Systematic Review and Meta-Analysis

# Comparison between dexmedetomidine and lidocaine for attenuation of cough response during tracheal extubation: A systematic review and meta-analysis

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**Submitted:** 17-Aug-2023
**Revised:** 05-Mar-2024
**Accepted:** 10-Mar-2024
**Published:** 12-Apr-2024

| Access this article online |
| --- |
| Website: https://journals.lww.com/ijaweb |
| DOI: 10.4103/ija.ija_790_23 |
| Quick response code |

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## ABSTRACT

**Background and Aims:** Tracheal extubation often causes cardiovascular and airway responses, potentially resulting in hazardous consequences. It remains unknown whether dexmedetomidine or lidocaine is more effective for cough suppression. Hence, we conducted a systematic review and meta-analysis of randomised controlled trials to compare the effectiveness and safety of dexmedetomidine and lidocaine in reducing cough response after tracheal extubation in adult patients. **Methods:** A thorough search of electronic databases, including PubMed, Embase, Cochrane Library, and Web of Science, was conducted to identify relevant studies (from inception to 31 January 2023). Randomised controlled trials comparing intravenous (IV) dexmedetomidine versus IV lidocaine administration during emergence from anaesthesia to prevent tracheal extubation response in adult patients under general anaesthesia were included. The primary outcome was the incidence of post-extubation cough. Secondary outcomes included emergence time, extubation time, residual sedation, and incidences of bradycardia. Statistical analysis was conducted using RevMan software. The Cochrane risk of bias tool was used to evaluate the potential risk for bias. **Results:** In total, seven studies with 450 participants were included. There was no statistically significant difference in the incidence of cough between dexmedetomidine and lidocaine groups [Risk Ratio = 0.76; 95% Confidence Interval: 0.46, 1.24]. Emergence and extubation times were not significantly different between the two groups. Meta-analysis revealed a higher incidence of bradycardia and residual sedation in dexmedetomidine compared to the lidocaine group. **Conclusion:** This meta-analysis found no difference in cough, emergence, and extubation time between dexmedetomidine and lidocaine after tracheal extubation. However, residual sedation and bradycardia were more significant in dexmedetomidine than in lidocaine.

**Keywords:** Anaesthesia, dexmedetomidine, emergence, extubation, lidocaine, meta-analysis, randomised controlled trial

## INTRODUCTION

Airway management is routine part of general anaesthesia, and associated with airway and hemodynamic responses like hypertension, tachycardia, dysrhythmias, myocardial ischemia, coughing, bronchospasm, postoperative bleeding, and raised intracranial pressure.[1–4] Studies have been carried out to assess the efficacy of various drugs in suppressing



**How to cite this article:** Purohit A, Kumar M, Kumar N, Bindra A, Pathak S, Yadav A. Comparison between dexmedetomidine and lidocaine for attenuation of cough response during tracheal extubation: A systematic review and meta-analysis. Indian J Anaesth 2024;68:415-25.

tracheal extubation responses.[5–7] Dexmedetomidine is a potent, highly selective alpha-2 adrenoceptor agonist that effectively reduces the airway and circulatory response during emergence from general anaesthesia.[8] Dexmedetomidine has some unique properties, such as sympatholysis, sedation, and analgesia without respiratory depression, for which it is considered an appropriate drug for suppressing the cough response at the time of tracheal extubation. In addition, lidocaine can be used in various forms, such as intravenous (IV), intratracheal, endotracheal cuff inflation, and aerosolised to suppress extubation response during emergence from anaesthesia. In a systematic review and meta-analysis by Sun *et al*.[9] evaluating the efficacy and safety of IV lidocaine to prevent opioid-induced cough (OIC) during tracheal intubation, they found that the lowest effective dose of IV lidocaine was 0.5mg/kg. Another meta-analysis found that IV lidocaine may prevent tracheal intubation, extubation response, and OIC in a dose-dependent manner in both adults and children.[6] Recently, a systematic review and meta-analysis conducted by Fan *et al*.[10] comparing IV dexmedetomidine and remifentanil showed no difference in the incidence of moderate and severe cough during extubation. Although both drugs were reported to be effective, the difference between IV dexmedetomidine and lidocaine in attenuating cough response during emergence from anaesthesia remains unclear.

Therefore, we conducted a systematic review and meta-analysis of randomised controlled trials (RCTs) to compare the efficacy and safety of IV dexmedetomidine and lidocaine in adult patients on the attenuation of cough response following tracheal extubation during emergence from general anaesthesia.

## METHODS

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42023392464).

### Eligibility criteria

**Inclusion criteria:** Studies comparing IV dexmedetomidine versus IV lidocaine administration during emergence from anaesthesia to prevent tracheal extubation response in adult patients under general anaesthesia without any regional anaesthesia, studies containing data on incidence and grading of cough during emergence, only RCTs, published in the English were included. The studies were selected as per the PICOT (Population, Intervention, Control, Outcome, and Time) format presented in in Table 2.

**Exclusion criteria:** Non-RCTs (retrospective studies, case reports, systematic review, and meta-analysis and protocols), paediatric patients (<18 years of age), placebo control, and cases wherein dexmedetomidine and/or lidocaine was administered at the beginning of the surgery and not at the end of the surgery were excluded.

**Information sources:** A comprehensive search from PubMed, Embase, Cochrane Library, and Web of Science electronic databases was done from inception to 31 January 2023.

**Search strategy:** The electronic search combined terms related to dexmedetomidine, lignocaine, lidocaine, extubation, cough response, airway response, and anaesthesia. In addition, a reference list of all included RCTs was reviewed for potential publications. The detailed search strategy for each database is presented in Supplementary File S-2.

**Study selection:** Two authors (AP and MK) independently searched the databases and performed study selection. Finally, studies fulfilling the inclusion criteria were included after screening full-text articles. Any disagreements between the two authors in the study selection process were resolved with the opinion of the third author (NK).

**Data extraction:** Two authors (AP and MK) independently extracted data from the included studies using a pre-defined standardised data collection form. Any disagreements were settled by a third author (NK).

**Data items:** Data extracted using the standardised form included the first author name, year of publication, country of origin, age of the patient, weight, gender, number of patients, American Society of Anesthesiologists (ASA) physical status classification, type of surgery, dose of dexmedetomidine/lidocaine, route of administration, timing of administration, incidence/or grade of cough of cough, emergence time, extubation time, hemodynamic changes [mean arterial pressure and heart rate (HR)], incidences of residual sedation, and incidences of bradycardia.

The primary outcome was the incidence of post-extubation cough. The post-extubation period

was defined as the time of extubation to 30 minutes after the endotracheal tube removal. Coughing severity was classified using the 3-point scale described by Minogue *et al*.[12]: 1 = mild, single cough, 2 = moderate (lasting for <5 seconds) cough, and severe (lasting for >5 seconds) cough. Secondary outcomes included emergence time, extubation time, residual sedation, and incidences of bradycardia (HR < 60 bpm). The time for emergence was the time between discontinuing anaesthetics and eye-opening (spontaneously or on verbal prompting repeated every 2 minutes). The time for extubation was measured as the time between discontinuation of anaesthetics and tracheal extubation. These outcomes were assessed during the first 30 minutes after the extubation.

**Risk of bias assessment:** The risk of bias of the included RCTs was assessed using Cochrane risk of bias tool 2 (Cochrane Collaboration).[13] Two independent authors (AP and MK) separately evaluated the methodological quality of all RCTs. Any discrepancies regarding quality assessment were resolved through discussion with the third author (NK). RCTs were assigned as low, high, or unclear risk of bias for each bias domain. We evaluated the studies according to the following points: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants (performance bias), blinded outcome assessment (detection bias), incomplete data reporting (attrition bias), selective reporting (reporting bias), and other potential sources of bias.

**Statistical analysis:** For continuous variables, mean and standard deviation (SD) were extracted for each group to obtain mean difference (MD) with a 95% confidence interval (CI) as a pooled result. Dichotomous outcomes were expressed as a pooled risk ratio (RR) with a 95% CI. The statistical analysis was performed using RevMan software (version 5.4, Copenhagen, Denmark, the Nordic Cochrane Centre, and the Cochrane Collaboration). A random effect model was used for the pooled analysis of the primary endpoint. Heterogeneity within the trials was evaluated using the Chi-square test and $I^2$ statistics. Substantial heterogeneity was defined as $I^2 \geq 50\%$.[14] A $P$ value of <0.05 was considered statistically significant. Publication bias was assessed using a funnel plot and Egger test.[15] The Grading of Recommendation, Assessment, Development, And Evaluation (GRADE) system was adopted to assess the overall quality of evidence for each outcome. The system classified the evidence into very low, low, moderate, and high quality of evidence according to the following five categories: the risk of bias, inconsistency, indirectness, imprecision, and publication bias.[16] The included trials' methodological quality was assessed using the modified Jadad score scale. The modified Jadad score ranges from 0 to 8. A score less than or equal to 3 was considered low quality, and a score greater than or equal to 4 was referred to as high-quality studies.[17] Meta-regression analysis was performed based on lidocaine doses, dexmedetomidine doses, route of administration, administration time, and types of surgery.

## RESULTS

### Study selection

A PRISMA flow diagram summarises the database search and inclusion of studies [Figure 1]. Finally, seven studies fulfilled the inclusion criteria and were included for systematic review and meta-analysis.[18–24]

### Study characteristics

The study characteristics of the included studies are summarised in Table 1. The selection of these studies were as per predefined 'PICOT' [Table 2]. Seven RCTs[18–24] consisting of 450 participants were included; 225 participants were allocated to the dexmedetomidine group, and 225 were allocated to the lidocaine group. Most of the included studies had a low risk of bias as per the risk-of-bias assessment [Figure 2].

The route of administration of drugs was IV in all the included studies. Three out of the seven included studies gave the drugs as boluses, while one study administered the drug as a bolus followed by infusion. The dose used for dexmedetomidine in the included studies was 0.5 μg/kg for all included studies except one study by Moustafa *et al*.,[21] where a dose of 0.1 μg/kg was used. The dose of lignocaine used was 1.5 mg/kg in all studies except one study by Moustafa *et al*., where 1 mg/kg was used.

**Primary outcome:** Six studies[18–23] out of seven reported cough incidence. A random effect model was used, and significant heterogeneity was observed ($I^2$ = 65%). The meta-analysis revealed no significant difference between the dexmedetomidine and lidocaine groups (RR = 0.76; 95% CI: 0.46, 1.24; $P$ = 0.27; Figure 3a).

**Secondary outcome:** Three studies[19,20,24] out of seven reported emergence time. A fixed effect model

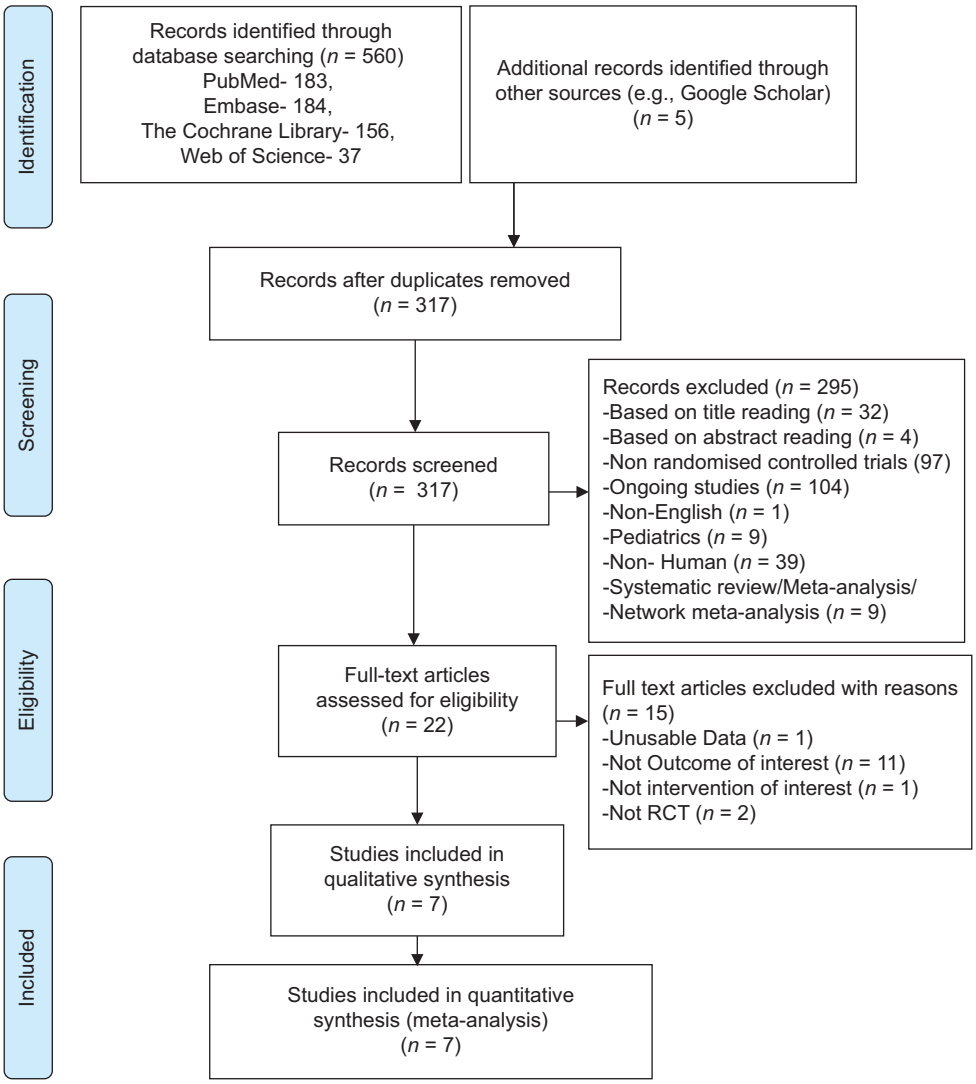


**Figure 1:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart. RCT=randomised controlled trial

was used, and no significant heterogeneity was observed ($I^2$ = 21%). The meta-analysis revealed no significant difference between the dexmedetomidine and lidocaine groups (MD = 0.12; 95% CI: -0.22, 0.45; $P$ = 0.49; Figure 3b).

Three studies[19,20,24] out of seven studies reported extubation time. A fixed effect model was used, and no significant heterogeneity was observed ($I^2$ = 0%). The meta-analysis revealed no significant difference between the dexmedetomidine and lidocaine groups (MD = 0.29; 95% CI: -0.05, 0.62; $P$ = 0.09; Figure 3c).

Three studies[19,20,22] out of seven studies reported an incidence of bradycardia. A fixed effect model was used, and no significant heterogeneity was observed ($I^2$ = 27%). The meta-analysis revealed a higher incidence of bradycardia in dexmedetomidine compared to the lidocaine group (RR = 10.25; 95% CI: 2.39, 43.97; $P$ = 0.002; Figure 3d).

Two studies[18,20] out of seven reported residual sedation incidence. A fixed effect model was used, and no significant heterogeneity was observed ($I^2$ = 0%). The meta-analysis revealed a higher incidence of residual sedation in dexmedetomidine compared to the lidocaine group (RR = 30.45; 95% CI: 4.31, 215.13; $P < 0.001$; Figure 3e).

**Sub-group analysis:** Our sub-group analysis revealed no difference between the two drugs based on the technique of drug administration, timing of drug administration, or type of surgery. The drugs were administered either as a bolus or infusion or as bolus and infusion. On comparing the various timings of drug administration, no significant difference was observed; the overall heterogeneity

**Table 1: Characteristics of included Randomised Controlled Trials**

| Author | Year | Country | ASA Physical status | Surgery | Study medication | Patients (*n*) | Sex M/F (*n*) | Age (years) | Weight (kg) | Dose | Route of administration | Administration Time |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kothari D[18] | 2014 | India | I-II | Craniotomies | Dexmedetomidine | 25 | 13/12 | 36 (12.09) | 56 (8.31) | 0.5μg/kg/kg | intravenous | 5 min before extubation over a period of 60s |
| | | | | | Lignocaine | 25 | 14/11 | 35 (13.25) | 55.8 (8.19) | 1.5 mg/kg | intravenous | 5 min before extubation over a period of 60s |
| Sharma V[19] | 2014 | India | I-III | Spinal Surgery | Dexmedetomidine | 20 | 15/5 | 39.1 (9.4) | 66.1 (15.5) | 0.5μg/kg | bolus | over 60s |
| | | | | | Lignocaine | 20 | 10/10 | 42.7 (13.7) | 63.9 (14) | 1.5 mg/kg | bolus | over 60s |
| Gosai ND[20] | 2015 | India | I-II | Intracranial Surgery | Dexmedetomidine | 25 | 16/9 | 39.1 (13.1) | 55.96 (11) | 0.5μg/kg | intravenous | over 60s |
| | | | | | Lignocaine | 25 | 11/14 | 40.5 (12.24) | 54.92 (1 1.9) | 1.5 mg/kg | intravenous | over 60s |
| Moustafa AM[21] | 2015 | Egypt | I-III | Orthopaedic procedure | Dexmedetomidine | 20 | 10/10 | 49 (16) | 74 (12) | 0.1μg/kg | intravenous | 5 min before tracheal extubation |
| | | | | | Lignocaine | 20 | 8/12 | 52 (14) | 80 (7) | 1.0 mg/kg | intravenous | 5 minutes before tracheal extubation |
| Hu S[22] | 2019 | China | I-II | Thyroid Surgery | Dexmedetomidine | 60 | 23/37 | 47.6 (7.8) | 57.6 (5.7) | 0.5μg/kg/h loading, 0.4μg/kg/h infusion | intravenous bolus + infusion | Over 10 min before induction of anaesthesia, followed by a continuous intravenous infusion of dexmedetomidine 0.4 μg/kg made up to 20 ml and 20 ml normal saline every hour until 30 min before the end of the surgery, respectively |
| | | | | | Lignocaine | 60 | 23/35 | 48.4 (8.8) | 58.8 (6.9) | 1.5 mg/kg loading, 1.5 mg/kg/h infusion | intravenous bolus + infusion | Over 10 min before induction of anaesthesia, followed by a continuous intravenous infusion of lidocaine 1.5 mg/kg made up to 20 ml and 20 ml normal saline every hour until 30 min before the end of the surgery, respectively |
| Pradhan A[23] | 2021 | India | I-II | Laparoscopic Surgery | Dexmedetomidine | 50 | | | | 0.5 μg/kg | bolus | 60s prior to extubation |
| | | | | | Lignocaine | 50 | | | | 1.5 mg/kg | bolus | 60s prior to extubation |
| Safneedha[24] | 2021 | India | I-II | Craniotomies | Dexmedetomidine | 25 | 14/11 | 40.64 (15.81) | 59.72 (11.6) | 0.5 μg/kg | bolus | 10 min during skin closure |
| | | | | | Lignocaine | 25 | 12/13 | 42.64 (12.49) | 62.52 (5.93) | 1.5mg/kg | bolus | 60s prior to extubation |

*Contd...*

**Table 1: Contd...**

| Cough Grade | | | | | Heart rate (bpm) | Mean Arterial pressure (mmHg) | Extubation time (mins) | Emergence time (mins) | Residual sedation/Sedation score | | | | | Bradycardia | Jadad Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (0) No cough | (1) slight cough | (2) Moderate coughing | (3) Severe coughing | Poor extubation | | | | | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Grade 6 | |
| 25 | 0 | 0 | 0 | 0 | 81.8 (9) | | | | 0 | 7 | 18 | 0 | 0 | 0 | 5 |
| 20 | 5 | 0 | 0 | 0 | 87.63 (8.36) | | | | 20 | 7 | 18 | 0 | 0 | 0 | |
| 16 | 4 | 0 | 0 | 0 | | | 9.2 (4) | 7.7 (3.8) | | | | | | 1 | 8 |
| 13 | 7 | 0 | 0 | 0 | | | 7.9 (1.9) | 6.5 (1.9) | | | | | | 0 | |
| 15 | 9 | 1 | 0 | 0 | 76.26 (14.88) | 97.04 (11.53) | 10.1 (1.4) | 8.7 (2.6) | | | 11 | | | 6 | 5 |
| 9 | 13 | 3 | 0 | 0 | 87 (10.57) | 114 (17.25) | 9.3 (2.1) | 7.3 (7.2) | | 14 | | | | 1 | |
| 2 | 4 | 9 | 3 | 2 | | | | | | | | | | | 6 |
| 7 | 8 | 4 | 1 | 0 | | | | | | | | | | | |
| 41 | 11 | 5 | 3 | 0 | 79.4 (8.1) | 88.2 (14.5) | | | | | | | | 35 | 7 |
| 43 | 9 | 6 | 2 | 0 | 80.7 (12.4) | 84.8 (14.4) | | | | | | | | 0 | |
| 45 | 5 | 0 | 0 | 0 | 91.94 (11.81) | 103.86 (10.99) | | | | | | | | 0 | 6 |
| 36 | 15 | 0 | 0 | 0 | 103.68 (12.70) | 107.62 (8.96) | | | | | | | | 0 | |
| | | 1.88 (0.66) | | | 94.36 (12.19) | 97.88 (4.634) | 14.84 (5.44) | 19.52 (5.29) | | | 3.08 (0.86) | | | | 5 |
| | | 2.60 (0.577) | | | 110.46 (14.91) | 115.32 (4.63) | 14.60 (4.97) | 20.72 (4.62) | | | 4.72 (0.79) | | | | |

Data summarised as mean (standard deviation) or numbers




**Figure 2:** Assessment of the risk of bias via the Cochrane RoB 2 tool displayed by means of a traffic light plot of each included clinical study (a), and weighted plot for the distribution of the overall risk of bias within each bias domain via the Cochrane RoB 2 tool (b)

was 30.8% ($P = 0.204$). Similar results were obtained from sub-group analysis based on different types of surgeries, such as craniotomy, spinal surgery, orthopaedic surgeries, and laparoscopic surgery analysis (Supplementary File S-3).

**Publication bias**: Assessment of publication bias using the Begg test revealed no potential publication bias amongst the included trials (Begg test; $P = 0.188$; Figure 4).

Summary of findings (GRADE): The certainty of evidence (CoE) for the incidence of cough was deemed low. The CoE for emergence time was moderate. The CoE for extubation time was moderate. The CoE of bradycardia was low. The CoE for residual sedation was low (Supplementary File S-4).

Modified Jadad score: The quality of the seven included studies[18–24] was evaluated using a modified Jadad score, and all included studies were found to be of high quality (Jadad score >4) (Supplementary File S-5).

**Meta-regression analysis**: To comprehensively investigate the sources of heterogeneity within our meta-analysis, we undertook a meta-regression

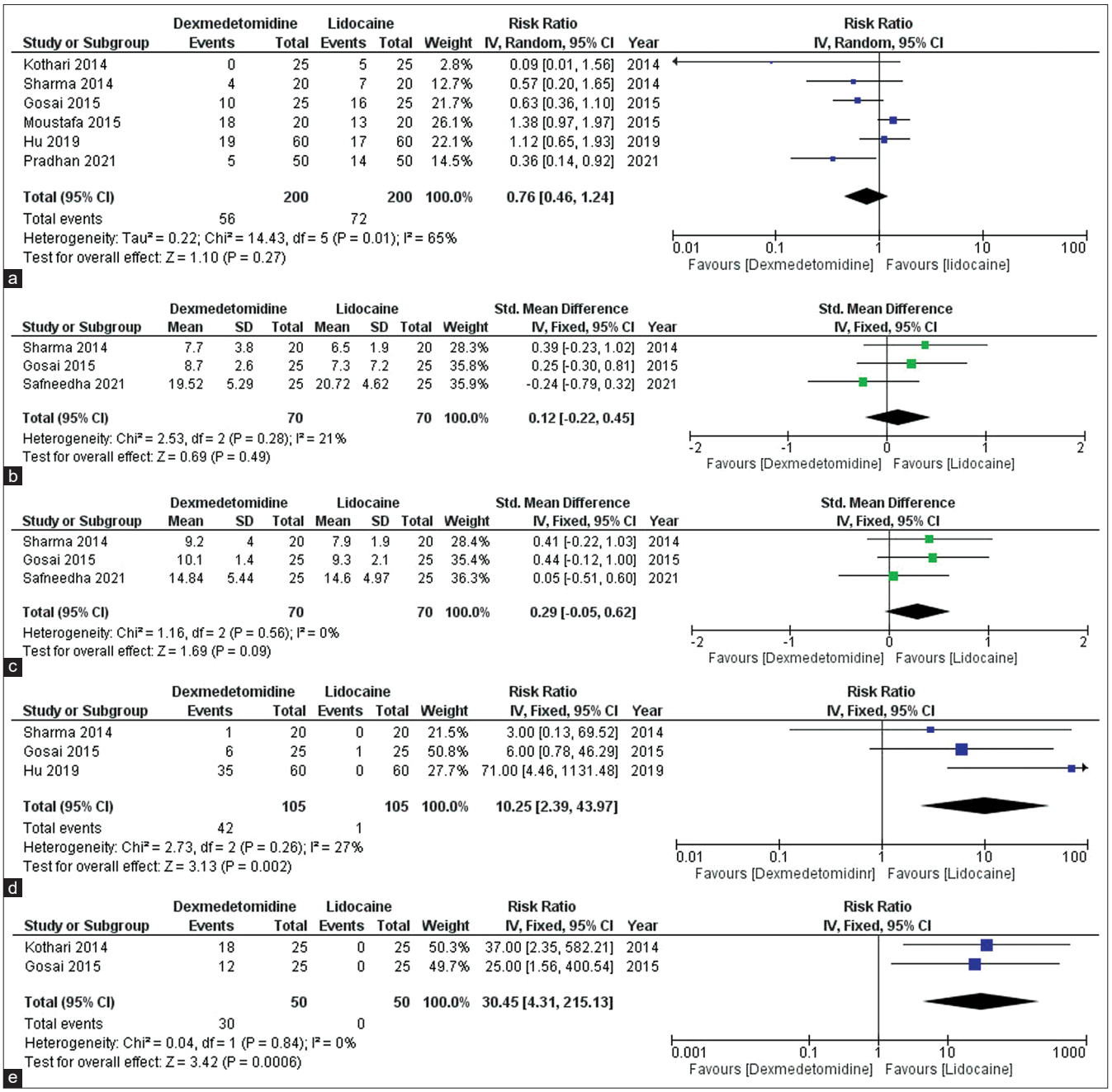


**Figure 3:** Forest plots (a) incidence of cough, (b) emergence time, (c) extubation time, (d) bradycardia, (e) residual sedation. IV = Inverse Variance, CI = Confidence Interval

analysis, examining key factors, including the type of injection, dose variations, timing, and type of surgery. We intended to discern any potential associations among these variables that could contribute to the observed heterogeneity. However, upon analysis **[**Table 3**]**, no statistically significant associations were identified ($P > 0.05$).

**Trial sequential analysis:** Trial sequential analysis (TSA) was performed to ascertain the requisite sample size. Subsequently, we generated TSA monitoring boundaries by using STATA (StataCorp. 2023; Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC) and R software (v4.1.2; R Core Team (2021); R Foundation for Statistical Computing, Vienna, Australia). The TSA results are visually represented in Figure 5. The included studies with a sample size of 400 had only 21% power to accept the findings. This observation implies that our conclusions lack robustness without sufficient evidence. Consequently, it is imperative to conduct additional studies to garner conclusive evidence.

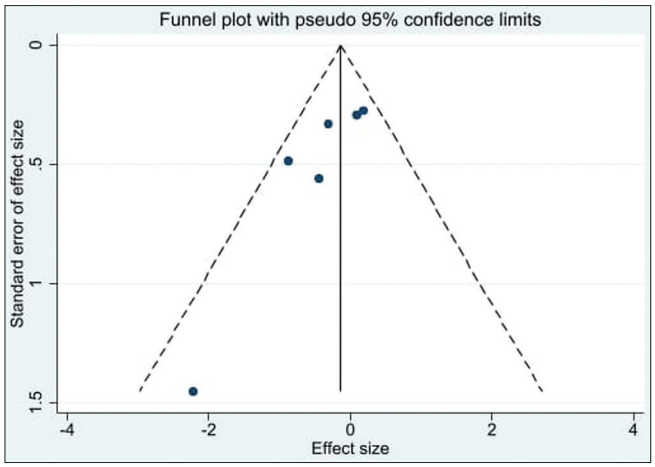


**Figure 4:** Funnel plot for assessment of publication bias in incidence of cough

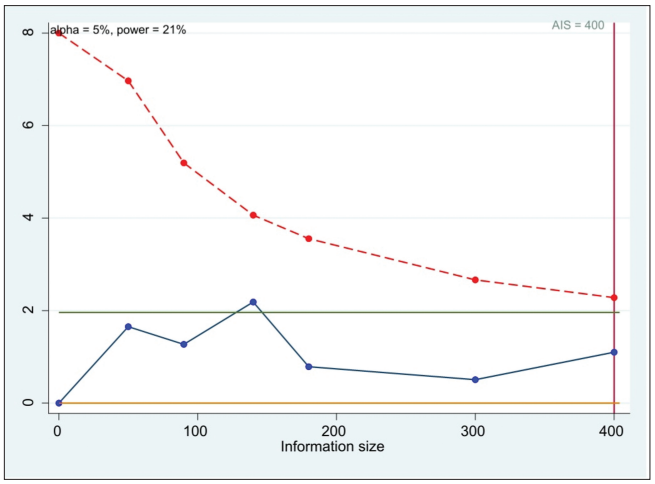


**Figure 5:** Trial sequential analysis

## DISCUSSION

This meta-analysis demonstrated no difference between dexmedetomidine and lidocaine in the incidence of cough, emergence time, and extubation time. In addition, the incidence of sedation and bradycardia was higher in the dexmedetomidine group compared to the lidocaine group.

The exact mechanism of cough is unknown, but the proposed mechanism is the excitation of sensory C-fibres and secondary neuroplasticity.[25] The mechanism for cough suppression with lidocaine is yet to be completely understood. Still, various mechanisms to explain the cough suppression by lidocaine include desensitising peripheral cough receptor suppression of sensory C-fibre and reduction of release in neuropeptides.[25–27] The cough suppression effect of lidocaine may last till the end of the short surgical procedure because the half time ($t_{1/2}$) of lidocaine is approximately 2 hours.[28,29] Lidocaine is an amide local anaesthetic and can potentially suppress cough (incidence and severity) response during emergence from anaesthesia. Lam *et al*.[30] included 19 trials and 1566 patients. They showed that intracuff lidocaine significantly decreased postoperative sore throat and coughing compared to the control group in patients receiving endotracheal intubation for general anaesthesia. Tung *et al*.[31] also showed that intracuff and topical lidocaine significantly reduced moderate-to-severe emergence cough compared to placebo or no medication. A few studies reported that the return of consciousness was delayed in the lidocaine group compared to the control group.[32,33] No adverse effects have been reported within the recommended IV dose of 1–2 mg/kg of lidocaine.[34] Dexmedetomidine reduces anaesthetic requirements, induces analgesia, improves sleep quality postoperatively, and has anti-inflammatory properties.[35,36] In a meta-analysis of nine RCTs, Miao *et al*.[37] found that dexmedetomidine enhances the quality of recovery and decreases postoperative nausea and vomiting without increasing adverse events in the early postoperative period. Wang *et al*.[38] investigated the optimal dose of dexmedetomidine for cough prophylaxis. They found that 0.5 and 0.6 μg/kg infusion rates effectively mitigate emergency cough and sleep disturbances with a slight delay in extubation compared to the saline control group in patients scheduled for endovascular interventional procedures. In a cohort study, Duan *et al*.[39] found that

**Table 2: PICOT table**

| Criteria | Determinants |
|---|---|
| Population | Adult patients underwent elective surgery and extubation under general anaesthesia |
| Intervention | Dexmedetomidine |
| Control | Lidocaine |
| Outcome | Primary - Incidence of cough<br>Secondary - Emergence time, extubation time, residual sedation, and incidences of bradycardia (HR <60 bpm) |
| Time | During tracheal extubation |

PICOT: P=Patient, I= Intervention, C= Control, O= Outcome, T=Time, HR= Heart rate, bpm= beats per minute

**Table 3: Meta-regression analysis for comparison between dexmedetomidine and lidocaine for attenuation of cough response during tracheal extubation**

| Variables | β coefficient | Standard error | *P* |
|---|---|---|---|
| Lidocaine doses | −5.44 | 2.92 | 0.06 |
| Dexmedetomidine doses | 1.36 | 1.52 | 0.37 |
| Route of administration | 2.51 | 1.47 | 0.08 |
| Administration time | 1.91 | 1.47 | 0.19 |
| Types of surgery | 5.77 | 2.95 | 0.05 |

intraoperative dexmedetomidine use can significantly decrease the incidence of sleep disturbance in a patient undergoing non-cardiac surgery as compared to the control group. It is used as an adjuvant to anaesthetic drugs for various surgical procedures.[40] Yang *et al*.[41] conducted a meta-analysis to evaluate the effect of dexmedetomidine on emergence agitation and found that dexmedetomidine significantly reduced the incidence of emergence excitation; however, emergence time and extubation time were prolonged as compared to those in the saline group. Residual sedation is a possible adverse effect of dexmedetomidine. Kim *et al*.[42] demonstrated that alertness level was lowered in the dexmedetomidine group compared to the control group. On the contrary, Aouad *et al*.[35], in another study, showed that sedation levels were similar between dexmedetomidine and the control group. As the reporting of adverse effects and hemodynamic parameters was not adequately mentioned in the studies, examining these parameters was difficult. Dexmedetomidine inhibits the sympathetic nervous system (SNS) and is effective in blunting hypertension and tachycardia during extubation.[43,44]Aouad *et al*.,[35] in a dose-finding study, showed that 1 μg/kg of dexmedetomidine provides the best quality of emergence and prevents cough and agitation but with dose-dependent hypotension versus the control group in a patient undergoing elective surgeries under general anaesthesia. In a Cochrane review by Jessen Lundorf *et al*.[45] (7 RCTs with 492 patients), it has been found that dexmedetomidine increases the risk of hypotensive episodes in patients undergoing abdominal surgery. Demiri *et al*.[46] included 56 studies with 4868 patients that also showed that dexmedetomidine increases the risk of hypotension and bradycardia.

The major strength of our meta-analysis was that the PRISMA guideline was followed, and the GRADE system was used to evaluate the quality of evidence. This meta-analysis also has some limitations. Firstly, the number of included RCTs was limited, and the included studies had relatively small sample sizes. Secondly, reporting of adverse effects was not appropriate for the included studies. Another limitation is the clinical heterogeneity related to medication doses of dexmedetomidine and lidocaine. The heterogeneity may alter the observed effect using sub-therapeutic or dose-dependent doses in the included studies. In our meta-analysis, medication was studied in low-risk patients and not high-risk populations. Another limitation is intra-observer variability because of the subjective nature of the assessment of cough and its severity.

## CONCLUSION

This meta-analysis demonstrated that dexmedetomidine and lidocaine had no difference in the incidence of cough, emergence, and extubation time following tracheal extubation. However, the incidence of residual sedation and bradycardia was higher in the dexmedetomidine than in the lidocaine group. Thus, given the lack of studies comparing dexmedetomidine and lidocaine for attenuation of cough response, high-quality RCTs are needed in the future to confirm the results of this meta-analysis.

### Acknowledgments

We would like to acknowledge Rohit Bhardwaj and Department of Neuroanaethesiology and Critical Care, AIIMS, New Delhi.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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## SUPPLEMENTARY FILES FOR ONLINE

### PubMed search history

| Supplementary File S-2: Search History | | | | | |
|---|---|---|---|---|---|
| Search Number | Query | Sort By | Filters | Search Details | Results |
| 1 | ((dexmedetomidine [MeSH Terms])) AND (lignocaine OR lidocaine [MeSH Terms]) OR dexmedetomidine, lignocaine, lidocaine, extubation | | | (“dexmedetomidine”[MeSH Terms] AND (“lidocain”[All Fields] OR “lidocaine”[MeSH Terms] OR “lidocaine”[All Fields] OR “lignocaine”[All Fields] OR “lidocaine s”[All Fields] OR “lignocain”[All Fields] OR “lidocaine”[MeSH Terms])) OR ((“dexmedetomidine”[MeSH Terms] OR “dexmedetomidine”[All Fields] OR “dexmedetomidine s”[All Fields]) AND (“lidocain”[All Fields] OR “lidocaine”[MeSH Terms] OR “lidocaine”[All Fields] OR “lignocaine”[All Fields] OR “lidocaine s”[All Fields] OR “lignocain”[All Fields]) AND (“lidocain”[All Fields] OR “lidocaine”[MeSH Terms] OR “lidocaine”[All Fields] OR “lignocaine”[All Fields] OR “lidocaine s”[All Fields] OR “lignocain”[All Fields]) AND (“airway extubation”[MeSH Terms] OR (“airway”[All Fields] AND “extubation”[All Fields]) OR “airway extubation”[All Fields] OR “extubated”[All Fields] OR “extubation”[All Fields] OR “extubations”[All Fields] OR “extubate”[All Fields] OR “extubating”[All Fields])) | 183 |

### Embase search history

Embase

Session Results

.....

No. Query Results Results Date

#1. (‘dexmedetomidine’/exp OR dexmedetomidine) AND (‘lignocaine’/exp OR lignocaine OR ‘lidocaine’/exp OR lidocaine) AND (‘extubation’/exp OR extubation) 184 30 Jan 2023

### Cochrane Search History

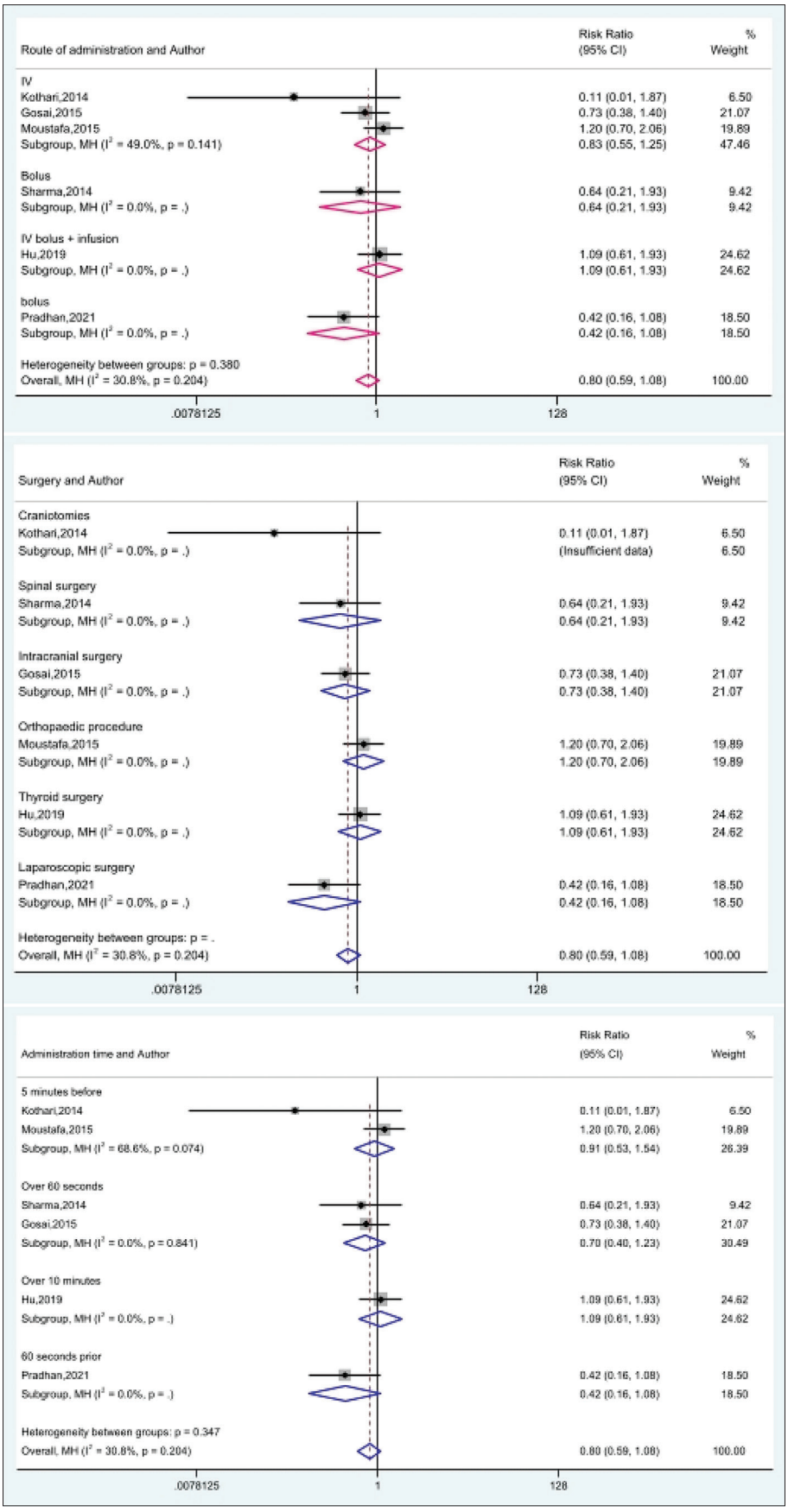
Search Name:

Date Run: 30/01/2023 07:42:18

Comment:

| ID | Search | Hits |
|---|---|---|
| #1 | MeSH descriptor: [Dexmedetomidine] explode all trees | 2261 |
| #2 | MeSH descriptor: [Lidocaine] explode all trees | 6495 |
| #3 | #1 AND #2 | 102 |
| #4 | (Dexmedetomidine): ti, ab, kw AND (lignocaine OR lidocaine): ti, ab, kw AND (extubation): ti, ab, kw | 61 |
| #5 | #3 OR #4 | 156 |

| Web of Science search history | | | | | |
|---|---|---|---|---|---|
| **Entitlements** | **#** | **Search Query** | **Database** | **Results** | **Date Run** |
| WOS.SCI: 1956 to 2023 | 1 | ((ALL=(Dexmedetomidine)) AND ALL=(Lidocaine)) AND ALL=(Extubation) | Web of Science Core Collection | 37 | Mon Jan 30 2023 11:15:21 GMT +0530 (India Standard Time) |




**Supplementary File S-3:** Sub-group analysis

**S-4: GRADE evidence profile**

**Question:** Dexmedetomidine compared to Lidocaine for attenuation of cough response, emergence time, extubation time, bradycardia and residual sedation during tracheal extubation.

**Setting:** Hospitals

**Bibliography:** Dexmedetomidine versus Lidocaine for attenuation of cough response, emergence time, extubation time, bradycardia, and residual sedation during tracheal extubation. Cochrane Database of Systematic Reviews

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Dexmedetomidine | Lidocaine | Relative (95% CI) | Absolute (95% CI) | | |
| **Incidence of cough** | | | | | | | | | | | | |
| 6 | randomised trials | not serious | serious[a] | not serious | serious[b] | none | 56/200 (28.0%) | 72/200 (36.0%) | **RR 0.76** (0.46 to 1.24) | **86 fewer per 1,000** (from 194 | ⊕⊕◯◯ Low | |
| **Emergence time** | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious | serious[c] | none | 70 | 70 | - | SMD **0.12 higher** (0.22 lower to | ⊕⊕⊕◯ Moderate | |
| **Extubation Time** | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious | serious[c] | none | 70 | 70 | - | SMD **0.29 higher** (0.05 lower to | ⊕⊕⊕◯ Moderate | |
| **Bradycardia** | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious | very serious[a,c] | none | 42/105 (40.0%) | 1/105 (1.0%) | **RR 10.25** (2.39 to 43.97) | **88 more per 1,000** (from 13 more to | ⊕⊕◯◯ Low | |
| **Residual Sedation** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | very serious[a,c] | none | 30/50 (60.0%) | 0/50 (0.0%) | **RR 30.45** (4.31 to 215.13) | **0 fewer per 1,000** (from 0 fewer to | ⊕⊕◯◯ Low | |

**CI:** confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference

## Explanations

a. Downgrade quality of evidence -1 due to serious inconsistency ($I^2$ value is > 50 %)

b. Downgrade quality of evidence -1 due to severe imprecision (wide 95% CIs)

c. Downgrade quality of evidence -1 due to serious imprecision (small number of participants)

**GRADE Working Group grades of evidence**

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty**: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**Supplementary File S-4:** GRADE evidence profile

**Supplementary File S-5: Modified Jadad score**

| Corresponding author | Was the research described as randomised? | Was the approach of randomisation appropriate? | Was the research described as blinding? | Was the approach of blinding appropriate? | Was there a presentation of withdrawals and dropouts? | Was there a presentation of the inclusion/ exclusion criteria? | Was the approach used to assess adverse effects described? | Was the approach of statistical analysis described? | Total |
|---|---|---|---|---|---|---|---|---|---|
| Kothari 2014[18] | +1 | 0 | +1 | 0 | 0 | +1 | +1 | +1 | 5 |
| Sharma 2014[19] | +1 | +1 | +1 | +1 | +1 | +1 | +1 | +1 | 8 |
| Gosai 2015[20] | +1 | +1 | 0 | 0 | 0 | +1 | +1 | +1 | 5 |
| Moustafa 2015[21] | +1 | +1 | +1 | 0 | 0 | +1 | +1 | +1 | 6 |
| Hu 2019[22] | +1 | +1 | 0 | +1 | +1 | +1 | +1 | +1 | 7 |
| Pradhan 2021[23] | +1 | 0 | +1 | 0 | +1 | +1 | +1 | +1 | 6 |
| Safneedha 2021[24] | +1 | 0 | 0 | +1 | 0 | +1 | +1 | +1 | 5 |