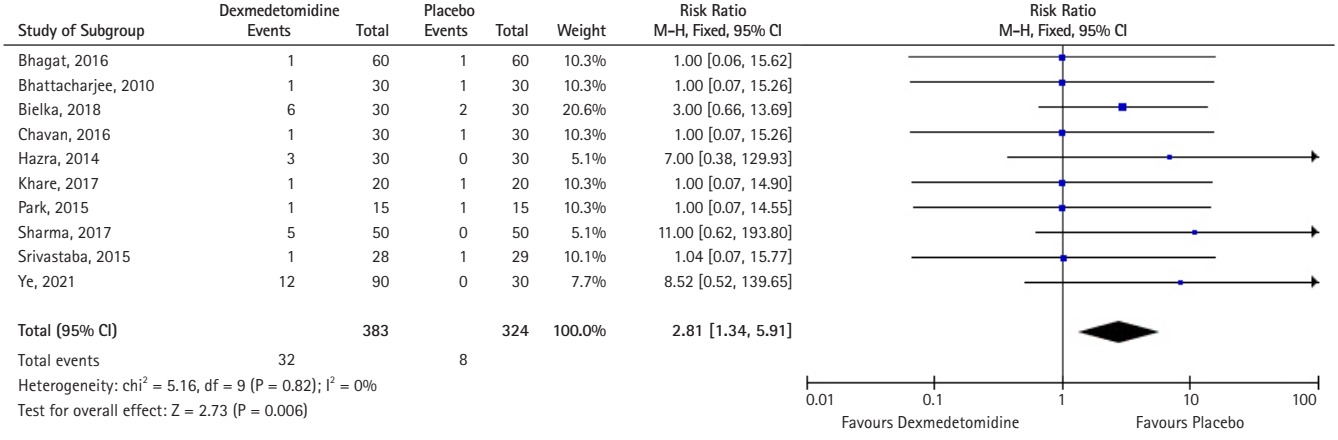

Fig. 3. Intraoperative bradycardia forest plot. Forest plot of intraoperative bradycardia.

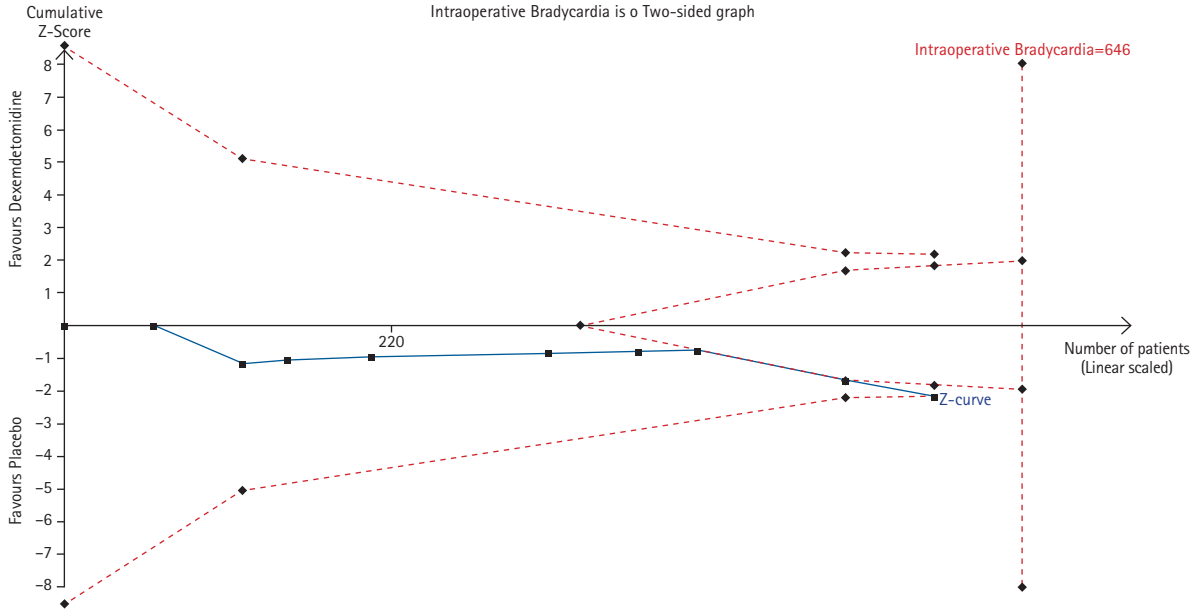

Fig. 4. Intraoperative bradycardia trial sequential analysis (TSA). Trial sequential analysis TSA of intraoperative bradycardia. The blue line represents cumulative evidence. The red horizontal lines represent monitoring boundaries for benefit (upper line), monitoring boundaries for harm (lower line), and futility boundaries (middle lines). The red vertical line corresponds to the required sample size.

Anesthetics

Six studies reported the anesthesia requirements at anesthesia induction [4,13,18,20,21,24]. The use of dexmedetomidine as an adjuvant allowed for a lower total dose of anesthetics for intubation (Table 1).

Only a few of the studies described the intraoperative opioid requirements [20,23] and hypnotics [23] and therefore a meta-analysis was not performed. Both of these studies employed a continuous infusion of dexmedetomidine during surgery and found a significant association between dexmedetomidine use and lower opioid and hypnotic intraoperative consumption.

Postoperative analgesics and side-effects

We performed a meta-analysis of the five studies evaluating PONV, which revealed a lower risk of PONV for patients receiving dexmedetomidine (Table 1). Two studies evaluated shivering and found a statistically significant difference in favor of dexmedetomidine (Chilkoti et al. [18]: 0% vs. 12.5% and Bielka et al. [16]: 3.3% vs. 13.2%). Postoperative rescue analgesics were evaluated in two studies with different results. Park et al. [23] found no differences in the use of analgesics, while Khanduja et al. [20] reported a lower need for analgesics in the postoperative period for those who received dexmedetomidine.

Sensitivity analysis

Excluding the continuity correction did not change the effect estimation for any of the outcomes where the correction was applied (intraoperative bradycardia: RR 5.70, 95% CI [1.84, 17.76], P = 0.003, I^2 = 0%; intraoperative hypotension: RR 1.96, 95% CI [0.99, 3.86], P = 0.05, I^2 = 21%). Given that no meta-analysis with low heterogeneity was found and only two studies [17,25] were at low risk of bias, the other two preplanned sensitivity analyses were not performed.

Publication bias

The Egger test was performed for intraoperative bradycardia HR and MAP outcomes, both of which included at least ten studies. Publication bias was not evident for any of the examined outcomes: intraoperative bradycardia (P = 0.755), MAP at intubation (P = 0.635), or HR outcomes (P = 0.124). For the other outcomes, notwithstanding the lack of clear asymmetry on visual inspection, a definite interpretation of the funnel plots was not possible due to the paucity of studies (Supplemental Data S5).

Subgroup analyses

Subgroup analysis forest plots are available as supplementary material (Supplemental Data S7).

Dexmedetomidine dose

Five studies used a dexmedetomidine dose ≥ 0.70 μg/kg [4,14,17,19,21], one study used a dose between 0.70 and 0.40 μg/

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kg [24], and three studies used a low dose regimen (< 0.40 μg/kg) [15,16,23], while one study [25] used all three regimens. There were no differences regarding the occurrence of intraoperative bradycardia when considering the three different dose regimens (P = 0.47, I^2 = 0% for subgroup differences).

Intraoperative dexmedetomidine infusion

All studies except two [19,25] used a dexmedetomidine continuous infusion protocol during surgery. There were no statistically significant differences among the subgroups associated with the intraoperative dexmedetomidine infusion (P = 0.23, I^2 = 29.6% for subgroup differences).

Anticholinergic premedication

None of the patients that received an anticholinergic drug at anesthesia induction developed bradycardia (RR: 1.86, 95% CI [0.52, 6.66], P = 0.34, I^2 = 0%); however, the difference was not statistically significant among the groups (P = 0.46).

Discussion

Our meta-analysis shows that premedication with dexmedetomidine for endotracheal intubation during laparoscopic cholecystectomy is associated with a higher risk of intraoperative bradycardia than placebo or no intervention. Moreover, patients receiving dexmedetomidine, despite requiring less anesthetics at anesthesia induction, developed lower blood pressure and HR during 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 the patient's physiology due to increased intra-abdominal pressure, cephalic displacement of the diaphragm with alterations in intrathoracic pressure, carbon dioxide accumulation, and 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 outcomes, sympathetic stimulus control during anesthesia is of paramount importance. Particularly, uncontrolled intraoperative tachycardia is associated with an increased risk of perioperative myocardial infarction [28] and mortality [29]. Dexmedetomidine is employed for sedation in different care settings and has been shown to reduce the plasma levels of catecholamines even at low concentrations [30]. Our meta-analysis suggests that the administration of dexmedetomidine before endotracheal intubation compared to no dexmedetomidine or placebo may be associated with a lower HR and BP. These findings confirm the results of a previous meta-analysis, which showed that dexmedetomidine use was associated with a reduction in the adrenergic response at induction, surgical incision, and extubation [6].

However, blunting of the adrenergic response should be weighed 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 approximately 5 out of every 100 patients.

While two previous meta-analyses evaluated the effects of dexmedetomidine administered during tracheal intubation [5,6], our group [6] investigated the effect of dexmedetomidine during all surgical procedures (laparoscopic, robotic, and open surgeries). We found an association between bradycardia and dexmedetomidine administration (one in every 12 patients) and concluded that it therefore should be administered with caution in daily practice.

Of note, Demiri et al. [5] recently studied the incidence of perioperative adverse events after the administration of α^2-agonist where 31% of the patients also received clonidine. These authors highlighted the finding that patients receiving dexmedetomidine but not clonidine were at a higher risk for intraoperative bradycardia than those who received both medications.

While the aforementioned studies were based on all surgical procedures (open or laparoscopic) [5,6], the present study focused only on laparoscopic cholecystectomy. Our study findings suggest that caution should be taken regarding routine dexmedetomidine use during laparoscopic surgery. Indeed, dexmedetomidine should not be used as a first choice in patients undergoing cholecystectomy, given the hemodynamic alterations discussed above. Rather, its use should be reserved and considered along with a risk-benefit analysis for patients with a strict need for sympathetic response control, even if data regarding this specific population are still insufficient for strong recommendations. If dexmedetomidine is administered, a dose of 0.5 μg/kg is preferable to a higher dose (e.g., 1.0 μg/kg) given the lower incidence of bradycardia associated with this dose in the general population [6]. As an additional note, the present study confirms the potential benefit of dexmedetomidine in reducing PONV [6].

Our study has a few limitations. First, although we focused only on laparoscopic cholecystectomy, which decreased clinical heterogeneity, we recognize that the heterogeneity associated with dif-

ferent anesthesia protocols and cut-off values for identifying some complications limits our conclusions. Second, to avoid increasing type I errors, we did not consider other potentially interesting outcomes (such as intraoperative hemodynamics).

In conclusion, patients undergoing laparoscopic cholecystectomy that receive dexmedetomidine during tracheal intubation are more likely to develop intraoperative bradycardia and hypotension. This effect may be attenuated by the administration of an anticholinergic agent.

Funding

None.

Conflicts of Interest

PN received royalties from Intersurgical for Helmet Next invention and speaking fees from Draeger, Intersurgical, Getinge, Philips, Resmed, MSD, Gilead and Novartis. The other authors have no other competing interests to declare.

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Paolo Navalesi (Conceptualization; Supervision; Writing – review & editing)
Annalisa Boscolo (Conceptualization; Supervision; Writing – review & editing)

Supplementary Materials

Supplemental Data S1. Search Strategy
Supplemental Data S2. Study characteristics
Supplemental Data S3. ROB2
Supplemental Data S4. Forest Plot
Supplemental Data S5. Funnel Plot
Supplemental Data S6. Grade
Supplemental Data S7. Subgroup+sensitivity

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