Efficacy of perioperative intravenous dexmedetomidine administration for the prevention of postoperative sore throat: a meta-analysis

Yuanhui Liu ⓘ, Dongmei Ai and Xiaobin Wang

Abstract

Objective: Postoperative sore throat (POST) is an undesirable intubation-related complication after surgery. Several studies have investigated the efficacy of perioperative intravenous dexmedetomidine administration for the prevention of POST, but the results have been inconsistent. We aimed to summarize all existing evidence and draw a more precise conclusion to guide future clinical work.

Methods: PubMed, Cochrane Library, EMBASE and China National Knowledge Infrastructure databases were comprehensively searched for all randomized controlled trials published before 1 February 2021 that investigated the efficacy of dexmedetomidine for the prevention of POST.

Results: Nine studies involving 400 patients were included in our meta-analysis. Compared with the control groups (i.e., saline and anesthetic drugs), perioperative intravenous use of dexmedetomidine significantly reduced the incidence of POST [risk ratio (RR): 0.56; 95% confidence interval (CI): 0.40–0.77; $I^2 = 0\%$) and coughing on the tube during extubation (RR: 0.58; 95% CI: 0.41–0.82; $I^2 = 0\%$). Additionally, patients in the dexmedetomidine group were more likely to develop bradycardia (RR: 2.46; 95% CI: 1.28–4.71; $I^2 = 0\%$) and hypotension (RR: 3.26; 95% CI: 1.14–9.33; $I^2 = 0\%$) during the administration of dexmedetomidine than those in the control group.

Conclusion: Perioperative intravenous administration of dexmedetomidine has a positive effect on the prevention of POST.

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Introduction

Postoperative sore throat (POST) caused by transient irritation to the local mucosa of the oropharynx or trachea after intubation-related manipulations[1–3] is one of the most undesirable intubation-related complications[4] with an estimated incidence of 14.5% to 65%.[1,5,6] POST can significantly reduce the patients' satisfaction level[7] and affect their recovery.[8,9] Moreover, POST increases the cost of hospitalization for patients. In 2015, Mayhood *et al.* reported that patients with POST experienced a longer length of stay in postanesthesia care units and were discharged almost 1 hour later from these facilities than those without POST.[10] Therefore, reducing the incidence and severity of POST is urgently needed to improve patients' postoperative satisfaction and alleviate their burden of hospitalization costs.

Recently, several pharmacological and non-pharmacological approaches for the prevention of POST have gained widespread acceptance in clinical settings. These include the use of smaller endotracheal tubes,[11] topical or intravenous application of corticosteroids or local anesthetics,[12,13] ketamine gargle,[14] topical application of magnesium[15] and others. Dexmedetomidine, a selective α2-adrenaline receptor agonist, has a dose-dependent sedative effect on respiration with minimal depressive effects. It also attenuates the inflammatory response and inhibits pain signals.[16–18]

Several clinical experiments have been conducted to investigate the efficacy and safety of dexmedetomidine for the prevention of POST; however, there are inconsistencies among the results of these studies. For instance, several studies concluded that perioperative intravenous use of dexmedetomidine significantly reduced the incidence of POST, whereas other clinicians reported opposite findings.[19]

We aimed to summarize all existing evidence and perform a meta-analysis to assess the efficacy of perioperative intravenous dexmedetomidine administration for the prevention of POST and draw a more convincing conclusion, thereby providing guidelines for future clinical work.

Methods and materials

We conducted this systematic review and meta-analysis according to the rules of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[20] PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses that can be used as a basis for reporting systematic reviews of different types of research. This manuscript is a review article and does not involve a research protocol requiring approval by a relevant institutional review board or ethics committee. Informed consent was also not applicable.

Search strategies

The PubMed, Cochrane Library, EMBASE and China National Knowledge Infrastructure (CNKI) databases were comprehensively searched for randomized

controlled clinical trials (RCTs) published before February 2020 that investigated the efficacy of dexmedetomidine for the prevention of POST. In addition, the reference lists of all included studies were checked for any potential additional publications. Searches were performed again just before the final analysis to identify any further studies meeting the inclusion criteria. Unpublished studies were not assessed. We used the keywords of *dexmedetomidine, alpha 2 adrenergic receptor agonists, endotracheal intubation, intratracheal intubation and intubation*. The detailed search strategies for each database were presented in Supplementary Table 1.

Inclusion and exclusion criteria

For a published article to be included in our study, it had to meet the following criteria: (1) an RCT design, (2) investigated the efficacy of perioperative intravenous dexmedetomidine administration for the prevention of POST and (3) available full-text and data.

Studies were excluded if they were duplicate publications, reviews or meta-analyses, editorials, abstracts, comments, case reports, meetings or animal experiments.

Data extraction

Two reviewers (Xiaobin Wang and Dongmei Ai) independently screened the titles, abstracts and full texts, then selected relevant studies. The same two reviewers independently extracted the data from the studies according to a prespecified protocol with any disagreement settled by a third reviewer (Yuanhui Liu).

The following items were extracted: name of the first author; publication year; type of surgery; sample size (classified by the participants' sex); participants' age; anesthesia technique and type of intratracheal tube; method of dexmedetomidine

use; and incidence of POST, coughing on the tube during the extubation process, postoperative hoarseness, bradycardia and hypotension.

The primary outcome of this meta-analysis was the incidence of POST, which was defined as sore throat after the extubation process with an unlimited pain level. The secondary outcomes included the incidence of coughing on the tube (the coughing response within the period from the first body movement to the time of extubation), postoperative hoarseness (alteration in vocal voice) and bradycardia (heart rate < 60 bpm) and hypotension (mean arterial pressure ≤ 60 mmHg or decreased by 30% compared with the baseline value) during the intervention.

Statistical synthesis and analysis

This meta-analysis was conducted using Review Manager (RevMan) Version 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Cochran's Q test and the statistical I^2 test were used to assess the statistical heterogeneity of the pooled results. If $0\% \leq I^2 < 25\%$, the results showed no heterogeneity; if $25\% \leq I^2 < 50\%$, the results showed a low level of heterogeneity; if $50\% \leq I^2 < 75\%$, the results showed a medium level of heterogeneity; and if $75\% \leq I^2 \leq 100\%$, the results showed a high level of heterogeneity. Data were pooled from all eligible RCTs, and the Mantel–Haenszel method was used to calculate the risk ratio (RR) with 95% confidence intervals (CIs) for these dichotomous outcomes. A pooled estimate of RRs was computed using the DerSimonian and Laird random-effects model. This model provides an appropriate estimate of the average treatment effect when studies are statistically heterogeneous, and it typically yields relatively wide CIs resulting in a more conservative statistical claim.

The risk of bias assessment was performed using the Cochrane Collaboration tool (Cochrane, London, UK). We conducted subgroup analyses by classifying these included studies according to their different control drugs and intubation methods.

In addition, a sensitivity analysis was performed to assess the robustness of the results by excluding specific studies and applying different effect models. Finally, a funnel plot was used to assess potential publication bias. All included studies were represented by small circles. The X-axis refers to the RR value for each study included in this meta-analysis. The Y-axis refers to the standard error, which reflects the sample size. In other words, the larger the standard error, the smaller the sample size. The dotted line parallel to the Y-axis represents the synthesized RR values. Two reviewers (Dongmei Ai and Xiaobin Wang) independently synthesized the data with any disagreement settled by a third reviewer (Yuanhui Liu). A p-value of less than 0.05 was considered statistically significant.

Results

Literature search

The literature search identified 968 articles, including nine articles[19–21,23–28] that met the inclusion criteria (Supplementary Figure 1). The characteristics of the nine studies involving 400 participants were summarized in Supplementary Table 2. All raw data extracted from the original articles were presented in the Supplemental Materials.

Bias assessment

As shown in the risk of bias graph (Supplementary Figure 2), one study[2] was rated as high risk for performance bias because the researcher did not follow the rules of blinding to participants and personnel. Regarding publication bias, there was no significant asymmetry in the funnel plot (Supplementary Figure 3), suggesting the absence of significant publication bias.

Primary outcome

After synthesizing the data, the results showed that perioperative intravenous administration of dexmedetomidine significantly reduced the incidence of POST (RR: 0.56; 95% CI: 0.40–0.77; $p = 0.0004$; $I^2 = 0\%$) (Figure 1).

Subgroup analysis

Awake nasal intubation vs. traditional oral intubation: Of the nine included studies, three studies[21,23,24] reported intravenous administration of dexmedetomidine among patients undergoing traditional oral intubation, whereas the patients in six studies[19,22,25–28] were infused with dexmedetomidine during awake nasal intubation. As shown in Figure 2, only patients in the traditional oral intubation group experienced a lower incidence of POST (RR: 0.51; 95% CI: 0.34–0.76; $p = 0.0009$; $I^2 = 0\%$) compared with those in the awake nasal intubation group (RR: 0.66; 95% CI: 0.36–1.20; $I^2 = 12\%$).

Different control groups: As shown in Figure 3, the infusion of dexmedetomidine did not show superiority over the administration of opioids (RR: 0.96; 95% CI: 0.47–1.99; $I^2 = 0\%$), midazolam plus opioids (RR: 0.40; 95% CI: 0.08–1.92; $I^2 = 48\%$) or propofol (RR: 0.40; 95% CI: 0.09–1.83). However, it had a positive effect on the prevention of POST compared with an equal volume of normal saline (RR: 0.51; 95% CI: 0.34–0.76; $p = 0.0009$; $I^2 = 0\%$).

Secondary outcomes

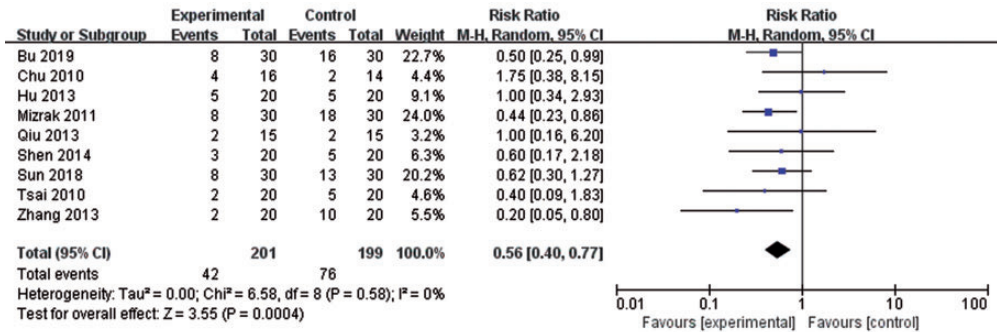We also synthesized data regarding coughing on the tube during the extubation

Figure 1. Meta-analysis of nine randomized controlled trials on the perioperative administration of dexmedetomidine for the prevention of postoperative sore throat.
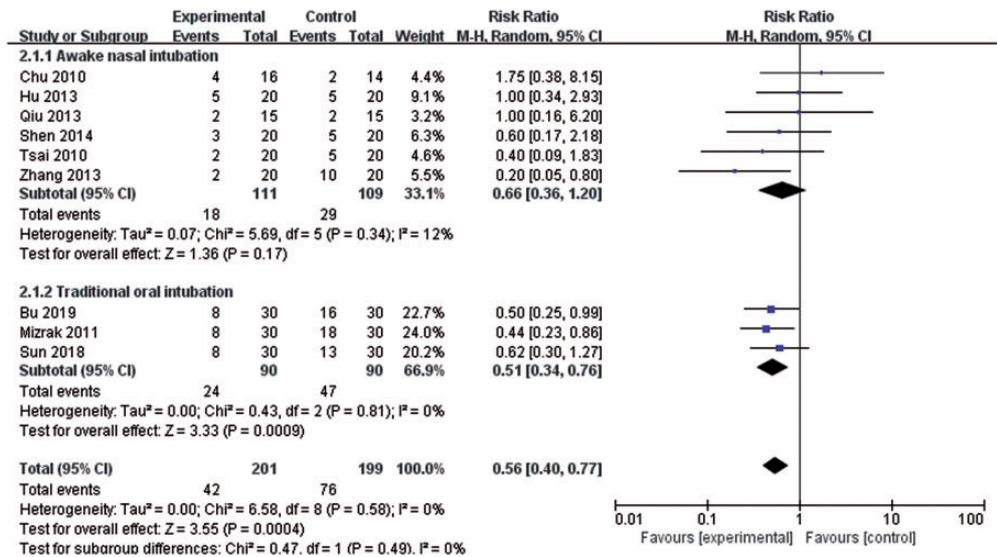CI, confidence interval.

Figure 2. Subgroup analysis by different intubation methods.
CI, confidence interval.

process, postoperative hoarseness and hypotension and bradycardia during the infusion of dexmedetomidine. **Hypotension:** Patients in the dexmedetomidine group were more likely to experience hypotension during the administration of dexmedetomidine (RR: 3.26; 95% CI: 1.14–9.33; p = 0.03; $I^2 = 0\%$) (Supplementary Figure 4). **Bradycardia:** As shown in Supplementary Figure 5, patients

in the dexmedetomidine group had a higher incidence of bradycardia than those in the control group (RR: 2.46; 95% CI: 1.28–4.71; p = 0.007; $I^2 = 0\%$). **Postoperative hoarseness:** The synthesized data showed that there was no significant difference between the dexmedetomidine group and the control group regarding the complication of postoperative hoarseness (RR: 0.79;
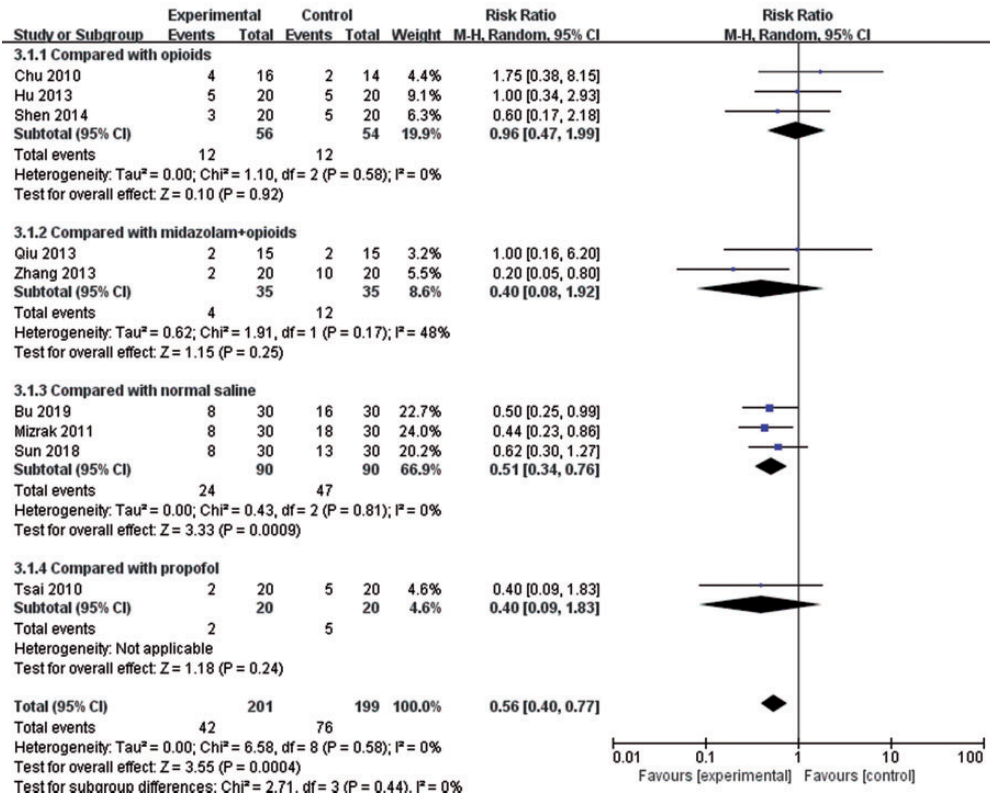
Figure 3. Subgroup analysis by different adjuvant drugs.
CI, confidence interval.

95% CI: 0.41–1.50; $I^2 = 0\%$) (Supplementary Figure 6). **Coughing on the tube:** Another advantage was that perioperative infusion of dexmedetomidine had a positive effect on the prevention of coughing on the tube during the extubation process compared with the control group (RR: 0.58; 95% CI: 0.41–0.82; p = 0.002; $I^2 = 0\%$) (Supplementary Figure 7).

Sensitivity analysis

We performed a sensitivity analysis by excluding the study of *Bu et al,*[23] which was rated as high risk for performance bias (Supplementary Figure 8). We also changed the calculation model from a random-effects model to a fixed-effects

model and re-performed the analysis (Supplementary Table 3). The results were similar after both sensitivity analyses, indicating the robustness of our meta-analysis.

Discussion

POST is an important risk factor affecting the recovery of patients after surgery.[29] Several studies have reported various methods to reduce the incidence and severity of POST.[11,13,15] Dexmedetomidine selectively activates α2-adrenaline receptors in the locus coeruleus and is a derivative of medetomidine, which inhibits the sympathetic nervous system and reduces the release of norepinephrine.[30] It also attenuates the inflammatory response, significantly

improves the sleep quality of critically ill patients, induces analgesia and reduces anesthetic requirements. Accordingly, it has been widely used as an adjunctive drug by anesthetists during clinical procedures and surgeries.[17,18,31,32]

Tracheal intubation may be one mechanism contributing to POST. Tracheal intubation, the most commonly used airway management method during general anesthesia, is safe for patients and convenient for anesthetists to manage patients' airways. However, the manipulations in the oral cavity may cause transient irritation to the local mucosa of the oropharynx or trachea.[1] During inhalational anesthesia with volatile anesthetic drugs, the intracuff pressure is reportedly increased by the diffusion of these volatile anesthetic drugs into the cuff, resulting in the formation of a local mucosa lesion.[2,3] These injuries may cause several undesirable complications related to intubation, especially POST. POST is one of the most undesirable intubation-related complications[4] that can result in a lower patient satisfaction level,[7] longer length of hospital stay and longer recovery phase. Because of its anti-inflammatory effects, dexmedetomidine can be used to reduce the incidence and severity of POST.

Our meta-analysis based on a sample size of nine original studies suggested that only patients in the traditional oral intubation group experienced a lower incidence of POST, and no positive effect of dexmedetomidine on the prevention of POST was observed in the awake nasal intubation subgroup. The subgroup analysis based on different control drugs suggested the superiority of dexmedetomidine over normal saline for the prevention of POST; however, there was no significant difference between dexmedetomidine and other anesthetic drugs, such as fentanyl, sufentanil, midazolam plus fentanyl or propofol. Of note, the three studies that performed oral intubation all used normal saline as the control medication.[19,23,24] In the awake nasal intubation subgroup, the control groups of all six[20,21,25-28] studies were anesthetic drugs, including fentanyl, sufentanil, midazolam plus fentanyl and propofol, instead of normal saline because sedation was induced first during awake intubation. As a result, they could not compare dexmedetomidine with normal saline due to its lack of a sedative effect.

Hypotension and bradycardia are the most common adverse effects of dexmedetomidine and are caused by its inhibition of the sympathetic nervous system.[33] It is not surprising that patients in the experimental group experienced a higher incidence of hypotension and bradycardia. However, these are transient adverse effects, and all patients in the included RCTs were effectively treated with atropine and vasoactive agents.[34] Previous studies have demonstrated that the perioperative use of dexmedetomidine improved patient prognosis and shortened their length of hospital stay without long-term adverse events.[35] Coughing on the tube may be life-threatening due to increased cerebral, intrathoracic, intraocular, intraabdominal and blood pressures, which may cause intracranial hemorrhage, postoperative wound hemorrhage, myocardial ischemia, tachycardia, bronchospasm and other life-threatening complications.[36,37] Our results suggested that perioperative administration of dexmedetomidine significantly reduced the incidence of coughing on the tube during the extubation process, mostly because of its sedative effects.

The incidence of hoarseness after surgery was not reduced by the administration of dexmedetomidine. Sound production is a complicated process[38] because it requires the use of several structures in a coordinated manner, such as the lungs, vocal tracts, vocal cords and vocal cavity.[39] Vocal complications, such as hoarseness or vocal failures, may occur after inappropriate voice

use and habits or vocal distortion.[38] It is understandable that patients suffered hoarseness after surgery because of transient vocal distortion, which may be caused by compression of their vocal cords by the endotracheal tube during surgery. This may explain why the anti-inflammatory and sedative effects of dexmedetomidine did not reduce the incidence of postoperative hoarseness.

Regarding the dosage of medication, four studies[19,21,26,27] reported a single bolus administration of 0.5 μg/kg or 1 μg/kg dexmedetomidine over 10 to 15 minutes before induction, whereas patients in the experimental group of the other five studies[20,23–25,27] were administered a loading dose of 0.5 μg/kg to 1.5 μg/kg for 10 minutes followed by the continuous infusion of dexmedetomidine at a rate of 0.4 μg/kg/hour or 0.5 μg/kg/hour until the end of surgery or 30 minutes before the anticipated end of surgery.

Although there was no significant heterogeneity in our study, we still performed sensitivity analyses by excluding the high-risk study[23] and changing the calculation model (random-effects model versus fixed-effects model). The results of the sensitivity analyses were similar to our previous results, indicating the stability and robustness of our meta-analysis.

Several limitations in our study should be acknowledged. First, the sample size of the nine RCTs in our study was relatively small. However, the practical and precise strategies used for comprehensive searches of four official databases, clear inclusion and exclusion criteria and strict consideration of study quality might have compensated for this limitation. Second, among the six studies comparing dexmedetomidine with other anesthetic drugs, only one study had a control group with propofol, two studies reported midazolam plus opioids as a control group, and three studies included control groups with opioids.

All six studies were performed among patients undergoing awake intubation and included relatively small sample sizes. Therefore, further studies should be focused on comparing dexmedetomidine with different anesthetic drugs among patients undergoing awake intubation. Third, we stated that perioperative intravenous administration of dexmedetomidine reduced the incidence of coughing on the tube based on the patient populations of the studies in our meta-analysis who would likely be at low risk for these adverse events. The statements above regarding this being a relevant and important issue are applicable to high-risk patients. Therefore, further studies should be focused on patients that are at high risk, as mentioned in our discussion on the incidence of coughing on the tube. Finally, six of the nine articles analyzed were related to patients undergoing oral surgery under awake nasal intubation, and there was a limited number of studies reporting dexmedetomidine use during different types of surgeries under traditional oral intubation. Thus, future studies should address this research gap.

Conclusion

Perioperative intravenous administration of dexmedetomidine has a positive effect on the prevention of POST. However, this positive effect may only be evident among patients undergoing traditional oral intubation. This article contributes to the existing literature on treatment options for POST and may guide clinicians during their daily work.

Declaration of conflicting interest

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Supplemental material

Supplemental material for this article is available online.

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