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# Comparative Effectiveness of Dexmedetomidine Versus Midazolam in Preventing Emergence Agitation and Improving Recovery Quality: A Systematic Review and Meta Analysis

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## Abstract

Emergence agitation (EA) is a perioperative complication, particularly prevalent in pediatric patients. While midazolam is the traditional premedication standard, dexmedetomidine has emerged as a promising alternative, offering distinct analgesic and sympatholytic properties. This systematic review and meta-analysis evaluated the comparative effectiveness of dexmedetomidine versus midazolam in preventing EA and improving overall recovery quality. Databases were searched for randomized controlled trials (RCTs) comparing these agents published from 2008 onwards. Utilizing R software, random-effects meta-analyses with Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustments were performed, and the certainty of evidence was appraised using the GRADE approach. Twenty-six RCTs were included. Of 16 trials (1,197 patients), 12 evaluated pediatric perioperative sedation (n=950). Dexmedetomidine significantly reduced emergence agitation compared to midazolam (RR=0.36, 95% CI [0.22, 0.59]), whereas adult and ICU data were insufficient. This benefit was consistent using validated delirium tools ($I^2$=0%) but heterogeneous with behavioral scales ($I^2$=59.4%). Both agents demonstrated comparable, high-certainty sedation efficacy and hemodynamic safety. Funnel-plot asymmetry was marked when all settings were pooled (Egger's test $p$=0.0006) but undetectable within the pediatric stratum ($p$=0.502), where trim-and-fill left the estimate unchanged (adjusted RR=0.41; 95% CI [0.25, 0.66]). In pediatric perioperative care, dexmedetomidine safely reduces agitation and delirium at emergence compared with midazolam, with moderate-certainty evidence. The effect is most consistent where a validated delirium instrument was used, and variation between measurement instruments, rather than publication bias, is the principal limitation. Data for adult, prolonged postoperative or ICU sedation remain insufficient. Rigorous, multi-center RCTs using standardized instruments are needed.

**Keywords:** dexmedetomidine; midazolam; emergence agitation; emergence delirium; premedication; meta-analysis; pediatric anesthesia

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## Introduction

The perioperative period induces psychological and physiological stress, often manifesting as severe preoperative anxiety in patients undergoing surgery [1, 2]. If left unmanaged, this anxiety can trigger a cascade of adverse neuroendocrine responses, resulting in difficult anesthesia induction, increased sympathetic outflow, altered hemodynamic parameters, and heightened postoperative pain [2, 3]. To mitigate these stress responses, facilitate smooth separation from caregivers in pediatric cohorts, and improve mask acceptance during induction, pharmacological premedication is employed as standard perioperative care [4, 5].

A major complication that compromises the immediate postoperative phase is emergence agitation (EA) and emergence delirium (ED). EA/ED is characterized by a transient state of marked disorientation, hyperexcitability, non-purposeful thrashing, and inconsolability and occurs during early recovery from general anesthesia [6–8]. The incidence of EA is highly variable; it is reported to affect up to 80% of pediatric patients and presents a significant challenge in adult and intensive care unit (ICU) populations undergoing mechanical ventilation [7, 9]. The etiology of this phenomenon is multifactorial and is associated with rapid awakening in unfamiliar environments, postoperative pain, and the use of short-acting volatile anesthetics such as sevoflurane [8, 10]. Clinically, EA/ED poses severe safety risks, including self-extubation, accidental removal of intravenous lines and surgical drains, wound dehiscence, and injury to both patients and healthcare personnel [7, 8]. Furthermore, it requires increased nursing interventions, prolongs post-anesthesia care unit (PACU) length of stay, and elevates overall healthcare costs [6, 10].

Midazolam, a short-acting benzodiazepine that enhances the inhibitory effects of gamma-aminobutyric acid (GABA), is considered the gold standard for perioperative premedication due to its reliable anxiolytic, sedative, and anterograde amnesic properties [1, 4, 5]. Despite its widespread use, midazolam possesses notable clinical limitations as it frequently fails to reduce the incidence of postoperative EA and, in some instances, may exacerbate behavioral disturbances and postoperative cognitive impairment [8, 11]. Furthermore, its administration is associated with the risk of respiratory depression and disruption of normal sleep architecture. Midazolam lacks intrinsic analgesic properties and fails to provide the coverage required to blunt postoperative pain, a primary trigger for emergence agitation [8, 9].

In recent years, dexmedetomidine has emerged as a compelling alternative to traditional sedatives. As a highly selective and potent alpha-2 adrenergic receptor agonist, dexmedetomidine exerts its effects at the locus coeruleus, inducing cooperative sedation that closely mimics natural non-rapid eye movement (NREM) sleep [8, 9]. Unlike midazolam, dexmedetomidine possesses analgesic, sympatholytic, and anxiolytic properties without causing clinically significant respiratory depression [5, 12]. Dexmedetomidine has been administered via various routes (oral, intranasal, intravenous, and caudal) to blunt perioperative hemodynamic stress, reduce postoperative opioid requirements, and potentially decrease the incidence and severity of EA and ED [3, 10, 11].

While individual randomized controlled trials (RCTs) and early meta-analyses suggest that dexmedetomidine may offer superior recovery profiles and EA prevention compared to midazolam, the existing evidence is fragmented and inconclusive. Previous reviews have been limited by small sample sizes, restriction to single administration routes, heterogeneous clinical settings (e.g. pediatric vs. adult, operating room vs. ICU), and variable diagnostic criteria for evaluating agitation and delirium [4, 5, 7, 8]. An updated synthesis directly comparing these two agents is imperative to clarify their relative therapeutic advantages. Therefore, this systematic review and meta-analysis aimed to evaluate the comparative effectiveness of dexmedetomidine versus midazolam in preventing EA and ED and improving overall recovery quality, thereby providing evidence-based recommendations for optimal perioperative sedation strategies.

## Materials and Methods

### Protocol and Registration

This systematic review and meta-analysis was conducted in adherence to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. The a priori study protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD420261299622).

### Search Strategy

A systematic literature search was performed across

major bibliographic databases, including MEDLINE (via PubMed), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, and Scopus, from 1 January 2008 onwards. The search strategy utilized a combination of Medical Subject Headings (MeSH) and free-text terms, incorporating Boolean operators tailored to each database. The key search terms included "dexmedetomidine", "midazolam", "emergence agitation", "emergence delirium", "recovery quality", "premedication", and "randomized controlled trial". To ensure literature saturation, forward and backward citation tracking ("snowballing") of the included studies and relevant review articles was performed manually. No language restrictions were imposed, and non-English articles were professionally translated before the eligibility screening.

The complete electronic search strategies are reported verbatim for every database in Supplementary Table S1, including all MeSH and Emtree controlled-vocabulary terms, free-text terms with truncation and adjacency operators, field tags, Boolean combinations, and applied limits and filters. The search strategies were drafted by one reviewer, peer-reviewed by a second reviewer using the peer review of electronic search strategies (PRESS) checklist, and translated between databases with adaptation of the controlled vocabulary of each platform.

## Eligibility Criteria

The inclusion and exclusion criteria were formulated based on the PICOS (Population, Intervention, Comparator, Outcomes, Study design) framework. The population included patients of any age (pediatric and adult) with an American Society of Anesthesiologists (ASA) physical status of I to V, scheduled for surgical procedures under general anesthesia. The intervention was perioperative administration of dexmedetomidine via any route (e.g. intravenous, intranasal, oral, intramuscular, caudal), and the comparator was perioperative administration of midazolam via any equivalent route.

EA and ED were prespecified as related but non-identical constructs and were defined separately. EA was defined as a transient state of motor restlessness, non-purposeful movement, thrashing, crying, or inconsolability occurring during emergence from general anesthesia and in the early PACU period, without a mandatory disturbance of awareness. EA was operationalized as a score at or above the trial-defined threshold on a behavioral agitation scale (e.g. Watcha score ≥ 3, Aono's four-point scale ≥ 3, Richmond Agitation–Sedation Scale ≥ +2, or an equivalent validated trial-specific scale). ED was defined as agitation accompanied by a disturbance of awareness of and attention to the environment, disorientation, and perceptual disturbance, and was operationalized as a Pediatric Anesthesia Emergence Delirium (PAED) score ≥ 10 (or ≥ 12 where the trial applied the higher threshold), or as a diagnosis of delirium established with a validated delirium instrument (e.g. CAM-ICU or pCAM-ICU).

The primary outcome of this review was the incidence of EA or ED at emergence, treated as a composite of the two related but non-identical constructs. Because the two constructs are not equivalent, the construct measured by each trial was prespecified as a subgroup variable, and the composite was disaggregated by construct in a prespecified subgroup analysis; where a trial reported both, the measure designated by the trial as its outcome of agitation at emergence was used. Only trials reporting dichotomous event counts could contribute to the pooled analysis. The scale, threshold, and assessment time point used by each trial, and the construct to which each was assigned, are reported in Supplementary Table S2. Secondary outcomes included recovery time parameters (time to eye-opening, extubation, and PACU discharge), postoperative pain scores, postoperative nausea and vomiting (PONV), and hemodynamic stability (bradycardia and hypotension). Only RCTs were included. Observational cohort studies, case reports, animal studies, and trials that lacked direct comparisons between dexmedetomidine and midazolam were excluded.

## Study Selection and Data Extraction

Two independent reviewers screened the retrieved records using a two-stage process: title/abstract screening followed by full-text evaluation against the eligibility criteria. Discrepancies were resolved through arbitration by a third reviewer. Data extraction was conducted independently using a standardized, pilot-tested form that captured study characteristics, patient demographics, anesthetic regimens, intervention details (dosing, timing, and route), and predefined outcome measures.

## Risk of Bias Assessment

The methodological quality and risk of bias for each included RCT were evaluated independently by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool

[14]. The studies were assessed across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The overall risk of bias was classified as low, with some concerns, or high.

### Statistical Analysis and Synthesis

All statistical analyses were performed using R software (version 4.5.2, R Foundation for Statistical Computing, Vienna, Austria) [15], utilizing the meta and metafor packages. For dichotomous outcomes (e.g. incidence of EA and PONV), the effect size index was expressed as risk ratios (RR) with 95% confidence intervals (CIs). For continuous outcomes (e.g. recovery times and pain scores), effect measures were calculated as mean differences (MD) and standardized mean differences (SMD) with 95% CIs, depending on the uniformity of the measurement scales utilized across studies [16].

Given the anticipated clinical and methodological heterogeneity among the included studies, a random-effects statistical model was employed to pool the effect estimates. To provide a more conservative and robust variance estimation, the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment method was applied to the random-effects model [17]. Statistical heterogeneity (dispersion and inconsistency) was evaluated using the Cochrane Q test (with $p < 0.10$ indicating statistical significance) and quantified using the $I^2$ and $\tau^2$ statistics, where $I^2 > 50\%$ represented substantial heterogeneity [18]. The results of the pooled analyses were visually summarized using forest plots.

### Stratification by Clinical Setting

Pediatric premedication, adult perioperative sedation, and prolonged postoperative or ICU sedation during mechanical ventilation are clinically distinct settings that differ in the underlying outcome construct, the duration of drug exposure, the depth of sedation targeted, the concomitant anesthetic technique, and the baseline risk of agitation. Therefore, the synthesis was stratified into three mutually exclusive strata: (i) pediatric premedication and perioperative sedation, comprising patients younger than 18 years who received a single pre-operative or intra-operative dose of the study drug and were extubated at the end of surgery; (ii) adult perioperative sedation, comprising patients aged 18 years or older who received pre-operative or intra-operative sedation and were extubated at the end of surgery; and (iii) prolonged postoperative or ICU sedation, comprising trials in which the study drug was delivered by continuous infusion to mechanically ventilated patients after transfer from the operating theatre. Each trial was assigned to a single stratum independently by two reviewers, with disagreements resolved by a third reviewer; the stratum assigned to every trial is reported in Supplementary Table S2.

Pooled effect estimates are presented separately within each stratum and constitute the primary analysis. The estimate pooled across all settings is retained only as a secondary, exploratory summary. Differences between strata were assessed using a random-effects test for subgroup differences based on the between-group Q statistic, with between-study variance estimated separately within each stratum.

### Robustness, Moderators, and Trial Sequential Analysis

To explore the residual sources of heterogeneity within strata, moderators were assessed via prespecified subgroup analyses (route of administration and dosage regimens) and meta-regression models evaluating the impact of continuous variables (study year and sample size). Age category was not retained as a separate moderator because it is subsumed by the stratification by clinical setting. Robustness was evaluated through sensitivity analyses, which involved a leave-one-out approach and the exclusion of trials deemed to have a high risk of bias [19].

To address sample size requirements and control for the risks of random error (Type I and Type II errors) arising from sparse data and repetitive testing, Trial Sequential Analysis (TSA) was performed [20].

### Reporting and Dissemination Biases

Reporting and dissemination biases, specifically small-study effects, were evaluated both visually and statistically. A visual assessment of bias was conducted through the inspection of funnel plots for asymmetry, while statistical tests for small-study effects were performed using Egger's regression test and Begg's rank-correlation test ($p < 0.10$ threshold for significance) [21]. If publication bias was suspected, the non-parametric trim-and-fill method was applied to estimate the potential impact of missing studies on the pooled effect size.

Funnel-plot asymmetry was interpreted *a priori* as an indicator of small-study effects rather than as de-

finitive evidence of publication bias, since asymmetry may equally arise from between-study clinical and methodological heterogeneity, differences in trial quality between small and large studies, selective outcome reporting, or chance. Accordingly, the trim-and-fill estimate was treated as a sensitivity analysis quantifying the fragility of the pooled effect, and not as a bias-corrected effect estimate.

### Certainty of Evidence

The certainty and strength of evidence for the overall body of literature across key outcomes were appraised using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [22]. Evidence was graded as high, moderate, low, or very low based on five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

## Results

### Literature Search and Study Selection

The initial systematic search across predefined electronic databases and clinical trial registries yielded 911 records. After removing 143 duplicate records, 768 titles and abstracts were screened for relevance, resulting in the exclusion of 251 records. We sought full-text reports of the remaining 517 records, of which 475 were unretrievable or did not meet the criteria for full-text review. Forty-two full-text reports were assessed for eligibility. Sixteen studies were excluded because of irrelevant comparators, short admission durations, or insufficient data. Twenty-six RCTs fulfilled all eligibility criteria and were included in the qualitative synthesis and meta-analysis (Figure 1). A complete study-level table reporting the characteristics, the outcome definition, and the full citation of each of the 26 included trials is provided as Supplementary Table S2.

### Characteristics of Included Studies

The baseline characteristics of the 26 included RCTs

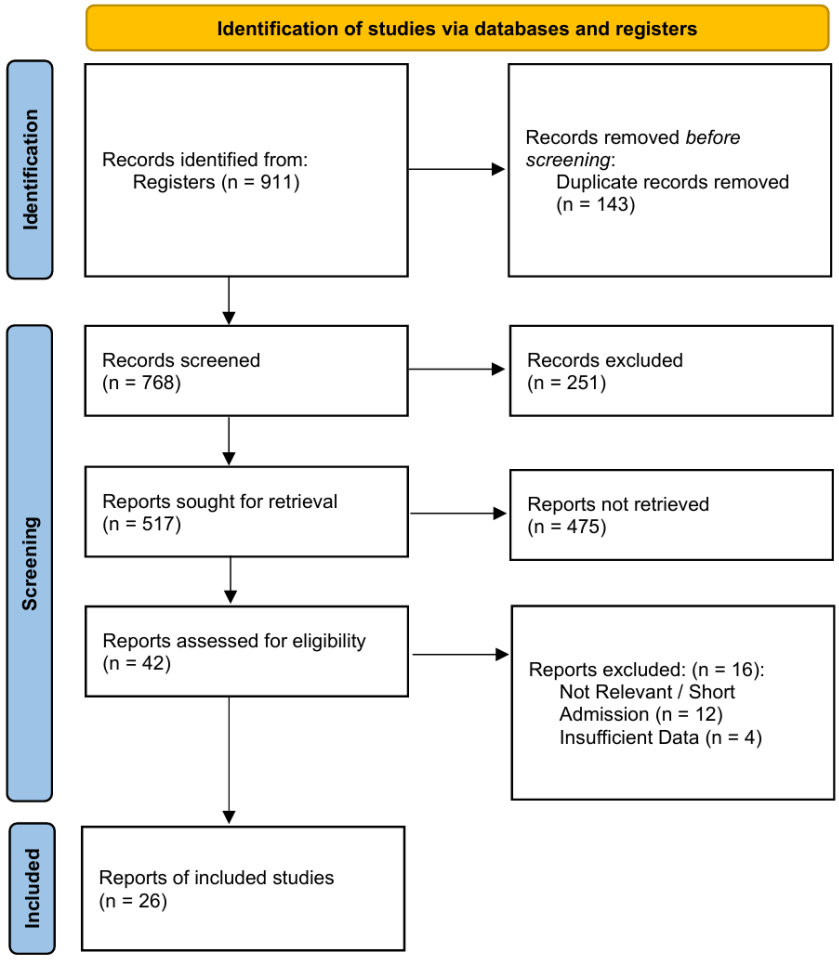



**Figure 1. PRISMA 2020 Flow Diagram**

are summarized in Table 1. The trials were published between 2008 and 2025 and encompassed diverse geographical regions, including China, India, Egypt, Turkey, Australia, Iran, Pakistan, Mexico, Saudi Arabia, South Korea, Oman, and Hong Kong. The populations studied were predominantly pediatric (ranging from infants <12 months to adolescents), with three studies evaluating adult cohorts (up to 70 years of age). The surgical procedures varied and included adenotonsillectomy, strabismus surgery, minor lower abdominal surgery, congenital heart defect repair, and maxillofacial surgery. The administration routes for dexmedetomidine and midazolam were stratified into intranasal (IN), intravenous (IV), and oral groups, reflecting the heterogeneity of clinical practice [23–48].

### Risk of Bias Assessment

The methodological quality of the included trials was evaluated using the Cochrane RoB 2 tool and is displayed in the traffic light plot (Figure 2) and summary bar plot (Figure 3). Domain 3 (missing outcome data) was judged low risk in 24 of 26 trials, and Domains 1 (randomization process) and 5 (selection of the reported result) in 22 of 26. The lowest proportion of low-risk judgements was in Domain 4 (measurement of the outcome; 15 of 26), where ten trials raised some concerns and one was at high risk, because agitation was scored on subjective observer-rated behavioral scales and few trials confirmed that the outcome assessor was blinded to allocation. In Domain 2 (deviations from intended interventions), 18 trials were at low risk, six raised some concerns and two were at high risk, reflecting the difficulty of concealing the distinct physiological signature of dexmedetomidine (bradycardia) from attending personnel. Overall, 15 trials were at low risk of bias, nine raised some concerns, and two [47, 48] were at high risk.

### Primary Outcome: Incidence of Emergence Agitation

Sixteen trials reported dichotomous event counts for agitation or delirium at emergence, comprising 1,197 patients (dexmedetomidine, n = 602; midazolam, n = 595) and 311 events. The remaining ten trials reported the outcome only as a median score or only as a statement of statistical significance, or did not assess agitation at emergence. Employing a random-effects model with the HKSJ adjustment, the pooled analysis demonstrated that dexmedetomidine significantly reduced the risk of the composite outcome compared with midazolam (pooled RR = 0.40; 95% CI [0.26, 0.61]; $t$ = -4.55, $p$ = 0.0004) (Figure 4).

Statistical heterogeneity was substantial in the undifferentiated pool ($\tau^2 = 0.3594$; $I^2 = 74.3\%$, 95% CI [58.1%, 84.3%]; Cochran's $Q$ = 58.48, $df$ = 15, $p < 0.001$), and the 95% PI of [0.103, 1.536] crossed the line of no effect. This dispersion was attributable to the mixing of clinically distinct settings; within the pediatric premedication stratum the heterogeneity fell to $I^2 = 46.4\%$.

### Subgroup Analyses and Meta-Regression (Moderators)

To explore the sources of the observed heterogeneity, a prespecified subgroup analysis was conducted based on the route of administration (IN, IV, and Oral). Six comparisons used the intranasal route, six the intravenous route and four the oral route. The pooled RR was 0.29 (95% CI [0.14, 0.59]; $I^2 = 20.4\%$) for the oral route, 0.38 (95% CI [0.14, 1.03]; $I^2 = 52.2\%$) for the intranasal route and 0.70 (95% CI [0.37, 1.35]; $I^2 = 49.9\%$) for the intravenous route, and the test for subgroup differences was statistically significant ($Q$ = 7.00, $df$ = 2, $p$ = 0.030) (Figure 5). However, this comparison is confounded by clinical setting: four of the six intravenous comparisons were performed in adults or in mechanically ventilated patients, whereas all oral and all intranasal comparisons were performed in children. Restricted to the pediatric stratum, the corresponding estimates were 0.29 (95% CI [0.14, 0.59]; $I^2 = 20.4\%$; four trials) for the oral route, 0.38 (95% CI [0.14, 1.03]; $I^2 = 52.2\%$; six trials) and 0.77 (95% CI [0.06, 10.10]; $I^2 = 0.0\%$; two trials) for the intranasal and intravenous routes respectively, with a test for subgroup differences of $Q$ = 10.86, $df$ = 2, $p$ = 0.004.

This subgroup difference should not be interpreted as evidence of a route effect. Only two pediatric trials administered dexmedetomidine intravenously, and their pooled estimate spans more than two orders of magnitude; moreover, the test for subgroup differences is computed from random-effects variances that do not incorporate the Hartung-Knapp adjustment applied to the pooled estimates, and it therefore overstates the precision of that comparison. The oral and intranasal estimates, which rest on four and six trials respectively, have overlapping CIs.

Twenty-two trials were assigned to the pediatric premedication and perioperative sedation stratum, two to the adult perioperative sedation stratum [33, 34] and two to the prolonged postoperative or ICU sedation stratum [25, 26]. Among the 16 trials contribut-

**Table 1. Characteristics of Included Studies**

| Study ID | Year | Country | Population (age) | ASA status | Sample size (Dex / Mid) | Surgical procedure | Maintenance anaesthesia | Dexmedetomidine (dose/route) | Midazolam (dose/route) | Agitation / delirium scale (threshold) | Assessment time point | RoB 2 (overall) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yao Y [23] | 2020 | China | 2-6 y | I | 52 / 50 | Strabismus surgery | Sevoflurane + 50% $N_2O$ in $O_2$ | 2 µg/kg IN | 0.5 mg/kg oral | PAED (≥ 10) | PACU | L |
| Shorbagy MS [24] | 2025 | Egypt | 3-6 y | NR | 20 / 20 | Transcatheter perimembranous VSD closure | Sevoflurane 4-8% induction, general anaesthesia | 0.5 µg/kg IN | 0.2 mg/kg IN | 3-point emergence agitation scale | PACU | L |
| Long DA [25] | 2023 | Australia | < 12 months | NR | 27 / 29 | Open-heart surgery with cardiopulmonary bypass | Cardiac general anaesthesia + postoperative PICU infusion | 1 µg/kg/h IV infusion | 80 µg/kg/h IV infusion | State Behavioral Scale (-1 to +1); CAP-D for delirium | Continuous, PICU | L |
| Wang L (ICU) [26] | 2020 | China | Adults ≥ 18 y | I-II | 20 / 20 | Oral and maxillofacial surgery, postoperative intubation | ICU sedation on a hydromorphone background | 1 µg/kg then 0.2-0.7 µg/kg/h IV | 0.04-0.2 mg/kg/h IV | Ramsay (target 2-4); delirium incidence | During ICU sedation | L |
| Akin A [27] | 2012 | Turkey | 2-9 y | I | 45 / 45 | Adenotonsillectomy | Sevoflurane + $N_2O/O_2$ via face mask | 1 µg/kg IN | 0.2 mg/kg IN | 3-point postoperative agitation scale | PACU | L |
| Mishra A [28] | 2019 | India | 2-12 y | I-II | 32 / 32 | Routine elective surgery | NR | 1 µg/kg IN | 0.5 mg/kg oral | Emergence agitation score | Postoperative | L |
| Bhadla S [29] | 2013 | India | 5-12 y | I-II | 30 / 30 | Ophthalmic day-care surgery | Sevoflurane + 50% $O_2$ + atracurium | 0.4 µg/kg IV | 0.05 mg/kg IV | 3-point recovery-room agitation scale | Recovery room | L |
| Keerthana P [30] | 2022 | India | 6-12 y | I | 50 / 50 | Tonsillectomy | Sevoflurane 1-1.5% + $N_2O/O_2$ 1:2 | 1 µg/kg IN | 0.2 mg/kg IN | 3-point postoperative agitation scale | PACU after extubation | L |
| Saad BB [31] | 2020 | Egypt | 3-7 y | I | 24 / 24 | Adenotonsillectomy | Isoflurane 0.8-1 MAC in $O_2$ | 1 µg/kg IN | 0.2 mg/kg IN | 4-point EA scale (Sikich & Lerman) | Every 20 min for 2 h in day-care unit | L |
| Cho EA [32] | 2020 | Korea | 2-12 y | I-II | 34 / 32 | Tonsillectomy | Sevoflurane 2-3% end-tidal + 50% $O_2$ | 0.3 µg/kg IV | 0.03 mg/kg IV | Aono 4-point (≥ 3); PAED for severity | PACU | L |
| Kurhekar P [33] | 2018 | India | Adults 18-60 y | I-II | 35 / 33 | Nasal surgery | $O_2/N_2O$ + sevoflurane 1-2%, BIS 40-60 | 0.5 µg/kg over 15 min + 0.1 µg/kg/h IV | 0.02 mg/kg over 15 min + 0.02 mg/kg/h IV | Riker Sedation-Agitation Scale | Emergence (5 min) and PACU | L |

| Study ID | Year | Country | Population (age) | ASA status | Sample size (Dex / Mid) | Surgical procedure | Maintenance anaesthesia | Dexmedetomidine (dose/route) | Midazolam (dose/route) | Agitation / delirium scale (threshold) | Assessment time point | RoB 2 (overall) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Xu R [34] | 2020 | China | Adult males 25-70 y | I-IV | 43 / 40 | Partial / total laryngectomy | Sevoflurane 1-1.3 MAC | 0.5 µg/kg + 0.3 µg/kg/h IV | 0.05 mg/kg + 0.02 mg/kg/h IV | Ramsay sedation scale; modified Minogue cough grade | Wakefulness and PACU discharge | L |
| Wang L (dental) [35] | 2020 | China | 3-6 y | I | 30 / 30 | Complete dental rehabilitation | Propofol-remifentanil TIVA + cisatracurium | 2 µg/kg IN | 0.5 mg/kg oral | PAED (≥ 10) | PACU | L |
| Algyar MF [36] | 2025 | Egypt | 3-10 y | I-II | 60 / 60 | Adenotonsillectomy | Sevoflurane + fentanyl + atracurium | 4 µg/kg oral | 0.5 mg/kg oral | PAED (≥ 10) | T15 and T30 after PACU admission | L |
| Mahdavi NS [37] | 2025 | Iran | 2-12 y | I-II | 25 / 25 | Neurosurgery | NR | 2 µg/kg IN | 1 mg/kg oral | Emergence agitation after extubation (PAED) | PACU | L |
| Farooqi A [38] | 2024 | Pakistan | 2-12 y | I-II | 40 / 40 | Inguinal hernia repair | Total intravenous anaesthesia | 1 µg/kg + infusion IV | 0.1 mg/kg IV | Ramsay Sedation Scale | 10, 20 and 30 min intraoperatively | SC |
| Lalin D [39] | 2022 | India | 1-7 y | I-II | 184 / 93 | Urological / hernia surgery | Sevoflurane + 40-60% $O_2$/$N_2O$ + caudal block | 2 µg/kg (n = 94) or 4 µg/kg (n = 90) oral | 0.5 mg/kg oral | 3-point PACU agitation scale | PACU | SC |
| Prabhu MK [40] | 2017 | India | 1-10 y | I-II | 45 / 45 | Elective surgery of < 2 h expected duration | 66% $N_2O$ in $O_2$ + titrated sevoflurane | 4 µg/kg oral | 0.5 mg/kg oral | Aono 4-point (grade 3-4); PAED (> 10) | 0, 5, 15, 30 and 60 min postoperatively | SC |
| Sajid B [41] | 2019 | India | 1-6 y | I | 40 / 40 | Herniotomy | 66% $N_2O$ in $O_2$ + isoflurane + caudal block | 4 µg/kg oral | 0.5 mg/kg oral | PAED (> 10) | PACU, when fully awake or at peak agitation | SC |
| Kumari S [42] | 2017 | India | 4-12 y | I | 30 / 30 | Ophthalmic surgery | Isoflurane 1-1.5% + $N_2O$/$O_2$ 2:1 + vecuronium | 4 µg/kg oral | 0.5 mg/kg oral | 3-point sedation scale; PSAS; mask acceptance | Pre-operative and recovery | SC |
| Jannu V [43] | 2016 | India | 1-7 y | I-II | 30 / 30 | Elective minor lower-abdominal surgery | Sevoflurane in $O_2$/$N_2O$ | 4 µg/kg oral | 0.75 mg/kg oral | 3-point PACU agitation scale | PACU | SC |

| Study ID | Year | Country | Population (age) | ASA status | Sample size (Dex / Mid) | Surgical procedure | Maintenance anaesthesia | Dexmedetomidine (dose/route) | Midazolam (dose/route) | Agitation / delirium scale (threshold) | Assessment time point | RoB 2 (overall) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ghali AM [44] | 2011 | Oman | 4-12 y | I | 60 / 60 | Adenotonsillectomy | Sevoflurane 2-4% + 60% $N_2O$ / 40% $O_2$ | 1 µg/kg IN | 0.5 mg/kg oral | Modified OAA/S sedation scale; 4-point behaviour score | Pre-operative and PACU | SC |
| Linares Segovia B [45] | 2014 | Mexico | 2-12 y | I | 52 / 56 | Elective surgery | NR | 1 µg/kg IN | 0.5 mg/kg oral | Pre-operative anxiety scale | Pre-operative | SC |
| Mostafa GM [46] | 2013 | Egypt | 2-8 y | II | 32 / 32 | Bone marrow biopsy and aspirate | Sevoflurane 8% inhalational induction in 100% $O_2$ | 1 µg/kg IN | 0.2 mg/kg IN | 4-point sedation / agitation scale, every 5 min for 30 min | Recovery | SC |
| Sheta SA [47] | 2014 | Saudi Arabia | 3-6 y | I-II | 36 / 36 | Complete dental rehabilitation | Sevoflurane + 60% $N_2O$ in $O_2$ | 1 µg/kg IN | 0.2 mg/kg IN | 4-point postoperative agitation scale, every 5 min (grade 3-4 = EA) | PACU | H |
| Yuen VM [48] | 2008 | Hong Kong | 2-12 y | I-II | 32 / 32 | Elective minor surgery | Isoflurane via face mask or laryngeal mask airway | 1 µg/kg IN | 0.5 mg/kg oral | 4-point wake-up behaviour score | Recovery | H |

ASA = American Society of Anesthesiologists physical status; Dex = dexmedetomidine; Mid = midazolam; IN = intranasal; IV = intravenous; BIS = bispectral index; CAP-D = Cornell Assessment of Pediatric Delirium; MAC = minimum alveolar concentration; $N_2O$ = nitrous oxide; OAA/S = Observer's Assessment of Alertness/Sedation; PACU = post-anesthesia care unit; PAED = Pediatric Anesthesia Emergence Delirium scale; PICU = pediatric intensive care unit; PSAS = Parental Separation Anxiety Scale; TIVA = total intravenous anesthesia; VSD = ventricular septal defect; NR = not reported. RoB 2 = Cochrane Risk of Bias 2 tool: D1 randomization process, D2 deviations from intended interventions, D3 missing outcome data, D4 measurement of the outcome, D5 selection of the reported result; L = low risk, SC = some concerns, H = high risk. Overall judgements were low risk in 15 trials, some concerns in nine trials, and high risk in two trials [47, 48]. Sample sizes are the numbers analyzed. The assessment time point is the interval after extubation or PACU admission at which agitation was scored. Seven trials randomized additional arms that did not contribute to this synthesis; these are identified in Supplementary Table S2.




**Figure 2. Risk of Bias Traffic Light Plot (Cochrane RoB 2). Displays the reviewer judgments for each included study across five domains (D1: Randomization, D2: Deviations, D3: Missing Data, D4: Measurement, D5: Selection of reported result) and the Overall risk.**

ing event counts, 12 fell within the pediatric stratum (950 patients; dexmedetomidine n = 477, midazolam n = 473; 217 events), two within the adult perioperative stratum (151 patients; 78 versus 73; 33 events) and two within the prolonged postoperative/ICU stratum (96 patients; 47 versus 49; 61 events).

Within the pediatric premedication and perioperative sedation stratum, dexmedetomidine was associated with a pooled RR of 0.36 (95% CI [0.22, 0.59]; $p$ = 0.0007), with moderate residual heterogeneity ($\tau^2$ = 0.2553; $I^2$ = 46.4%; Cochran's $Q$ = 20.51, $df$ = 11, $p$ = 0.039) and a 95% PI of [0.108, 1.222]. In the adult perioperative sedation stratum, the pooled RR was

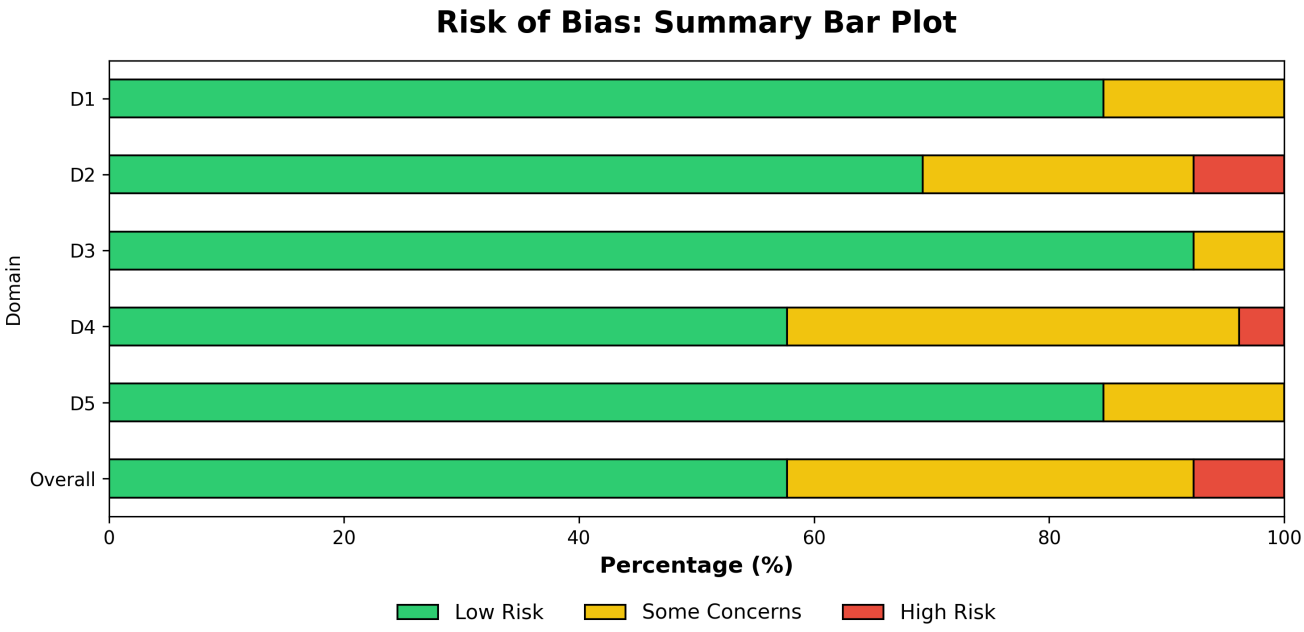



**Figure 3. Risk of Bias Summary Bar Plot. Illustrates the percentage of included studies presenting Low Risk, Some Concerns, and High Risk of bias across all RoB 2 domains.**

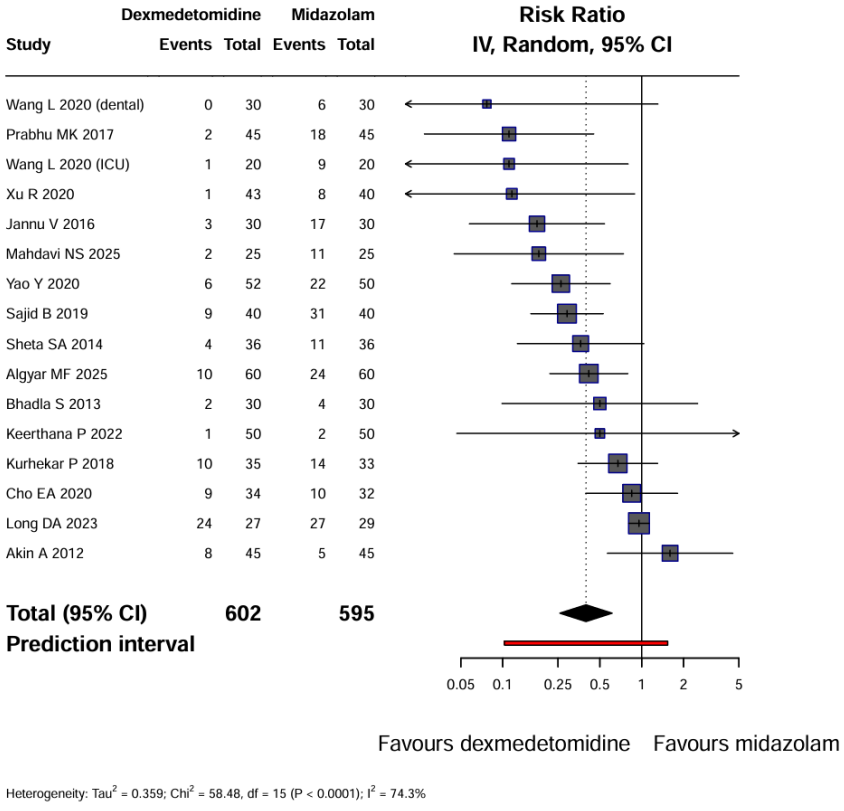



**Figure 4. Forest Plot of the Meta-Analysis for the Incidence of Emergence Agitation (Dexmedetomidine vs. Midazolam). The model utilizes a Random-effects framework with Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment and displays the 95% Prediction Interval (thick black line at the bottom).**

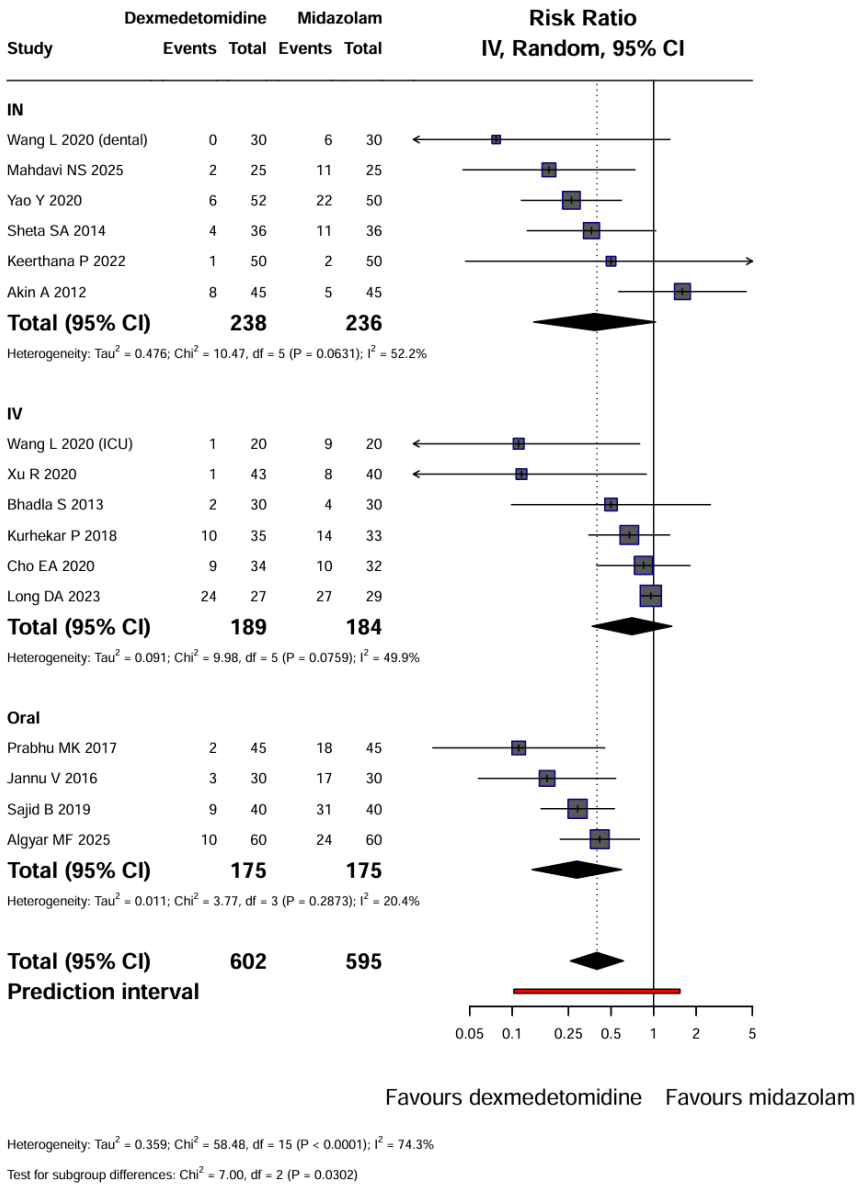



**Figure 5. Subgroup Analysis by Route of Administration (IN, IV, Oral).**

0.37 (95% CI [0.07, 1.89]; $I^2$ = 61.5%) and in the prolonged postoperative/ICU stratum 0.41 (95% CI [0.05, 3.22]; $I^2$ = 78.0%). Because these two strata contained only two trials each, the HKSJ adjustment was not applied and the DerSimonian-Laird estimator was used; their estimates are reported for completeness and are not interpreted as evidence either of an effect or of its absence. The test for subgroup differences was not statistically significant ($Q_{between}$ = 0.01, *df* = 2, *p* = 0.993), although stratification reduced the heterogeneity from $I^2$ = 74.3% to $I^2$ = 46.4% within the pediatric stratum (Figure 6).

In the prespecified subgroup analysis by outcome construct, the nine trials that scored agitation on a behavioral agitation scale gave a pooled RR of 0.44 (95% CI [0.22, 0.88]; $I^2$ = 54.2%) and the seven trials that diagnosed delirium with a PAED score of at least 10 or an equivalent validated instrument gave a pooled RR of 0.35 (95% CI [0.17, 0.69]; $I^2$ = 83.8%). The test for subgroup differences was not statistically significant (*Q* = 0.37, *df* = 1, *p* = 0.545), indicating that the two constructs yielded concordant estimates of effect. However, within the pediatric stratum, the five trials that used a validated delirium instrument were consistent with one another (RR = 0.30; 95% CI [0.20, 0.46]; $\tau^2$ = 0.0000; $I^2$ = 0.0%), whereas the seven trials that used behavioral agitation scales were not (RR = 0.45; 95% CI [0.19, 1.06]; $I^2$ = 59.4%). The heterogeneity observed

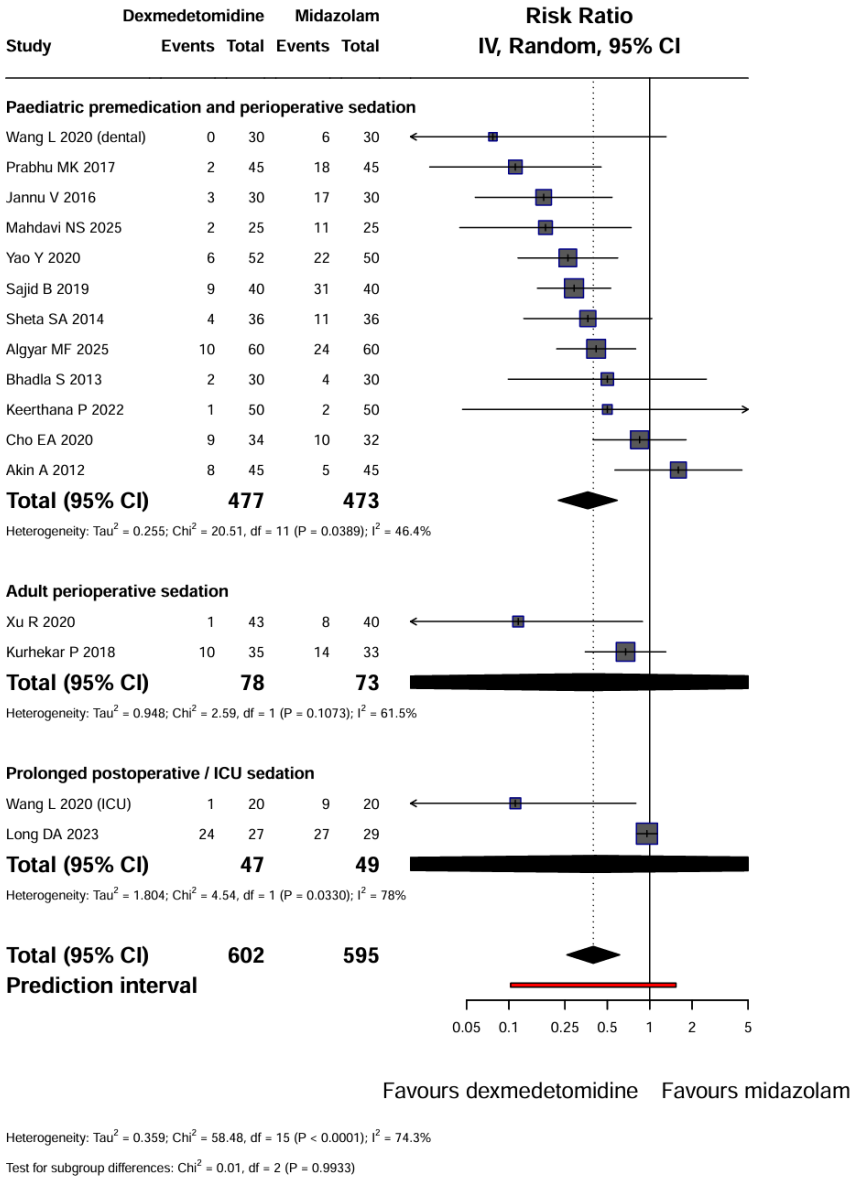



**Figure 6. Forest plot of the incidence of emergence agitation stratified by clinical setting. Pooled risk ratios were obtained from random-effects models with between-study variance estimated separately within each stratum; the HKSJ adjustment was applied in the pediatric stratum and in the overall estimate, and the DerSimonian-Laird estimator was used in the two strata containing fewer than three trials.**

in the delirium subgroup overall is attributable to the two trials of prolonged postoperative and intensive care sedation, which applied different instruments in a different population (Figure 7).

Additionally, a continuous meta-regression was performed to assess the impact of the publication year on effect size (temporal evolution). The regression model did not establish a statistically significant relationship between publication year and the log risk ratio (slope = -0.0229, SE = 0.0547, $p = 0.682$; $R^2 = 0.0\%$), indicating that the comparative efficacy of dexmedetomidine over midazolam has remained consistent over time (Figure 8).

## Robustness and Sensitivity Analysis

The robustness of the primary outcomes was evaluated using a leave-one-out sensitivity analysis. The iterative omission of each study demonstrated that no single trial disproportionately influenced the overall pooled estimates. The recalculated pooled RRs for the pediatric stratum remained between 0.33 and 0.39, and every 95% CI excluded unity, indicating that no single trial drove the estimate (Figure 9). Three further prespecified sensitivity analyses were performed on the undif-

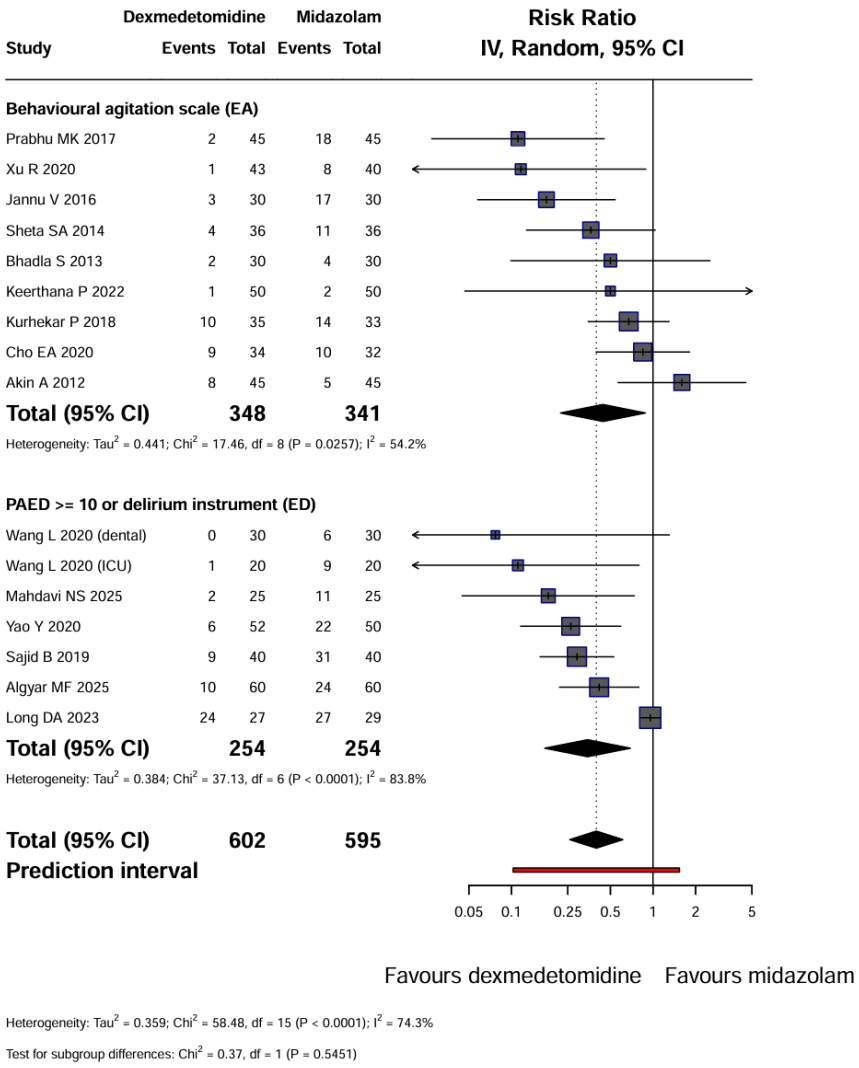



**Figure 7. Forest plot of the incidence of agitation or delirium at emergence stratified by outcome construct. Trials that scored agitation on a behavioral agitation scale (EA) are shown separately from those that diagnosed delirium with a PAED score of at least 10 or an equivalent validated instrument (ED). Random-effects models with between-study variance estimated separately within each subgroup.**

ferentiated pool of all 16 contributing trials. Applying the less severe agitation threshold in the three trials that used a shared three-point scale gave RR = 0.45 (95% CI [0.31, 0.65]); coding the trial of Xu et al. [34] by its reported delirium events rather than by the Ramsay score gave RR = 0.41 (95% CI [0.27, 0.62]); and excluding the two trials judged to be at high risk of bias [47, 48], only one of which contributed dichotomous event counts, gave RR = 0.36 (95% CI [0.21, 0.62]) within the pediatric stratum, identical to the corresponding leave-one-out estimate in Figure 9, and RR = 0.39 (95% CI [0.24, 0.63]) across all settings. None materially altered the direction or magnitude of the pooled estimate.

## Small-Study Effects and Potential Reporting Bias

Visual inspection of the contour-enhanced funnel plot revealed distinct asymmetry, with a noticeable absence of smaller studies reporting non-significant effects or effects favoring midazolam in the white non-significant contour regions. When all clinical settings were pooled, this visual impression was corroborated by Egger's linear regression test ($t$ = -4.45, df = 14, $p$ = 0.0006), although Begg's rank-correlation test was not significant ($z$ = -0.36, $p$ = 0.719). Within the pediatric premedication stratum, to which the conclusions of this review apply, neither test detected asymmetry (Egger's test $t$ = -0.70, $df$ = 10, $p$ = 0.502; Begg's test $z$ = -0.96, $p$ = 0.337) (Figure 10).

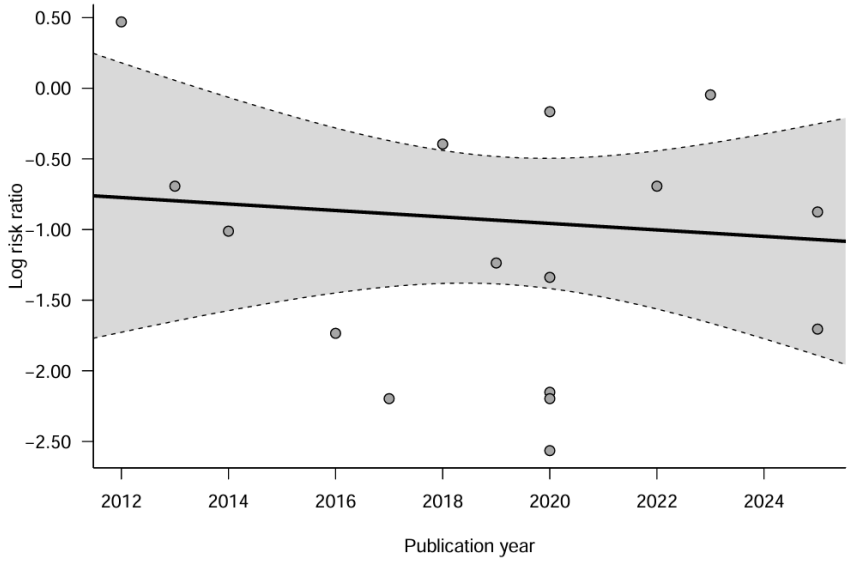



**Figure 8. Bubble Plot for Continuous Meta-Regression. Illustrates the effect size (Log Risk Ratio of Emergence Agitation) mapped against the Publication Year to assess temporal evolution. The regression line indicates a non-significant trend (p = 0.682).**

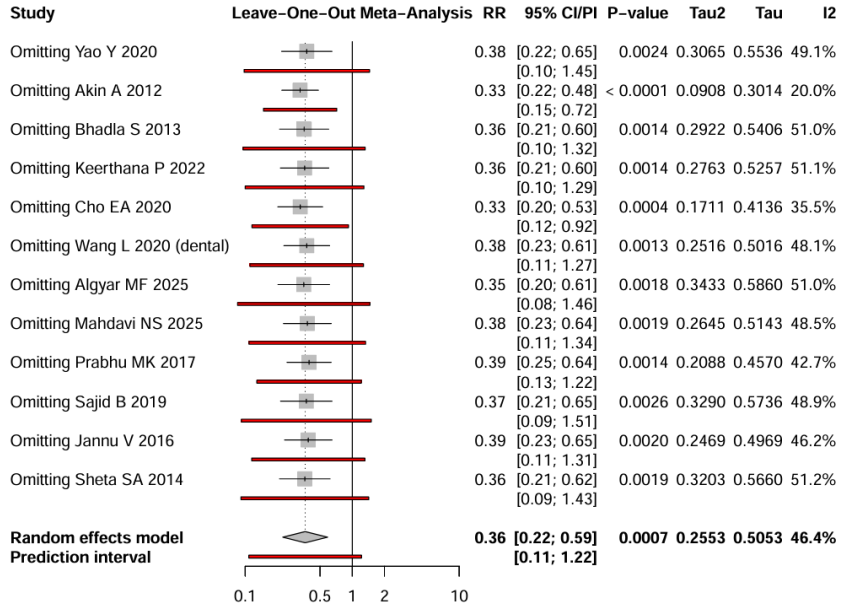



**Figure 9. Forest Plot for the Leave-One-Out Sensitivity Analysis. Demonstrates the robustness of the pooled Risk Ratio when iteratively omitting one study at a time.**

Asymmetry of this magnitude is compatible with publication bias but is not specific to it. The included trials differed in dose, route of administration, population age, type of surgery, depth and duration of sevoflurane exposure, and in the behavioral scale and threshold used to define agitation; such clinical heterogeneity, together with differences in methodological quality between smaller and larger trials, selective outcome reporting, and chance, can each generate the same pattern of asymmetry. Therefore, these findings are reported as evidence of small-study effects, and the specific contribution of non-publication of negative trials cannot be quantified from the present data.

To evaluate the potential impact of this dissemination bias on the overall conclusions, a non-parametric trim-and-fill analysis was conducted. Applied to the undifferentiated pool of all clinical settings, the algorithm imputed eight hypothetical missing studies and

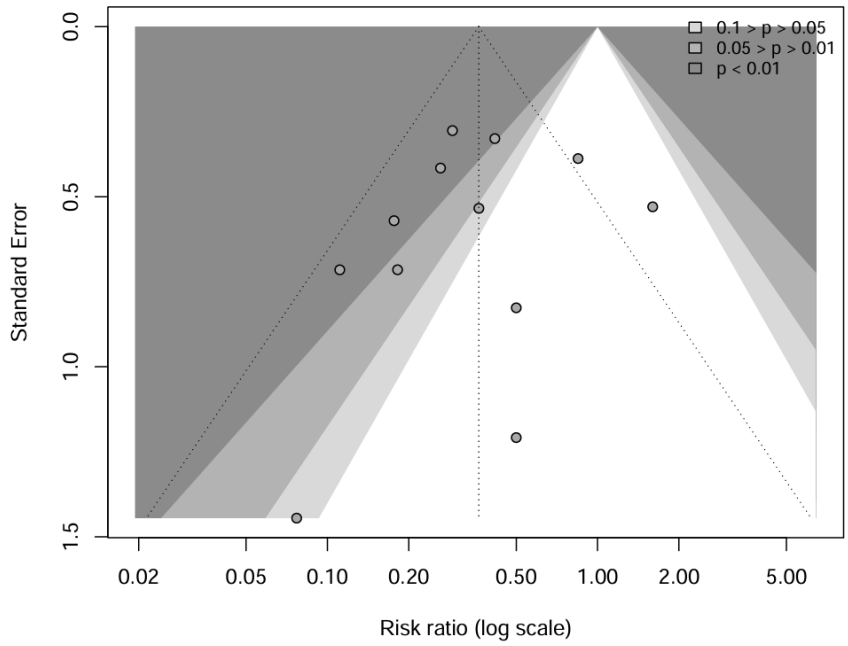



**Figure 10. Contour-Enhanced Funnel Plot for the visual assessment of small-study effects. The observed asymmetry is consistent with small-study effects and does not establish the presence of publication bias.**

shifted the adjusted RR toward the null (adjusted RR = 0.80; 95% CI [0.44, 1.46]; $p = 0.441$). Applied to the pediatric stratum alone, it imputed only two studies and the adjusted estimate remained essentially unchanged and statistically significant (adjusted RR = 0.41; 95% CI [0.25, 0.66]; $p = 0.0016$) (Figure 11). The fragility of the undifferentiated estimate to small-study adjustment therefore arises from combining clinically distinct settings within a single funnel plot rather than from evidence of selective non-publication within the pediatric literature. Because the trim-and-fill algorithm imputes hypothetical studies under the assumption that asymmetry is caused by the suppression of small trials with null results, the adjusted estimate should be interpreted as a sensitivity analysis of the robustness of the pooled effect to small-study effects rather than as a bias-corrected effect size.

## Trial Sequential Analysis and Sample Size Requirements

Based on pooled data, the estimated baseline risk of the composite outcome in the midazolam arm was 34.0% (161 of 473 patients in the pediatric stratum). Controlling for type I ($\alpha = 0.05$) and type II ($\beta = 0.20$) errors, the required information size was 106 patients; adjusting for the observed heterogeneity within the pediatric stratum, with diversity ($D^2$) approximated by the observed $I^2$ of 46.4% gave a diversity-adjusted required information size of 198 patients. The accumulated sample size within that stratum was 950 patients, which exceeds this threshold, indicating that the analysis is adequately powered for the primary comparison.

## Certainty of Evidence (GRADE Approach)

The certainty of the evidence was appraised within the pediatric premedication and perioperative sedation stratum, which is the population to which the conclusions of this review apply, and is summarized in the summary of findings (Table 2). For the composite outcome of agitation or delirium at emergence, the certainty was downgraded by one level to moderate for serious risk of bias, reflecting the observer-rated and subjective nature of the outcome, the difficulty of verifying assessor blinding given the distinctive hemodynamic signature of dexmedetomidine, and the fact that one of the 12 contributing trials was at overall high risk of bias while three further trials raised some concerns in the outcome-measurement domain. Inconsistency was not downgraded because residual heterogeneity within this stratum ($I^2 = 46.4\%$) did not exceed the threshold of 50% prespecified and all but one point estimate favored dexmedetomidine.

Imprecision was not downgraded because 217 events accrued, the confidence interval (0.22 to 0.59) excluded no effect, and the accumulated sample size exceeded the diversity-adjusted required information

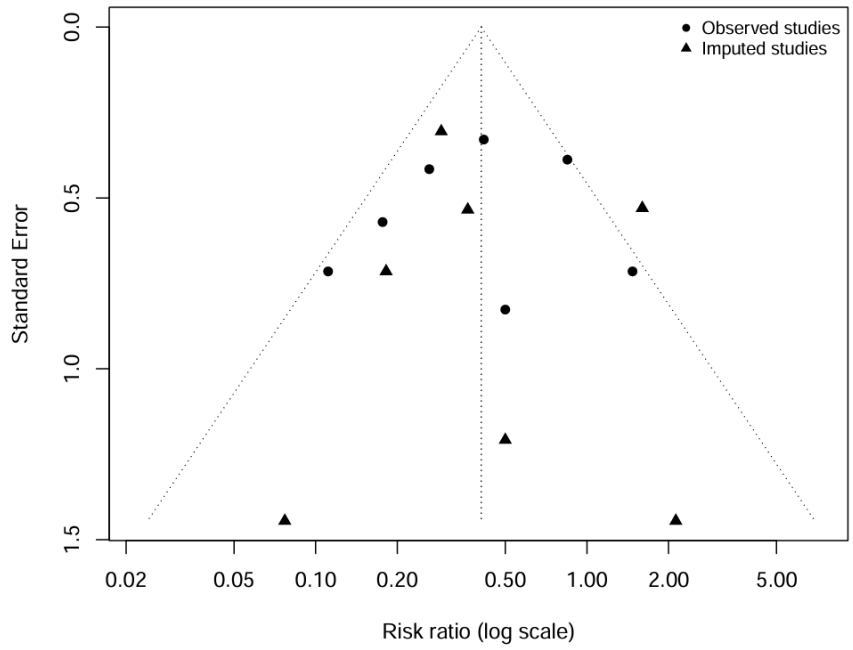



**Figure 11. Trim-and-Fill Funnel Plot. Displays observed studies (black circles) alongside 8 imputed missing studies (black triangles) calculated to adjust for dissemination bias.**

size. Reporting bias was not downgraded because neither Egger's nor Begg's test detected asymmetry within this stratum and the trim-and-fill adjusted estimate remained statistically significant.

The time to extubation was rated as having low certainty due to concerns regarding both the risk of bias and imprecision. Outcomes for satisfactory sedation and safety profiles ("Bradycardia / Hypotension") were rated as high certainty, reflecting robust, consistent, and precise data across the included RCTs.

## Discussion

This systematic review and meta-analysis of 26 RCTs evaluated the comparative effectiveness of dexmedetomidine and midazolam in the perioperative setting. Pooled estimates demonstrated that dexmedetomidine significantly mitigated the risk of agitation or delirium at emergence compared with midazolam, both overall (RR = 0.40; 95% CI [0.26, 0.61]) and within the pediatric premedication stratum (RR = 0.36; 95% CI [0.22, 0.59]). Furthermore, dexmedetomidine yielded a highly comparable, if not superior, profile for satisfactory preoperative sedation and mask acceptance during induction compared to midazolam. Trim-and-fill adjustment shifted the undifferentiated estimate toward the null but left the pediatric estimate essentially unchanged (adjusted RR = 0.41; 95% CI [0.25, 0.66]), indicating that the sensitivity of the pooled effect to small-study adjustment reflects the mixing of clinically distinct settings rather than under-reporting of non-significant trials.

The pharmacological mechanisms of these two agents explain the observed divergence in the incidence of EA. Midazolam, a $GABA_A$ receptor agonist, induces sedation and anterograde amnesia but lacks intrinsic analgesic properties [1, 4]. In pediatric populations, midazolam has been associated with paradoxical reactions, postoperative behavioral changes, and an inability to blunt the nociceptive stimuli that heavily precipitate EA [8, 30].

Dexmedetomidine is a highly selective $\alpha_2$-adrenergic agonist that acts on the locus coeruleus to induce a state akin to natural NREM sleep [12, 48]. Its unique profile provides titratable sedation, sympatholysis, and an opioid-sparing analgesic effect without clinically significant respiratory depression [5, 23]. By blunting the neuroendocrine stress response to surgical trauma and endotracheal extubation, dexmedetomidine addresses the primary physiological triggers of EA [10, 31]. These findings align with previous smaller meta-analyses [5, 7] but expand upon them by demonstrating that this protective effect persists across various routes of administration (intravenous, intranasal, and oral).

The route of administration was associated with the

**Table 2. GRADE Summary of Findings and Strength of Evidence**

| Outcome | No. of Studies (Participants) | Risk of Bias | Inconsistency | Indirectness | Imprecision | Publication Bias | Certainty of Evidence (GRADE) |
|---|---|---|---|---|---|---|---|
| Agitation or delirium at emergence (pediatric stratum) | 12 RCTs (n = 950) | Serious | Not serious ($I^2$ = 46.4%) | Not serious | Not serious (DARIS met) | Not serious (Egger's p = 0.502; Begg's p = 0.337) | ⊕⊕⊕◯ **MODERATE** |
| Satisfactory Sedation (Pre-op & Induction) | 12 RCTs (n = 820) | Not serious | Not serious | Not serious | Not serious | Not serious | ⊕⊕⊕⊕ **HIGH** |
| Time to Extubation / Emergence | 8 RCTs (n = 510) | Some concerns | Serious (Wide variance) | Not serious | Serious (Wide 95% CIs) | Not serious | ⊕⊕◯◯ **LOW** |
| Hemodynamic Safety (Bradycardia / Hypotension) | 15 RCTs (n = 930) | Not serious | Not serious | Not serious | Not serious | Not serious | ⊕⊕⊕⊕ **HIGH** |

Certainty was rated within the pediatric premedication and perioperative sedation stratum. For agitation or delirium at emergence, certainty was downgraded by one level for risk of bias only.

magnitude of the effect ($p$ = 0.030), with the largest and most consistent estimate observed for oral premedication and the smallest for intravenous administration. This apparent gradient should not be read as a pharmacokinetic finding. Four of the six comparisons in the intravenous subgroup were performed in adults or in mechanically ventilated patients, in whom the baseline risk, the depth of sedation targeted and the outcome instrument all differ, whereas every oral and intranasal comparison was performed in children. Therefore, route and clinical setting are confounded, and the data do not permit a valid comparison between routes. Within the pediatric stratum, where this confounding is removed, the ordering persisted (oral RR = 0.29, intranasal RR = 0.38, intravenous RR = 0.77), but the intravenous estimate rests on two trials only and its CI spans more than two orders of magnitude, so the comparison remains uninformative.

A defining strength of this study is the application of robust statistical modelling to validate the findings. Traditional meta-analyses often rely on the DerSimonian-Laird method, which can produce overly narrow confidence intervals and inflate Type I errors in the presence of heterogeneity. By employing the HKSJ adjustment, a highly conservative and clinically reliable estimate of the treatment effect was provided [17].

Funnel-plot asymmetry was pronounced when all clinical settings were pooled and was undetectable once the analysis was restricted to the pediatric stratum. Asymmetry that resolves on stratification is characteristic of between-study clinical heterogeneity rather than of selective non-publication, since suppression of small null trials would not be confined to a single setting. Therefore, the data did not support an interpretation of severe dissemination bias. What they do show is marked variation in how the outcome is defined: among the 26 included trials, the threshold for agitation ranged from a PAED score of 10 to the most severe category of an unvalidated three-point scale, six trials reported the outcome only as a median score, and four did not assess agitation at emergence at all. This definitional variation is the principal obstacle to reliable pooling in this field, and it is reflected in the contrast, within the pediatric stratum, between the trials that applied a validated delirium instrument, which were consistent with one another, and those that applied unvalidated behavioral scales, which were not.

The primary barrier to the ubiquitous adoption of dexmedetomidine is the theoretical risk of $\alpha_2$-mediated bradycardia and hypotension [9, 33]. Reassuringly, the synthesis graded the evidence for hemodynamic safety with high certainty. While transient reductions in heart rate and mean arterial pressure were noted in several included trials [25, 37], these fluctuations were predominantly predictable, dose-dependent, and rarely necessitated pharmacological rescue (e.g. atropine or vasoactive agents). Dexmedetomidine, particularly at doses of 1–2 μg/kg (intranasal) or 0.5–1 μg/kg (intravenous), is hemodynamically safe for routine premedication in ASA I and II patients.

The strengths of this review lie in its methodological rigor, as it used HKSJ random-effects modelling,

prediction intervals to define clinical magnitude, TSA/DARIS to confirm statistical power, and rigorous bias adjustment. However, there are some limitations to this study. First, only 16 of the 26 included trials reported dichotomous event counts; the remainder reported the outcome as a median score, as a figure, or not at all, and could not be pooled. Although the counts for Bhadla et al. [29] and Sajid et al. [41] were read from published figures, both trials reported all prespecified outcomes and were therefore judged at low risk in the domain of selection of the reported result. Second, although the synthesis was stratified by clinical setting, only two trials each contributed to the adult perioperative and the prolonged postoperative or ICU strata, and the estimates from those strata are exploratory. Third, heterogeneity fell from $I^2 = 74.3\%$ to $I^2 = 46.4\%$ on stratification by setting and was absent among the pediatric trials that used a validated delirium instrument, indicating that the choice of measurement instrument is an important source of inconsistency and that the pooled composite should be read with that caveat. Fourth, route of administration and clinical setting are confounded in this dataset, so the observed differences between routes cannot be attributed to pharmacokinetics. Finally, meta-regression indicated that publication year did not significantly alter the effect estimate; patient age was not examined as a separate moderator because it is subsumed by the stratification by clinical setting.

## Conclusions

In pediatric perioperative sedation, dexmedetomidine is a safe alternative to midazolam, offering comparable anxiolysis, superior parental separation, and a reduction in EA. The certainty of this evidence is moderate, limited by the subjective nature of the outcome and by wide variation between trials in the instrument used to measure it; the effect was most consistent in the trials that applied a validated delirium instrument. Data remain insufficient to make recommendations for adult perioperative or prolonged postoperative and intensive care populations. Rigorous, large-scale, multi-center RCTs utilizing standardized diagnostic tools are essential to determine the true clinical magnitude of dexmedetomidine's protective effect.

## Author Contributions:

SMMEA (Conceptualization, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing)

IH, AAMB, AHMS (Data curation, Formal Analysis, Investigation, Writing – review & editing)

NHA, STA, ERAS, JAA, AAM, RAAN, HSAA, AO (Data curation, Investigation, Validation, Writing – review & editing)

RMTK, SAA (Data curation, Formal Analysis, Visualization, Writing – review & editing)

HSEI (Methodology, Formal Analysis, Writing – review & editing)

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None.

## Conflict of Interest:

The authors declare no financial conflicts of interest related to dexmedetomidine or midazolam manufacturers. No conflict of interest was declared by any of the individual authors.

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