Effects of Dexmedetomidine vs Esmolol on Postintubation Hemodynamics: A Meta-Analysis

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Objective: Tracheal intubation (TI) consistently induces tachycardia and elevated blood pressure which may be deleterious to patients, particularly those with existing cardiac conditions. Use of dexmedetomidine or esmolol has been described to attenuate this sympathetic response. This study aimed to determine the effectiveness of dexmedetomidine vs esmolol in attenuating the hemodynamic response during TI.

Methods: A systematic review and meta-analysis were performed using PRISMA guidelines. A systematic literature search in electronic databases and grey literature was completed. Researchers assessed article eligibility, performed data extraction, and completed risk of bias assessment. Results were expressed as pooled differences for cardiovascular parameters between the drugs as the weighted mean difference with 95% CI. A $P < .05$ was considered statistically significant. Heterogeneity was quantified using the I^2 statistic. Subgroup analyses exploring different drug regimens were performed.

Results: Of 112 publications, 19 randomized controlled trials were included for descriptive analysis and 15 were selected for the meta-analysis with 948 patients. The use of dexmedetomidine vs esmolol provided lower heart rates and mean arterial pressures at 1, 3, 5, and 10 minutes and lower systolic and diastolic pressures at 1, 3, and 5 minutes after TI.

Conclusion: Dexmedetomidine blunts the hemodynamic response to TI more effectively vs esmolol.

Key Words: Dexmedetomidine; Esmolol; Hemodynamic; Laryngoscopy; Intubation.

Tracheal intubation (TI) during general anesthesia (GA) is known to increase sympathetic activity that may result in hypertension or arrhythmias.[1,2] Literature on the incidence of postintubation hemodynamic instability and its impact on patient outcomes is limited to critically ill patients.[3] In healthy individuals, this transient sympathetic response secondary to an increase of plasma catecholamines is likely of little significance.[4,5] It is well documented that hemodynamic responses can be pronounced and harmful in patients with cardiovascular comorbidities and lead to left ventricular failure, myocardial ischemia, and stroke.[6–8] For example, Roy et al[9] monitored the ST segment in electrocardiograms of 11 noncoronary and 29 coronary patients under GA. In the coronary group, 11 of the 29 patients developed an increase in heart rate (HR) and blood pressure (BP) followed by ST depression, an indicator of myocardial ischemia, during the intubation period but none in the noncoronary group.[9]

The extent, severity, and duration of the sympathetic reaction to TI is dependent on many factors including premedication and induction drugs.[10,11] Opioids, beta blockers, and α2 agonists have been used to blunt hemodynamic changes associated with TI.[10–12] In the last 2 decades, anesthesiologists have discussed opioid-sparing techniques to prevent opioid side effects (eg, postoperative ileus, urinary retention, postoperative nausea and vomiting, and postoperative respiratory complications).[13–15] A meta-analysis by Figueredo et al. concluded that esmolol, an ultrashort-acting beta blocker, is effective in a dose-dependent manner for attenuating the short-term sympathetic response triggered by TI.[16–19]

Alternatively, dexmedetomidine is a highly selective and potent α2 agonist used for anxiolysis, sedation, and analgesia.[20–22] Dexmedetomidine was initially approved in 1999 by the US Food and Drug Administration for intravenous (IV) administration for up to 24 hours of sedation in mechanically ventilated adult patients in the intensive care unit (ICU).[23] Later, dexmedetomidine was approved for perioperative sedation of nonintubated patients. Notably, its off-label use is frequently reported in the literature.[24] A meta-analysis by De Cassai et al[25] concluded that

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dexmedetomidine before TI significantly blunted patient hemodynamics during laryngoscopy with decreases in HR, systolic blood pressure (SBP), and mean arterial pressure (MAP) vs no dexmedetomidine. Thus, both esmolol and dexmedetomidine can attenuate the hemodynamic response after TI, leaving agent selection to the anesthesiologist's discretion.

Several clinical trials compared dexmedetomidine with esmolol for hemodynamic stability, yet there is no consensus on agent superiority. A meta-analysis by Li et al[26] concluded that dexmedetomidine had better HR and BP control than esmolol after rapid sequence induction (RSI).[26,27] To our knowledge, there is no systematic review comparing the hemodynamic stability of these 2 drugs following TI in the non-RSI context. Also, there is no agreement on optimal dosage and timing. The primary objective of this systematic review and meta-analysis was to compare dexmedetomidine with esmolol for hemodynamic response (eg, HR and BP) at 1, 3, 5, and 10 minutes after TI in non-RSI studies with patients undergoing noncardiac surgery. The secondary objective was to identify any adverse effects related to dexmedetomidine or esmolol such as tachycardia, bradycardia, hypotension, and extrasystoles.

METHODS

A systematic review and meta-analysis of all peer-reviewed randomized controlled trials (RCTs) that compared dexmedetomidine to esmolol as a sole or adjunct sedative agent to lessen hemodynamic effects of TI were performed. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement guidelines were used to prepare this manuscript.[28] A systematic literature search was performed to identify, screen, and include articles. This search was performed on April 26, 2023, with the help of the librarian using the following databases: PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Grey Literature (by screening the first 100 results in Google). The search was limited to RCTs published in English or French in peer-reviewed journals from 1946 to present date. The search items (including alternative spelling) are listed in Supplemental Table S1 (available online only). Titles and abstracts were uploaded to EndNote 20 (Clarivate Analytics), duplicates were removed, and relevant titles were selected and then imported into Covidence (Veritas Health Innovation) for study screening and selection. Full-text papers were reviewed for inclusion or exclusion based on predefined criteria. Reference lists were screened for relevant titles for search comprehensiveness.

Study Selections

Inclusion Criteri. *Type of Participants.* Studies including adult patients (≥18 years of age) undergoing elective noncardiac surgery in the operating room or ambulatory setting were reviewed.

Type of Interventions. Studies that compared dexmedetomidine to esmolol for the purpose of attenuating the hemodynamic response associated with TI were included.

Exclusion Criteria. Non-RCTs were excluded. Studies including the pediatric population (<18 years of age), cardiac or emergency surgery, or the ICU setting were excluded. Studies where the primary outcome was not presented as mean (SD) at 1, 3, 5 or 10 minutes postintubation were excluded for the meta-analysis part of the study.

Screening and Data Extraction

All abstracts were screened by the primary author (AS) and independent reviewer (SK). Reasons for inclusion or exclusion of studies were recorded in the PRISMA flowchart. Any disagreements were discussed with third reviewer (MW). The following information was collected: first author, country, year of the study, dexmedetomidine dose, esmolol dose, and total number of patients per group, American Society of Anesthesia physical status (ASA-PS), premedication use, anesthetic drugs at induction, laryngoscopy technique, outcome measured, and results.

Risk of Bias

Risk-of-bias (RoB 2) tool assessment was done as per the Cochrane Handbook for Systematic Reviews of Intervention.[29,30] Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants (performance bias), blinding of outcome assessment (detection bias), bias of incomplete outcome data (attrition bias) and selective reporting bias (reporting bias) were assessed. Also, the RoB 2 tool allowed assigning a judgment of high, low, or unclear risk of material bias for each item.[29] The overall risk of bias of studies was judged to be "low" if all domains were low risk, "moderate" if any domains are unclear, and "high" if any domains are high risk.[30]

Quantitative Data Synthesis

The statistical analysis was performed using the Review-Manager 5.3 software (the Nordic Cochrane Centre). Pooled differences of the hemodynamic responses to TI were expressed as mean difference (MD) with 95% CIs, and $P < .05$ was considered statistically significant. Studies that did not present data as standardized mean difference (SMD) or standard error of the mean (SEM) were excluded from the meta-analysis. Continuous data were analyzed by using random effect models. I squared (I^2) was

performed to measure the percentage of variation across studies that is due to heterogeneity.[31]

Subgroup Analysis

The authors decided to subdivide dexmedetomidine dosing as high dose (≥1 μg/kg) and low dose (<1 μg/kg) and compared it to esmolol dosing as high dose (≥1.5 mg/kg) and low dose (<1.5 mg/kg) to ascertain the effects of dosing on hemodynamic stability. This subdivision was based on loading doses specified by drug monographs.

Sensitivity Analyses

Studies that included patients who received anticholinergic medication (eg, glycopyrrolate or atropine) within 24 hours before surgery were analyzed for their effects on the data. Furthermore, to determine the influence of induction agents with vasodilatory properties like propofol and thiopental, we repeated the primary analysis of SBP and MAP only with the studies that used propofol for induction since its use is more common in North America and Europe.

RESULTS

Included Studies

A total of 112 article abstracts were found, and 81 studies were isolated after removing duplicates. A total of 29 trials were assessed as eligible, but 10 were ultimately excluded (Figure 1).[32–38] Therefore, 19 trials were included in the descriptive analysis.[39–57] The meta-analysis was performed with 15 of these publications[40–48,50–52,54,56,57]; however, 4 articles were excluded because the outcome of interest was not presented in MD.[39,49,53,55] In the meta-analysis, we analyzed data from 948 patients, of whom 473 received dexmedetomidine and 475 received esmolol. We did not identify any studies in French.

Risk of Bias

The overall risk of bias was graded as low for 2 studies (11%), moderate for 16 (84%) studies, and high for 1 study (5%; Figure 2). Most of the studies were thought to be somewhat susceptible to "selective reporting" bias as we were unable to acquire the original protocols for each study. Only 2 studies were registered clinical trials.[40,46] One study was at high risk of bias due to missing data.[45]

Description of Included Studies

Characteristics of the included RCTs are presented in Supplemental Table S2 (available online only). Fifteen trials took place in India,[39,40,42,43,45,46,48–54,56] 3 in Turkey,[44,55,57] and 1 in Malaysia.[47] The smallest study contained 60 patients, whereas the largest study included 100 patients. Studies included patients ranging from 18 to 80 years of age. Patients were classified as either ASA-PS I or II in most of the trials; 1 trial did not specify ASA-PS.[54] Four trials included well-controlled hypertensive patients.[39,41,54,55]

Dosing for dexmedetomidine was reported as 1 μg/kg in 13 trials,[39,41,44–48,50–55] 0.75 μg/kg in 1 trial,[40] and 0.5 μg/kg in 5 trials.[42,43,49,56,57] In 17 trials, dexmedetomidine was injected as a single 10-minute infusion prior to preoxygenation, induction, laryngoscopy, or intubation. Only 1 trial continued the infusion as maintenance throughout the surgical procedure. One trial did not specify the administration of dexmedetomidine as a bolus or infusion.[57] Esmolol dosing was variable (eg, empirical bolus, weight-based bolus, infusion). Some studies used an empirical 100 mg dose,[55] whereas other studies used weight-based doses ranging from 0.3 to 2 mg/kg. Koh et al[47] used an esmolol infusion of 0.05 mg/kg/min over 10 minutes. In 12 trials, esmolol was given as a bolus just before or 2 minutes prior to preoxygenation, induction, laryngoscopy, or intubation.[39,41–46,50,54–57] Some trials opted for a 10-minute infusion prior to preoxygenation, induction, laryngoscopy, or intubation.[40,47,49,51–53]

Four studies used glycopyrrolate in their anesthetic regimens,[40,45,52,54] and propofol was used in 5 studies.[40,46,54,56,57]

Almost all trials included in this review performed direct laryngoscopy. To our knowledge, none of the trials used video laryngoscopy. The main sources of clinical heterogeneity were surgery type, dexmedetomidine dose, esmolol dose, and the various anesthesia maintenance regimens.

Primary Outcome: HR and BP

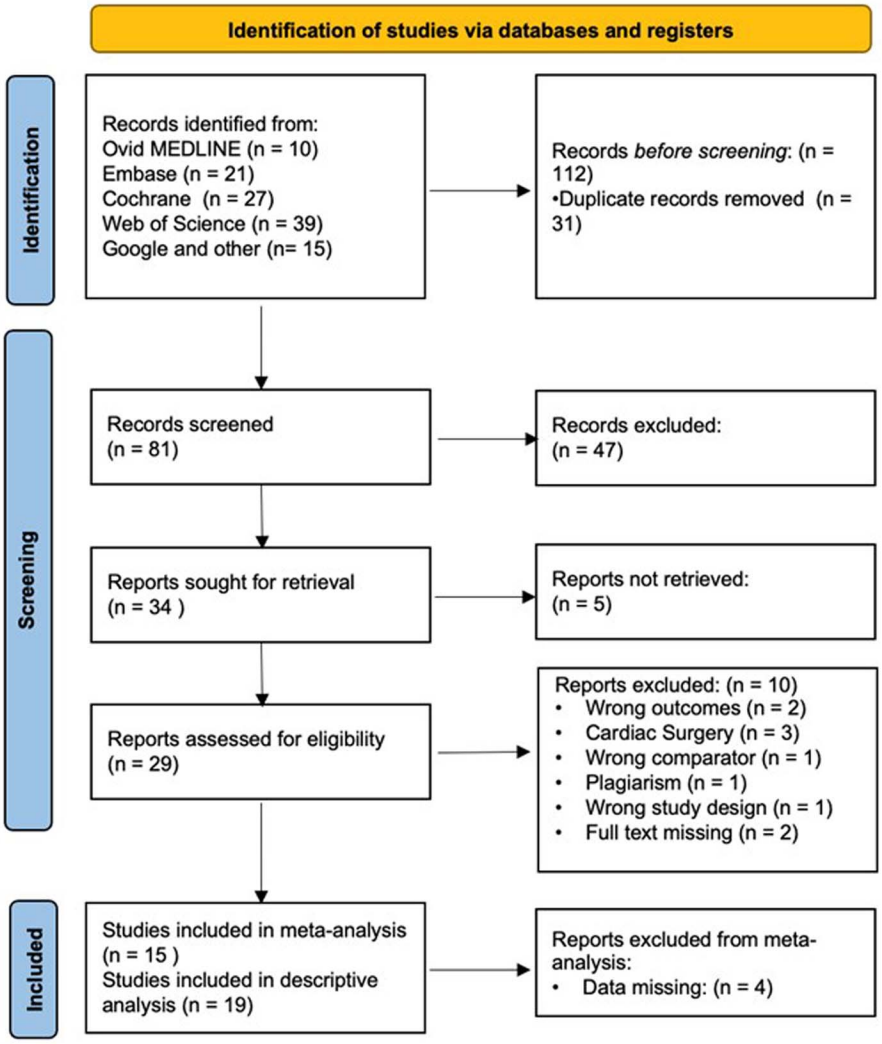
Dexmedetomidine attenuated the rise in HR (beats/min; bpm) more effectively than esmolol at 1, 3, 5, and 10 minutes following TI with MDs ranging from −11.81 to −7.15 bpm (95% CI, −14.64 to −2.49; $P \leq .003$; Figure 3).

Dexmedetomidine attenuated the rise in SBP more effectively than esmolol at 1, 3, and 5 minutes but not at 10 minutes following TI with MDs ranging from −13.43 to −11.13 mm Hg (95% CI, −20.08 to −6.36; $P < .001$; Figure 4).

Dexmedetomidine attenuated the rise in DBP more effectively than esmolol at 1, 3, and 5 minutes but not at 10 minutes following TI with MDs ranging from −7.11 to −5.29 mm Hg (95% CI, −10.73 to −1.66; $P \leq .004$; Figure 5).

Dexmedetomidine attenuated the rise in MAP more effectively than esmolol at 1, 3, 5, and 10 minutes following TI with MDs ranging from −6.29 to −3.42 mm Hg (95% CI, −9.33 to −1.55; $P \leq .004$; Figure 6).

Figure 1. PRISMA Flow Diagram



Subgroup Analysis: High/Low Dosing

All data and forest plots for the subgroup analysis are available as Supplemental Figures (Figures S7–14; available online only).

High-dose dexmedetomidine (≥1 μg/kg) attenuated the rise in HR more effectively than high-dose esmolol (1.5 mg/kg) at 1, 3, 5, and 10 minutes following TI with MDs ranging from −11.56 to −7.73 (95% CI, −14.70 to −1.54; $P \leq .01$; Supplemental Figure S7).

High-dose dexmedetomidine (≥1 μg/kg) attenuated the rise in SBP more effectively than high-dose esmolol (≥1.5 mg/kg) only at 1 and 3 minutes following TI with MDs ranging from −8.81 and −8.60 (95% CI, −14.39 to −2.87; $P \leq .003$; Supplemental Figure S8).

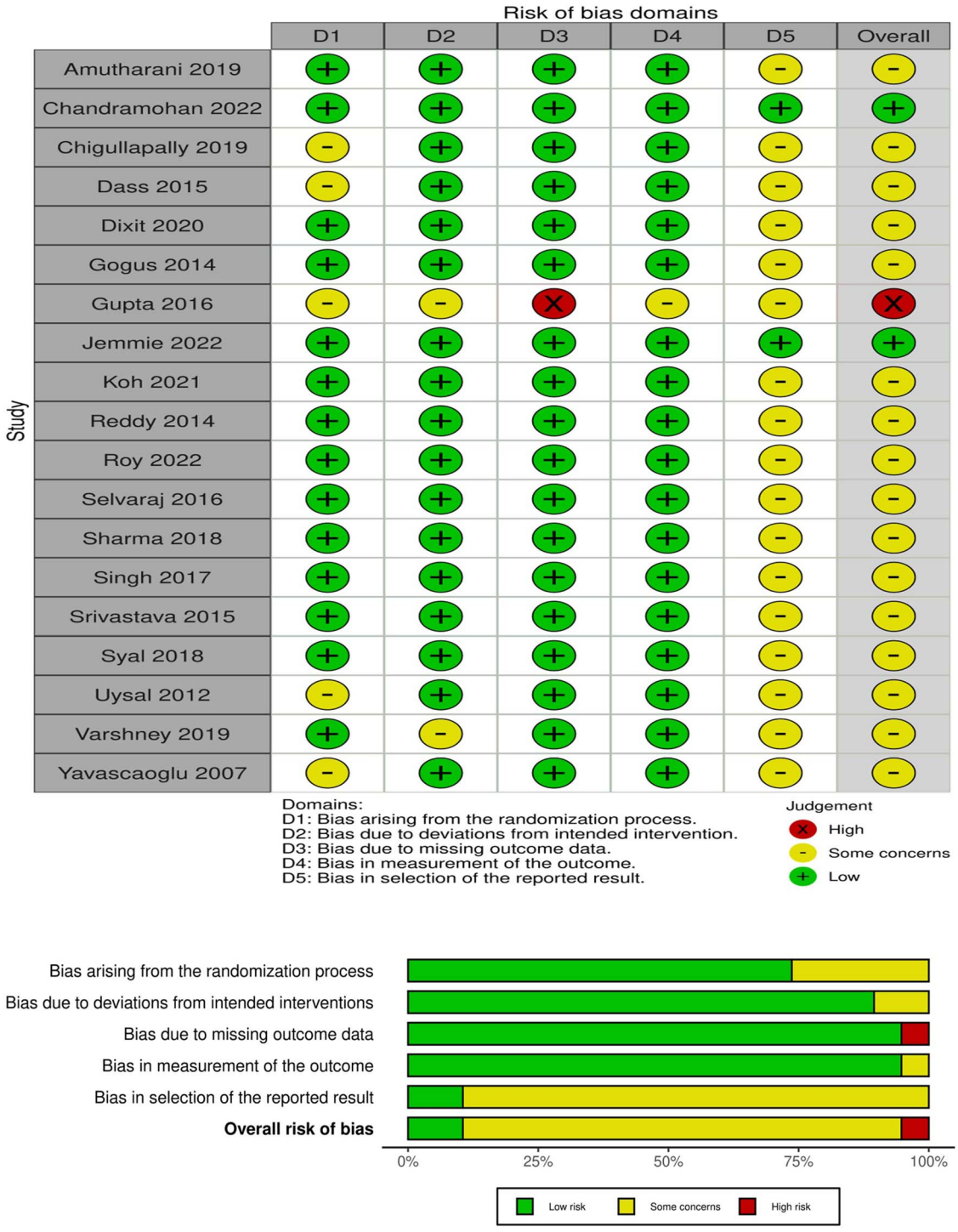
There was no difference in the DBP with high-dose dexmedetomidine (≥1 μg/kg) compared to high-dose esmolol (≥1.5 mg/kg) at 1, 3, 5, and 10 minutes following TI with MDs ranging from −3.28 to −0.07 mm Hg (95% CI, −7.26 to 2.65; $P \geq .11$; Supplemental Figure S9).

There was no difference in MAP with high-dose dexmedetomidine (≥1 μg/kg) compared to high-dose esmolol (≥1.5 mg/kg) at 1, 3, 5, and 10 minutes following TI with MDs ranging from −4.69 to 0.26 mm Hg (95% CI, −10.16 to 2.02; $P \geq .06$; Supplemental Figure S10).

Sensitivity Analysis

Anticholinergics. Glycopyrrolate was the preferred anticholinergic medication as none of the trials used atropine. Premedication with glycopyrrolate prior to intubation was not associated with significant differences in HR. Dexmedetomidine attenuated the rise in HR more effectively than esmolol with an anticholinergic agent at 1, 3, 5, and 10 minutes

Figure 2. Risk of Bias (RoB2) Summary



following TI with MDs ranging from −11.05 to −4.70 bpm (95% CI, −16.92 to −0.37; $P \leq .03$; Supplemental Figure S11). Additionally, dexmedetomidine attenuated the rise in HR more effectively than esmolol without an anticholinergic at 1, 3, 5, and 10 minutes following TI with MDs ranging from −12.93 to −8.74 bpm (95% CI, −16.58 to −1.92; $P \leq .01$; Supplemental Figure S12). Data and forest plots are available in Supplemental Figures (available online only).

Figure 3. Forest Plot for Heart Rate Response to Laryngoscopy and Tracheal Intubation Using Dexmedetomidine Compared With Esmolol

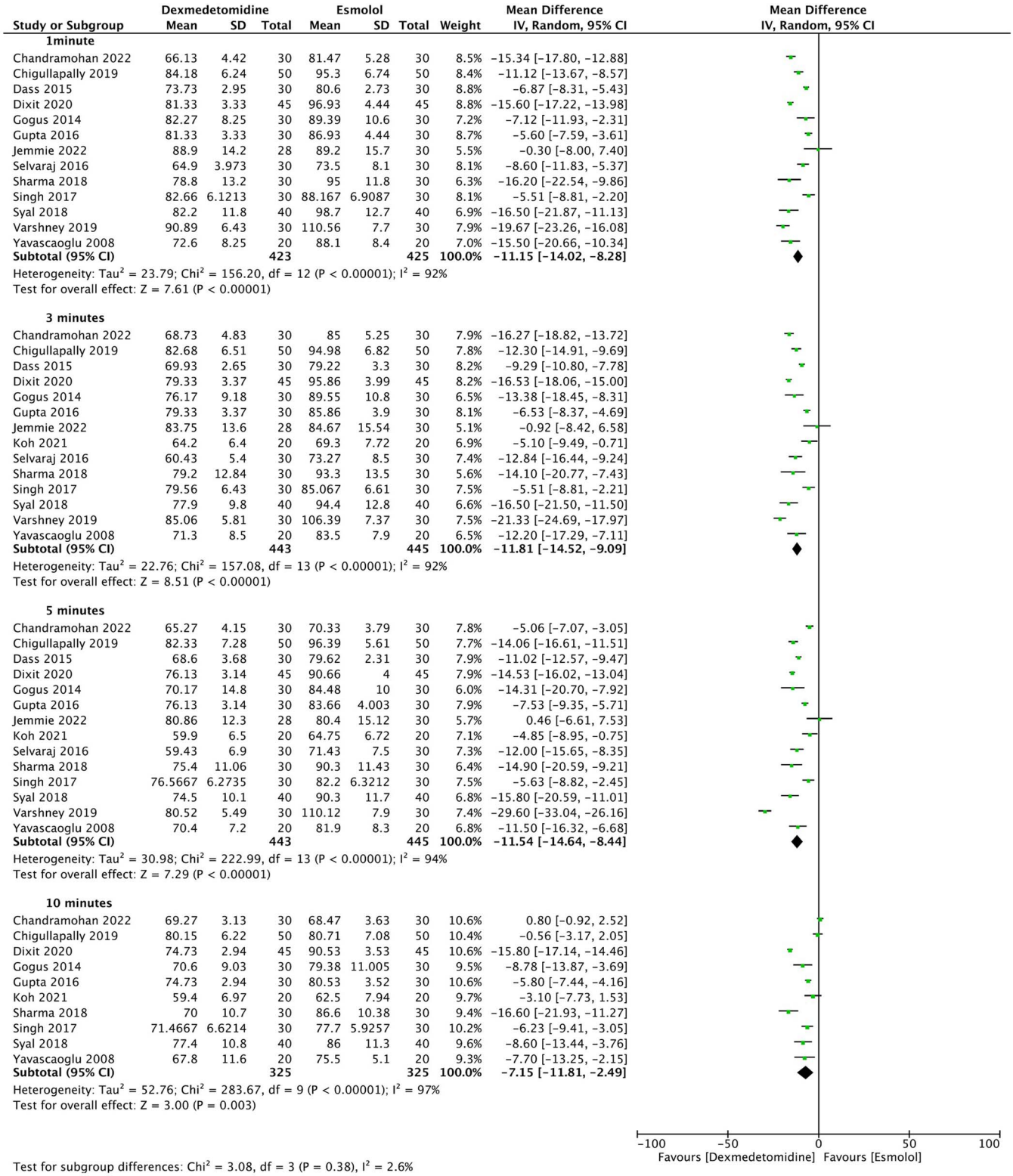
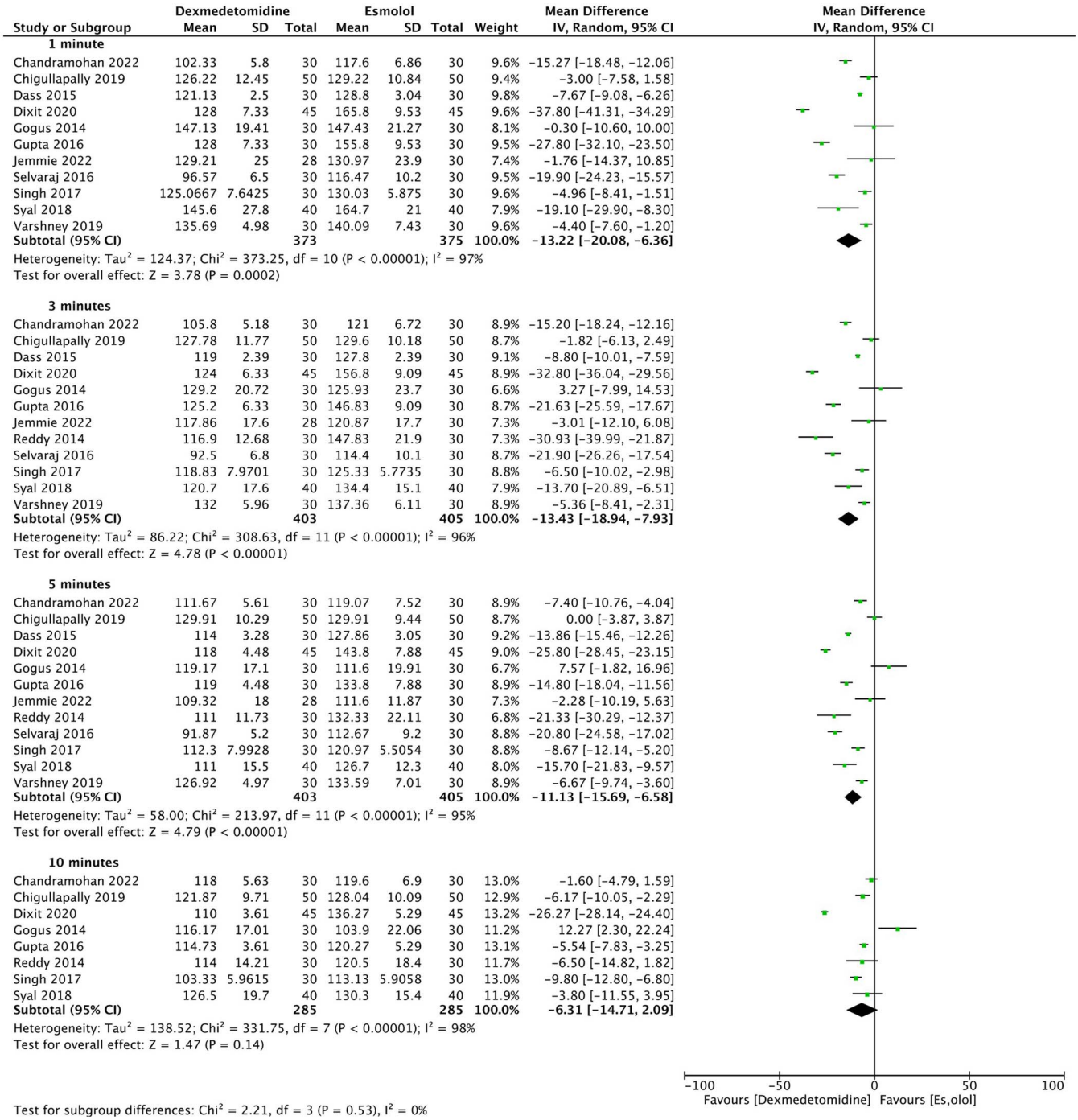
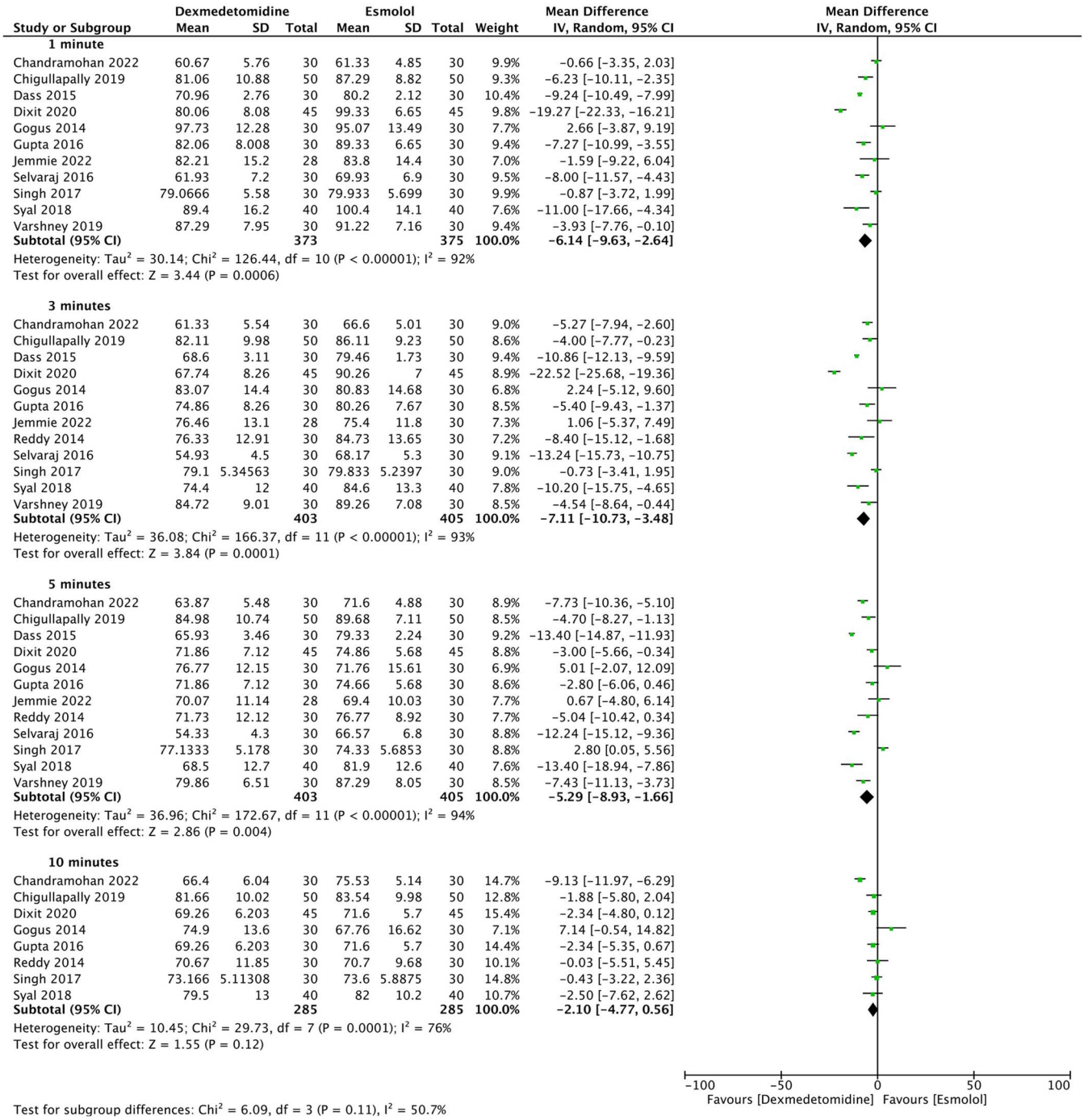


Figure 4. Forest Plot for Systolic Blood Pressure Response to Laryngoscopy and Tracheal Intubation Using Dexmedetomidine Compared With Esmolol



Propofol Induction. Dexmedetomidine attenuated the rise in SBP more effectively than esmolol at 1, 3, and 5 minutes but not at 10 minutes following TI with propofol used for induction with MDs ranging from −15.97 to −11.75 mm Hg (95% CI, −30.32 to −1.62; $P \leq .03$; Supplemental Figure S13). Similarly, dexmedetomidine attenuated the rise in MAP more effectively than esmolol at 1, 3, 5, and 10 minutes following TI with propofol used for induction with MDs ranging from −7.74 to −5.76 mm Hg (95% CI, −11.32 to −3.51; $P < .001$; Supplemental Figure S14). Forest plots are available in Supplemental Figures (available online only).

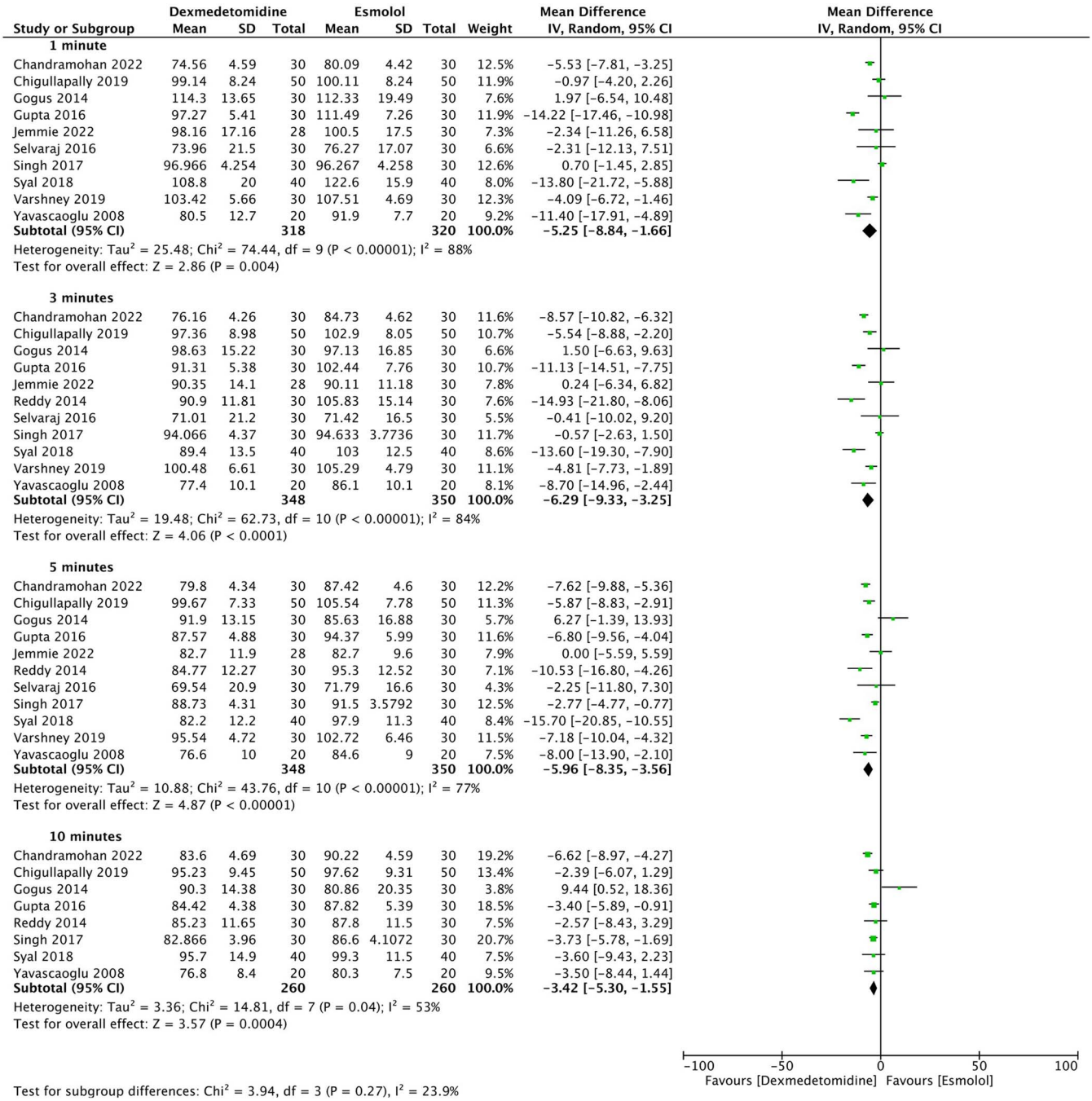
Figure 5. Forest Plot for Diastolic Blood Pressure Response to Laryngoscopy and Tracheal Intubation Using Dexmedetomidine Compared With Esmolol



Secondary Outcome

Twelve studies[44–46,48–56] reported adverse events. Patients receiving dexmedetomidine were at greater risk of bradycardia (5 dexmedetomidine cases[44,46,53] vs no esmolol cases), where bradycardia was defined as a HR less than 50 bpm.[43,51,56] In the 12 studies, hypotension was defined as a 20% decrease in SBP from baseline,[43,51] a 20% decrease in MAP from baseline, or a SBP less than 90 mm Hg.[56] One case of hypotension was identified after dexmedetomidine administration,[49] and 3 cases of hypotension were identified after esmolol administration.[49] No tachyarrhythmia or hypertensive events were reported.

Figure 6. Forest Plot for Mean Arterial Pressure Response to Laryngoscopy and Tracheal Intubation Using Dexmedetomidine Compared With Esmolol



DISCUSSION

Our systematic review and meta-analysis included 19 and 15 RCTs, respectively. These trials were published between 2008 and 2022. Our study identified statistically significant differences comparing the administration of dexmedetomidine vs esmolol on hemodynamic stability up to 10 minutes after tracheal intubation (TI) during non-RSI in adult patients undergoing noncardiac surgery. Examination of the reported mean differences may not infer clinical significance unless a patient is at a critical threshold where drug choice may be impactful.

Physiologically, airway manipulation by direct laryngoscopy and TI activates proprioceptors sensitive to tissue

irritation in the supraglottic region and trachea.[58] Hypertension and tachycardia is mediated by cardioaccelerator nerves and sympathetic chain ganglia, leading to the release of norepinephrine from adrenergic nerve terminals and the secretion of epinephrine from the adrenal medulla.[59] TI not only activates the autonomic nervous system but also stimulates the central nervous system, resulting in increased electroencephalographic (EEG) activity.[60]

Dexmedetomidine is proposed to achieve hemodynamic stability through the activation of peripheral presynaptic and postsynaptic α2 receptors, consequently reducing norepinephrine release.[23] Activation of central nervous system α2 receptors induces sedation, decreases anesthetic requirements, lowers sympathetic outflow, and enhances cardiovagal activity.[22] Furthermore, α2 receptors in the spinal cord modulate pain pathways, providing an analgesic effect.[22] Although the precise physiologic factors responsible for the potential superiority of dexmedetomidine over esmolol in mitigating the hemodynamic response to TI are not fully understood, its effectiveness can be potentially attributed to its peripheral, central, and analgesic effects.

In our systematic review, we observed a consistent dosing regimen of 0.5 to 1 μg/kg for dexmedetomidine across all the trials included. Most trials adopted a single 10-minute infusion of dexmedetomidine prior to preoxygenation, induction, laryngoscopy, or intubation. This dosing aligns with previous trials. For example, Scheinin et al[61] were first in examining the effects of a 0.6 μg/kg bolus of dexmedetomidine administered over 1 minute on the hemodynamic response to TI. The authors concluded that the administration of dexmedetomidine effectively mitigated the hemodynamic responses to TI.[61] Since then, numerous studies have employed different regimens. A systematic review conducted by De Cassai et al[25] examined 99 trials and determined that the most prevalent and efficacious regimen for attenuating the hemodynamic response to TI, as compared to a placebo, involved dexmedetomidine infusions ranging from 0.5 to 1 μg/kg administered for 10 minutes. In line with these findings, our systematic review included trials that uniformly employed comparable dosing for the dexmedetomidine group, indicating that none of the studies in our analysis administered an insufficient dose to the experimental group.

In contrast, the administration of esmolol varied considerably among the trials included in our systematic review. The average dose of esmolol ranged from 0.3 to 2 mg/kg, with 1 trial using an empirical dose of 100 mg.[55] Furthermore, there were variable timing and administration strategies. In 12 trials, esmolol was administered as a bolus either immediately before or 2 minutes prior to preoxygenation, induction, laryngoscopy, or intubation.[39,41–46,50,54–57] According to the product monograph, esmolol should be administered at a dose of 1.5 mg/kg (up to a maximum of 100 mg) as a bolus injection over 30 seconds, 1 to 2 minutes before TI to prevent postintubation tachycardia and hypertension.[17] In the remaining trials, a 10-minute infusion of esmolol was employed.[40,47–49,51–53] The monograph specifies that steady state is reached in 5 minutes with an infusion of 0.05 to 0.3 mg/kg/min or a dose of 0.5 mg/kg delivered over 1 minute.[17] In a Canadian multicenter trial, Miller et al[16] confirmed the effectiveness of a single 100 mg bolus dose of esmolol for controlling the hemodynamic response to TI.

In our systematic review, several studies chose to administer a dose of esmolol below 1.5 mg/kg or opted for a 10-minute infusion, likely to mimic the recommended dexmedetomidine regimen and to blind the providers, thereby minimizing bias but at the possible detriment to esmolol's effectiveness. For this reason, we conducted a preplanned subgroup analysis to assess if the dosing variation introduced bias towards the dexmedetomidine group. To investigate the impact of dosing, we excluded studies in which patients received less than 1.5 mg/kg of esmolol and reanalyzed the primary outcome of HR and BP at 1, 3, 5, and 10 minutes after TI. The subgroup analysis suggested that there may be no clinically significant difference in systolic, diastolic, and mean arterial blood pressure when esmolol is administered at doses exceeding 1.5 mg/kg. This subgroup analysis indicated that dexmedetomidine was superior to esmolol for HR control.

It is important to note that tachycardia has a detrimental effect on the heart by decreasing coronary flow time and increasing myocardial oxygen consumption.[62] Consequently, HR is regarded as the most significant factor influencing myocardial oxygen demand.[62] Based on this understanding, we consider a 0.5 to 1 μg/kg infusion of dexmedetomidine administered for 10 minutes to be superior to a 1.5 mg/kg dose of esmolol in lessening the hemodynamic response to TI. Nonetheless, compared to dexmedetomidine, esmolol possesses a faster onset of action and a shorter duration of effect.[17,18] These pharmacokinetic qualities may translate to a desired safety profile and make esmolol more practical for the busy operating room environment.

Our systematic review has several strengths. We applied a broad search strategy and clear inclusion criteria reducing selection bias. Two reviewers independently (AS and SK) reviewed the articles and assessed the risk of bias. In both cases, differences of opinion were resolved in consultation with another author (MW). Another strength of this meta-analysis is the large sample size of 948 patients. Furthermore, we addressed important insights from a study by Stoelting et al,[63] which established that the hemodynamic response to laryngoscopy and TI reaches its peak within the first minute after intubation and typically persists for a duration of 5 to 10 minutes. To address this time-dependent dynamic, we systematically extracted data at multiple times (1, 3, 5, and 10 minutes) following TI. This approach allowed for a more comprehensive understanding of the hemodynamic response during the postintubation period.

The main limitation of this meta-analysis was the presence of significant heterogeneity. Variables that may alter the hemodynamic response to TI in this study included the following: use and type of intraoperative opioid, type of volatile anesthetic agent used, type of intravenous induction agent, type of laryngoscopy used (eg, direct, or indirect), pretreatment with an anticholinergic, esmolol dosing, data collection, types of surgeries, and patient profiles. To address these potential confounders, we performed several sensitive analyses allowing us to improve the quality and strength of our conclusions. These analyses are discussed below. A subanalysis of hemodynamic instability beyond the 10-minute interval was not performed.

Among the trials included in our systematic review, few opioid regimens were used. Of the 19 trials, 17 opted for an average fentanyl dose of 2 μg/kg during induction. Only 2 trials performed an opioid-free induction,[52,55] and both concluded that dexmedetomidine provided better hemodynamic stability compared to esmolol when used in combination with an opioid-free induction.[52,55] The limited variance in the choice and dosing of opioids suggested that the use or type of opioid was not a significant confounding factor and could not explain the high heterogeneity.

Our sensitivity analyses suggested that the choice of IV induction agent (eg, propofol or thiopentone) did not significantly modify the blood pressure response (SBP and MAP) to TI within 10 minutes. The primary analysis was repeated with studies that only used propofol for induction as this drug is used more commonly in North America and Europe. Dexmedetomidine performed better than esmolol at controlling the blood pressure response to TI with a propofol induction. These results must be interpreted with caution as only 5 studies were included with a sample size varying from 180 to 348 patients for different times (eg, at 1, 3, 5, and 10 minutes) and the CIs were quite large (eg, SBP at 1 minute [−30.32, −1.62]). Furthermore, clinical significance is unclear from this data alone. For further details, refer to Supplemental Figures (available online only).

In our systematic review, 5 of the 19 studies reported using the Macintosh laryngoscope, while the others did not specify the intubation technique.[40,50–52,54] None of the studies required nasal intubation, and most trials mentioned the use of experienced providers for laryngoscopy and intubation. Therefore, we believe that the choice of laryngoscopy method was unlikely to have influenced the results of our study or explained the heterogeneity of the findings.

In current practice, indirect laryngoscopy via video laryngoscopy has gained popularity. The digital camera at the blade tip allows display of the glottis on an external monitor with gentler airway manipulation and stimulation,[64] thus reducing the hemodynamic response observed during TI.[65] However, studies comparing video laryngoscopy with direct laryngoscopy have yielded mixed results. A recent systematic review and meta-analysis by Hoshijima et al[65] concluded that video laryngoscope did not significantly reduce the hemodynamic response to TI compared to the Macintosh laryngoscope.

Our sensitivity analyses suggested that the use of glycopyrrolate did not significantly modify the change in HR. In the context of GA induction, glycopyrrolate is an anticholinergic agent employed to counteract unwanted physiologic side effects like bradycardia. Use of an anticholinergic agent can occasionally lead to tachycardia.[66] Our sensitivity analyses compared the effectiveness dexmedetomidine and esmolol in controlling the chronotropic response to TI both with and without the adjunct use of glycopyrrolate. The results indicated that dexmedetomidine performed better than esmolol in regulating HR, regardless of the presence or absence of glycopyrrolate. For more detailed information and specific data, interested readers are invited to consult Supplemental Figures (available online only).

The exact type of noncardiac surgery the patient underwent was poorly reported in the selected trials. We elected to exclude cardiac surgery from this systematic review to avoid introducing a source of bias because this surgical population is prone to develop arrhythmias with a reported incidence more than 90% vs the 16.3% to 61.7% found in patients undergoing noncardiac surgery.[67] Due to this lack of detailed information, we cannot ascertain whether the type of noncardiac surgery could have contributed to the heterogeneity observed or influenced the outcomes reported in the studies.

The patient population included in our systematic review was limited to Asia and the Middle East as no trials took place in North America or Europe. Specific reasons for this geographical distribution are unknown and may be reflect research priorities, regulatory and ethical considerations, and funding allocations.

Only 4 trials included geriatric patients who were older than 65 years of age.[47,49,54,55] None of the trials conducted subgroup analyses based on age, which hindered our ability to perform a preplanned subgroup analysis based on age. Consequently, it was not possible to determine whether age could have contributed to the observed heterogeneity. Therefore, caution must be exercised when extrapolating the findings to geriatric patients, as the data available for this specific population is limited.

Patients with known or suspected ischemic heart disease are those who would greatly benefit from blunting the hemodynamic response during TI.[9] Patients with severe disease are least likely to be included in prospective RCT groups.[68] This exclusion may occur if they have comorbidities, complications, or other factors (such as drug interactions) that could potentially interfere with study outcomes or introduce additional risks. As previously mentioned, most trials included stable ASA-PS I and II patients undergoing elective noncardiac surgeries. Extrapolating this study's results to patients with cardiac comorbidities must be done carefully. With the current evidence, we could not

determine if a subgroup of unstable patients may benefit from dexmedetomidine vs esmolol. However, 4 trials have included well-controlled hypertensive patients, and all concluded that dexmedetomidine was superior at controlling the hemodynamic response.[39,41,54,55] Amutharani et al[39] found that esmolol failed to protect against the cardiovascular response suggesting that dexmedetomidine may be preferable in that population. We suggest that selected doses be individualized considering clinical contexts.

Additionally, the impact of hemodynamic instability on perioperative outcomes is important even in healthy ASA-PS I and II patients.[69] A secondary analysis of the Vascular Events in Noncardiac Surgery Cohort Evaluation (VISION) study, a prospective international cohort study of noncardiac surgical patients by Abbott et al,[5] suggested that intraoperative tachycardia is related to myocardial injury, myocardial infarction, and mortality in a large population of patients undergoing noncardiac surgery. Also, Hartmann et al[70] concluded in a retrospective study of 28,065 patients that there is an association between intraoperative tachycardia and ICU admission, independent of accompanying disease. For this reason, it is the authors' opinion that anesthesiologists may consider using dexmedetomidine or an effective dose of esmolol to attenuate the hemodynamic response to TI in healthy ASA I and II subjects unless otherwise contraindicated.

The utility of dexmedetomidine in clinical contexts may be significantly influenced by factors, such as drug availability, its higher costs, infusion pump requirement, and longer onset. While there is statistical significance that favors dexmedetomidine vs esmolol, the clinical significance and effectiveness may not align.

The lack of consistent cut-off values across the trials for identifying complications like bradycardia and hypotension limited our ability to draw definitive conclusions on the secondary outcome. The rare report of complications in the studies indicated the safety of the doses used in ASA-PS I and II adult patients undergoing elective noncardiac surgeries. Caution should be exercised when extrapolating these findings to extremes of age, unstable patients, and emergency surgeries. In general, dexmedetomidine was associated with a higher incidence of bradycardic events compared to esmolol, consistent with existing literature.

Finally, 84% of the included trials had a moderate risk of bias, while only 11% had a low risk of bias, leading to a generally low certainty of evidence for the primary outcomes. Nevertheless, we conducted a thorough evaluation of the available evidence's methodological quality and provided readers with insights for interpreting our findings. To draw more robust conclusions, future primary studies of greater rigor are needed. It is crucial for future research to report the incidence of adverse events associated with dexmedetomidine or esmolol use during the induction period, including their potential impact on perioperative morbidity and mortality. This information is necessary to determine the suitability of these agents in attenuating the hemodynamic response to intubation.

CONCLUSION

Patients receiving dexmedetomidine vs esmolol prior to TI had less of a hemodynamic response (ie, lower MAP and HR) up to 10 minutes postinduction according to this meta-analysis; however, the clinical relevance of these findings should be determined on a case-by-case basis. Our subgroup analysis suggested that high-dose dexmedetomidine ($\geq$1 μg/kg) blunted HR increases more vs high-dose esmolol ($\geq$1.5 mg/kg) at 1, 3, 5, and 10 minutes following TI. Moreover, the risks of bradycardia and hypotension present with both agents warrant cautious evaluation of the risk-benefit ratio for each patient during daily practice. Additional validation is necessary to confirm our conclusions due to the unexplained heterogeneity noted in this study.

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