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REVIEW ARTICLE/BRIEF REVIEW

Preoperative intravenous dexamethasone prevents tracheal intubation-related sore throat in adult surgical patients: a systematic review and meta-analysis

La dexaméthasone intraveineuse préopératoire évite le mal de gorge dû à l'intubation trachéale chez des patients chirurgicaux adultes : revue systématique de la littérature et méta-analyse

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Abstract

Background *Postoperative sore throat related to tracheal intubation negatively affects patient recovery and satisfaction. Previous reviews suggested that intravenous dexamethasone diminishes postoperative sore throat. Nevertheless, they comprised a small number of studies with inconsistencies in outcome reporting. We performed a systematic review and meta-analysis to assess the efficacy and safety of preoperative intravenous dexamethasone in preventing postoperative sore throat in adult patients.*

Methods *We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to August 24, 2018. We included randomized-controlled trials that assessed the efficacy and safety of intravenous dexamethasone in adult surgical patients who required general anesthesia and endotracheal intubation. Our primary outcomes were the incidence and severity of sore throat at 24 hr after surgery/extubation and adverse events. We pooled the data using a random-effects model. We conducted a trial sequential analysis (TSA) on the incidence of sore throat.*

Results *We included 15 randomized-controlled trials involving 1,849 patients. In comparison with non-analgesic methods, intravenous dexamethasone was associated with a reduced incidence (risk ratio, 0.62; 95% confidence interval [CI], 0.51 to 0.75) and severity (standardized mean difference, − 1.06; 95% CI, − 1.80 to − 0.33) of postoperative sore throat. Serious adverse events were not associated with intravenous dexamethasone administration in the four studies where this was assessed. The TSA indicated that the evidence regarding the incidence of postoperative sore throat is adequate.*

Conclusions *Our study indicates that preoperative intravenous administration of dexamethasone alleviates postoperative sore throat more effectively than non-analgesic methods.*

Trial registration *PROSPERO (CRD42018086697); registered 29 January, 2018.*

Résumé

Contexte *Le mal de gorge postopératoire lié à l'intubation trachéale a une répercussion négative sur la récupération et la satisfaction des patients. Des synthèses antérieures ont suggéré que la dexaméthasone intraveineuse diminue le mal de gorge postopératoire. Néanmoins, elles n'incluaient qu'un petit nombre d'études avec des incohérences dans la présentation des résultats. Nous avons réalisé une revue systématique de la littérature et une méta-analyse pour évaluer l'efficacité et l'innocuité de la dexaméthasone intraveineuse préopératoire pour prévenir le mal de gorge postopératoire chez des patients adultes.*

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Méthodes *Nous avons recherché les essais contrôlés pertinents dans PubMed, EMBASE et le Cochrane Central Register depuis leur création jusqu'au 24 août 2018. Nous avons inclus les essais contrôlés randomisés ayant évalué l'efficacité et l'innocuité de la dexaméthasone intraveineuse chez des patients chirurgicaux adultes ayant nécessité une anesthésie générale et une intubation endotrachéale. Nos principaux critères d'évaluation étaient l'incidence et la sévérité du mal de gorge 24 heures après la chirurgie/extubation et les événements indésirables. Nous avons regroupé les données en utilisant un modèle à effets aléatoires. Nous avons mené une analyse séquentielle des essais sur l'incidence du mal de gorge.*

Résultats *Nous avons inclus 15 essais contrôlés randomisés ayant réuni 1 849 patients. Comparativement aux méthodes sans analgésiques, la dexaméthasone a été associée à une diminution de l'incidence (rapport de risque, 0,62; intervalle de confiance [IC] à 95 % : 0,51 à 0,75) et de la sévérité (différence des moyennes standardisées : -1,06; IC à 95 %, -1,80 à -0,33) du mal de gorge postopératoire. Aucun événement indésirable grave n'a été associé à l'administration intraveineuse de dexaméthasone dans les quatre études où ils ont été évalués. L'analyse séquentielle des essais a indiqué que la preuve concernant l'incidence du mal de gorge postopératoire est adéquate.*

Conclusions *Notre étude indique que l'administration intraveineuse préopératoire de dexaméthasone soulage plus efficacement le mal de gorge postopératoire que les méthodes sans analgésiques.*

Enregistrement de l'essai clinique *PROSPERO (CRD42018086697); enregistré 29 janvier 2018.*

Postoperative sore throat is common in patients who have undergone surgery under general anesthesia/endotracheal intubation, with a reported incidence of up to 68%.[1-7] It negatively affects patient recovery and satisfaction,[4,7-10] and considerable efforts have been undertaken to understand and treat this phenomenon. Mucosal trauma, erosion, and inflammation due to endotracheal intubation are proposed etiologies.[11-15] Randomized-controlled trials have suggested that inhaled[16] or topical[17] corticosteroids, topical benzydamine hydrochloride,[18] and topical licorice may help to prevent postoperative sore throat. Intravenous dexamethasone administration has also been proposed as a prophylactic measure. Two systematic reviews, based on data available in 20[13,19,20] suggested that preoperative intravenous dexamethasone helps to prevent postoperative sore throat. Nevertheless, those reviews comprised a limited number of studies and the outcomes could not be appropriately pooled because the reporting methods used by the original studies were inconsistent.

Since those reviews, further studies have assessed the effect of dexamethasone treatment on postoperative sore throat and these are better suited for pooling of their findings. Therefore, we performed a systematic review and meta-analysis of the efficacy and safety of preoperative intravenous dexamethasone administration to prevent postoperative sore throat in adults subjected to tracheal intubation for general anesthesia. We focused on the incidence and severity of postoperative sore throat, and reported adverse events and postoperative cough and hoarseness.

Methods

We adhered to the Cochrane Collaboration methodology[21] and PRISMA statement[22] for the conduct and reporting of this systematic review. Our protocol is registered at PROSPERO (CRD42018086697).

Eligibility criteria

Type of studies

We included randomized-controlled studies that compared preoperative intravenous dexamethasone with non-analgesic or active control treatment in adults who underwent elective surgery under general anesthesia. We excluded observational studies and quasi-randomized and non-randomized controlled trials.

Type of participants

We included adult patients aged $\geq$ 18 yr who underwent elective surgery under general anesthesia and endotracheal intubation. We excluded patients whose general anesthesia care included a supraglottic airway device or those who underwent head and neck surgery that might induce confounding pain in the laryngopharynx.

Type of interventions

The intervention included dexamethasone that was intravenously administered to prevent sore throat or postoperative pain elsewhere. We placed no restrictions on the dose or the number of doses of dexamethasone, as long as it was administered preoperatively. We excluded studies that administered dexamethasone postoperatively.

Comparators included non-analgesic methods or active controls that were administered preoperatively. Non-

analgesic strategies included no endotracheal tube lubrication, usual care, or the use of drugs without known analgesic potency, such as intravenous saline. Active controls involved agents that have known prophylactic effects against postoperative sore throat, such as topical ketamine or an analgesic combined with intravenous dexamethasone. We placed no restrictions on the dose or the number of doses of the comparators. We excluded studies that administered non-analgesic methods or active controls postoperatively.

Types of outcome measures

Our primary outcomes included 1) the incidence and 2) severity of postoperative sore throat at 24 hr after surgery/extubation and 3) adverse events. Because there is no established definition for postoperative sore throat, we accepted the investigators' definitions. Studies on postoperative sore throat frequently use a four-level classification system: none, mild, moderate, and severe. When a study used this classification system, we calculated the incidence of sore throat from the sum of mild, moderate, and severe cases. We accepted each study author's definition of adverse events.

Our secondary outcomes included 1) the incidence of moderate or severe sore throat, 2) cough, and 3) hoarseness at 24 hr after surgery/extubation. Since there are no established universal definitions for postoperative cough or hoarseness, we accepted the investigators' definitions. We calculated the incidence of cough or hoarseness based on the sum of mild, moderate, and severe cases, according to the commonly-used classification system.

Search strategy

We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for eligible studies. We reviewed the reference lists of the included publications and previous systematic reviews, and searched Google Scholar and ClinicaTrials.gov to identify further eligible studies. We did not search the grey literature. We placed no restrictions on publication status or language. Our search strategy is presented in Table 1. We updated the search on May 3, 2018.

Study selection

Two authors (A.K. and H.M.) independently, and in duplicate, reviewed the articles retrieved through the search and selected the eligible ones. We resolved disagreements by consensus ($\kappa = 0.92$).

Table 1 Search strategy

#1. pharyngitis [Mesh]
#2. "intubation, intratracheal"[Mesh]
#3. (sore* or inflamm* or infect*) near throat
#4. pharyngit*
#5. (endotracheal OR intratracheal) near intub*
#6. #1 OR #2 OR #3 OR #4 OR #5
#7. "adrenal cortex hormones"[MeSH Terms]
#8. (corticoid* or corticosteroid* or glucocorticoid*) tw
#9. prednisone
#10. prednisolone
#11. methylprednisolone
#12. dexamethasone
#13. cortisone
#14. hydrocortisone
#15. triamcinolone
#16. beclomethasone
#17. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18. randomized controlled trial [pt].
#19. controlled clinical trial [pt]
#20. randomized [tiab]
#21. placebo [tiab]
#22. drug therapy [sh].
#23. randomly [tiab]
#24. trial [tiab]
#25. groups [tiab]
#26. #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
#27. #6 AND #17 AND #26

Data extraction

These two authors then independently extracted the following data from each study: patient characteristics (age, sex, and American Society of Anesthesiologists [ASA] physical status), study characteristics (country and type of surgery), interventions used (dexamethasone dose, if reported, and comparators), and outcomes of interest.

Risk of bias assessment

The same authors independently and in duplicate evaluated the risk of bias with the Cochrane risk of bias assessment tool.[21] We considered a study to be at a low risk of performance bias when the original study blinded participants to the intervention they received until all assessments were complete, given that sore throat is a subjective outcome. We also reviewed for conflicts of interest or industry sponsorship. We resolved any inconsistency through discussion ($\kappa = 0.53$–1.0). When an e-mail address was available, we contacted the authors

of the original study for more information. Specifically, we attempted to retrieve information regarding the methodology of each trial and the outcomes of interest that were not presented in the articles. We deemed the authors to be unresponsive if they did not reply after three contact attempts.

Statistical analysis

We calculated the risk ratio (RR) and standardized mean difference (SMD) for dichotomous and continuous outcomes, respectively. When a trial had zero events in either arm, we applied continuity corrections by adding 0.5 to each cell of the 2 × 2 tables from the trial.[23] When a study presented the data as the median with interquartile range, we converted the values to the mean and standard deviation using the method proposed by Wan *et al.*[24] We pooled the data using the DerSimonian and Laird random-effects model.[25] We assessed statistical heterogeneity using Q and I^2 statistics.[26] We deemed $I^2 \geq 50\%$ as substantial statistical heterogeneity and conducted subgroup analysis by the type of non-analgesic method. Since there is no evidence to suggest that non-analgesic methods work similarly, we conducted subgroup analysis by the type of comparator. We anticipated that there would be no difference in effect size between the subgroups by the type of comparator. Because the number of studies for each outcome was less than ten, we did not test for publication bias.[21]

We performed primary analyses by the type of comparator. We pooled the data into a single arm when a study examined groups based on different dexamethasone doses. We conducted sensitivity analyses by excluding trials at an unclear or high risk of bias with regard to sequence generation, allocation concealment, blinding of participants and outcome assessors, and conflicts of interest/industry sponsorship. We also conducted another sensitivity analysis by presenting the pooled outcomes of risk difference.

We conducted subgroup analysis and meta-regression to estimate the dose-response relationship for the incidence of postoperative sore throat, which had been *a priori* planned in case the number of studies was sufficient and a variety of regimens were used. Unless the mean body weight for the dexamethasone group was reported, we converted the dexamethasone dose to the equivalent value in $mg \cdot kg^{-1}$ based on the assumption that the mean body weight was 60 kg (most eligible studies were conducted outside North America and reported approximately 60 kg as the mean body weight of participants). We conducted subgroup analysis according to the following dexamethasone doses: low dose (0.1 $mg \cdot kg^{-1}$) and intermediate dose (0.11–0.20 $mg \cdot kg^{-1}$).[27] We anticipated that the preventive effect of the intermediate dexamethasone dose might be larger than that of the lower dexamethasone dose.

To evaluate our findings' robustness against type 1 and type 2 errors, we conducted trial sequential analysis (TSA) with the O'Brien-Fleming alpha-spending function method.[28,29] We retained a 5% risk of type 1 errors and a power of 80%. Furthermore, we obtained the required information size according to relative risk reduction of 20% for postoperative sore throat, which is the most conservative value used for the power calculations employed in the included trials.[30] The threshold for statistical significance was set at $P < 0.05$. We used Stata SE, version 15.1 (StataCorp., College Station, TX, USA) to perform conventional meta-analyses, while we used the TSA software, version 0.9 beta (Copenhagen Trial Unit, Copenhagen, Denmark) to conduct the TSA.

Results

Overview of included studies

Our database search initially produced 1,892 titles and abstracts, and an additional search found five articles. We ultimately included 15 randomized-controlled trials involving 1,849 study participants for the analysis after applying our inclusion and exclusion criteria[30-44] (Fig. 1).

The mean age for the study participants ranged from 28–62 yr, and the proportion of females ranged from 16%–100% (Table 2). Twelve and three trials included patients with an ASA status of I–II and III, respectively. Eight trials listed the types of surgery as follows[30,32-35,38-40,42,43]: breast and abdominal surgery (including laparoscopic cholecystectomy), orthopedic surgery (including the limbs and spine), gynecologic surgery, middle ear surgery, and thoracic surgery (open pulmonary resection or video-assisted thoracoscopic surgery). The median sample size was 110 (range, 49–226).

Intravenous dexamethasone was administered as a single-dose infusion prior to surgery in all studies. The dose was fixed in eight studies (4 mg in one study[36]; 8 mg in five studies,[32,36,39,42,44] and 10 mg in three studies[34,40,41]) and was determined according to patient's body weight in five studies (0.05 $mg \cdot kg^{-1}$ in one study[33]; 0.1 $mg \cdot kg^{-1}$ in three studies,[30,33,35] and 0.2 $mg \cdot kg^{-1}$ in five studies).[30,31,35,37,43] The remaining study did not specify the dose. Intravenous saline was used as a non-analgesic control in 12 studies. Comparator agents with known analgesic effects included betamethasone[38] and triamcinolone gel[41] and were applied over endotracheal tubes (one study each); ketamine gargles[37,43] or ketamine gargles combined with intravenous dexamethasone[37,43] (two studies); and intravenous lidocaine[32] or

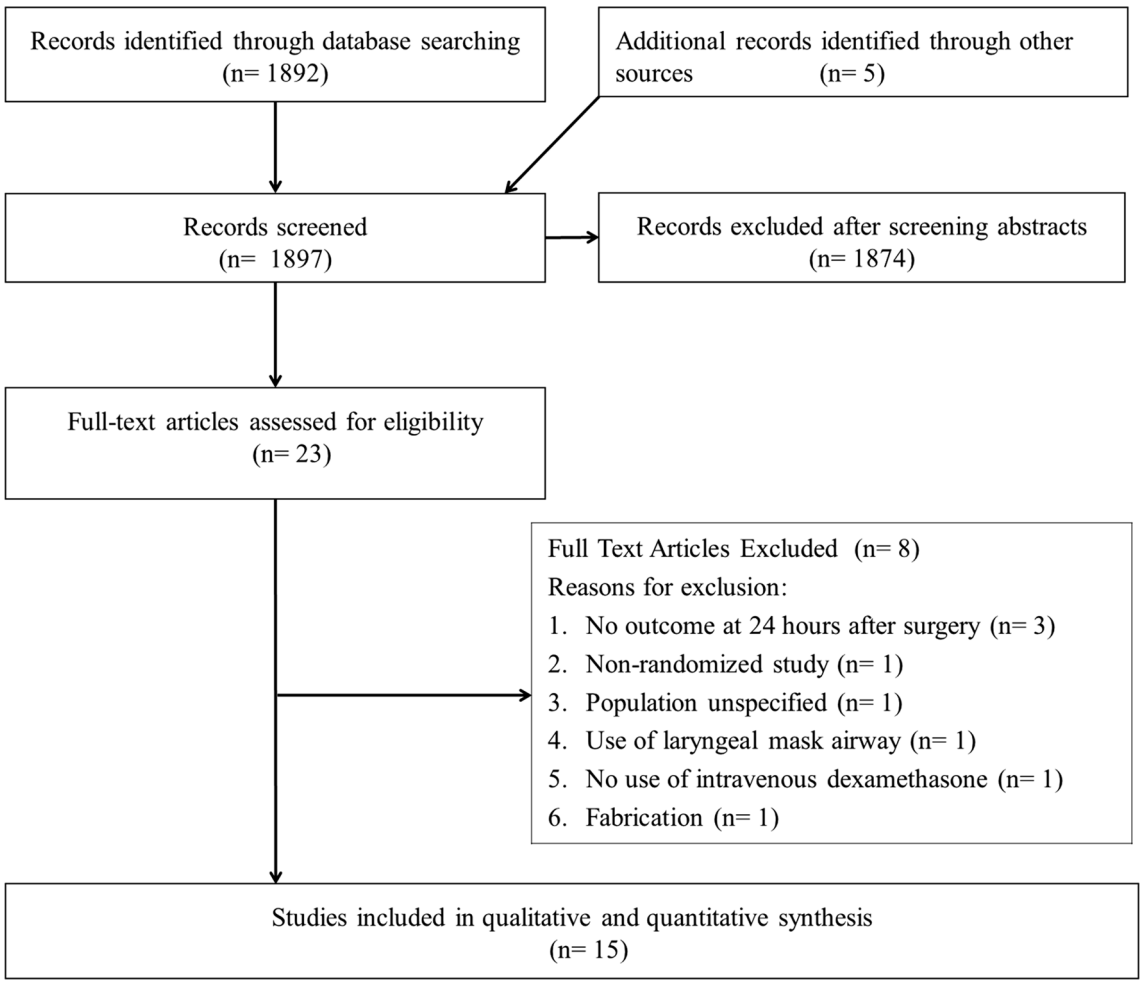

Fig. 1 Flow diagram illustrating the literature screening process and selection of studies

acetaminophen[34] combined with intravenous dexamethasone (one study each). Four trials were performed in South Korea,[30,32,34,35] three in India,[31,39,43] two each in Iran[37,38] and Thailand,[36,42] and one each in China,[40] Indonesia,[41] Nepal,[44] and the United States of America.[33] All studies were published as full text between 2007 and 2018. All studies but two were reported in English, with the remaining ones published in Chinese[40] and Indonesian.[41]

Eight studies used a four-level classification system to rate the severity of postoperative sore throat and confirm its presence.[30,31,34,37,40,41,43,44] Two studies used a visual analog scale[35,39] while two used a numeric rating scale to rate the severity.[33,42] Five studies reported the incidence of postoperative sore throat.[30,32,35,36,38] We contacted 11 study authors with a valid e-mail address for further information, and six responded.[31,32,34,36,41,44] Most studies were at relatively low risk of bias, as shown in Table 3. Nevertheless, in one study, the duration of patient intubation in the dexamethasone group was significantly longer compared with the control group (142 *vs* 121 min).[42] As duration of intubation is a known risk factor for postoperative sore throat,[8] we considered this study to have a high risk of bias.

Dexamethasone vs non-analgesic controls

Incidence of postoperative sore throat

Nine studies comprising 983 participants provided data on the incidence of sore throat at 24 hr after surgery/extubation.[30,31,35-38,40,43,44] Intravenous administration of dexamethasone was associated with a lower incidence of postoperative sore throat (RR, 0.62; 95% CI, 0.51 to 0.75; $P < 0.001$; df = 7; $I^2 = 0\%$; Fig. 2).

Severity of postoperative sore throat

Four studies including 431 participants provided data on the severity of sore throat at 24 hr after surgery/extubation.[33,35,39,42] Intravenous administration of dexamethasone was associated with a lower severity of

Table 2 Characteristics of included studies

Study/year	Country	Sample size (% female)	Mean age (yr)	ASA-PS	Surgery	ETT size (mm)	Cuff pressure (cmH_2O)	Intervention	Duration (min)	Postoperative sore throat measurement at 24 hr after surgery
Thomas (2007)[39]	India	110 (51)	43	I, II	Abdominal and limb surgery	8–8.5 (m) 7–7.5 (f)	NR	1. Iv dexamethasone 8 mg 2. Saline 2 mL	Surgery: 133	VAS (severity)
Park (2008)[35]	South Korea	166 (34)	47	I–III	Video-assisted thoracoscopic surgery or open pulmonary resection	37 Fr DLT (m) 35 Fr DLT (f)	NR	1. Iv dexamethasone 0.1 $mg{\cdot}kg^{-1}$ 2. Iv dexamethasone 0.2 $mg{\cdot}kg^{-1}$ 3. Saline placebo 4 mL	Intubation: 159	No. of incidence VAS (severity)
De Oliveira Jr (2011)[33]	USA	106 (100)	37	I, II	Outpatient gynecological laparoscopy	NR	NR	1.Iv dexamethasone 0.05 $mg{\cdot}kg^{-1}$ 2. Iv dexamethasone 0.1 $mg{\cdot}kg^{-1}$ 3. Saline placebo 100 mL	Surgery: 83	NRS (severity)
Bagchi (2012)[31]	India	95 (65)	37	I, II	Elective surgery	8–8.5 (m) 7–7.5 (f)	NR	1. Iv dexamethasone 0.2 $mg{\cdot}kg^{-1}$ 2. Saline 4 mL	Surgery: 115	Four-level scoring system (incidence/severity)
Ruangsin (2012)[36]	Thailand	105 (84)	42	I, II	Elective surgery	8 (m) 7.5 (f)	NR	1. Iv dexamethasone 4 mg 2. Iv dexamethasone 8 mg 3. Saline 2 mL	Surgery: 116	No. of incidence
Tabari (2013)[38]	Iran	225 (84)	42	I, II	Elective abdominal surgery	8.0 (m) 7.0 (f)	NR	1. Betamethasone 0.05% gel 2. Iv dexamethasone 3. Saline	Surgery: 101	No. of incidence
Safavi (2014)[37]	Iran	140 (16)	32	I, II	Elective surgery	7–8	18–22	1. Iv dexamethasone 0.2 $mg{\cdot}kg^{-1}$ 2. Ketamine (40 mg) gargle 3. Saline 4. Iv dexamethasone 0.2 $mg{\cdot}kg^{-1}$ + ketamine (40 mg) gargle	Surgery: 73 Intubation: 102 Anesthesia: 80	Four-level scoring system (incidence/severity)
Wijaya (2015)[41]	Indonesia	121 (61)	41	I, II	Elective surgery	7.5 (m) 7.0 (f)	< 26	1. Triamcinolone paste 2. Iv dexamethasone 10 mg	Surgery: 142	Four-level scoring system (incidence/severity)
Areeruk (2016)[42]	Thailand	49 (100)	43	I, II	Gynecological laparotomy surgery	NR	NR	1. Iv dexamethasone 8 mg 2. Saline	Surgery 111 Anesthesia: 132	NRS

Table 2 continued

Study/year	Country	Sample size (% female)	Mean age (yr)	ASA-PS	Surgery	ETT size (mm)	Cuff pressure (cmH_2O)	Intervention	Duration (min)	Postoperative sore throat measurement at 24 hr after surgery
Cho (2016)[32]	South Korea	70 (100)	44	I, II	Breast mass excision	7	< 20	1. Iv dexamethasone 8 mg 2. Iv dexamethasone 8 mg + lidocaine 3 $mg \cdot kg^{-1}$	Surgery: 35 Intubation: 55	No. of incidence NRS (severity)
Lee (2016)[30]	South Korea	147 (61)	62	I–III	Lumbar spine surgery	7.5–8 (m) 7–7.5 (f)	10–20	1. Iv dexamethasone 0.1 $mg \cdot kg^{-1}$ 2. Iv dexamethasone 0.2 $mg \cdot kg^{-1}$ 3. Saline 4 mL	Intubation: 154 Anesthesia: 161	No. of incidence Four-level scoring system (incidence/severity)
Wang (2016) [40]	China	100 (48)	52	I, II	Laparoscopic cholecystectomy	NR	NR	1. Iv dexamethasone 10 mg 2. Saline 2 mL	NR	Four-level scoring system (incidence/severity)
Lee (2017)[34]	South Korea	226 (49)	55	I–III	Urologic surgery	7.5 (m) 7 (f)	20	1. Iv dexamethasone 10 mg 2. Iv dexamethasone 10 mg + paracetamol 1000 mg	Intubation: 172	Four-level scoring system (incidence/severity)
Manandhar (2018) [44]	Nepal	110 (46)	44	I, II	Elective surgery	7.5 (m) 7 (f)	< 30	1. Iv dexamethasone 8 mg in 4 cc 2. Saline 4 mL	Intubation: 77	Four-level scoring system (incidence/severity)
Raikwar (2018)[43]	India	80 (48)	29	I, II	Middle ear surgery	8–8.5 (m) 7–7.5 (f)	18–22	1. Iv dexamethasone 0.2 $mg \cdot kg^{-1}$ 2. Saline (Iv and gargle) 3. Ketamine (40 mg) gargle 4. Iv dexamethasone 0.2 $mg \cdot kg^{-1}$ + ketamine (40 mg) gargle	Surgery: 83 Anesthesia: 101	Four-level scoring system (incidence/severity)

ASA-PS = American Society of Anesthesiologists-physical status; DLT = double-lumen endotracheal tube; ETT = endotracheal tube; f = female; Iv = intravenous; m = male; NR = not reported; NRS = numeric rating scale; USA = United States of America; VAS = visual analogue scale

Table 3 Risk of bias in included studies

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other source of bias	Industry sponsorship/conflict of interest
Thomas (2007)[39]	Low	Low	Low	Low	Low	Low	Low	Unclear
Park (2008)[35]	Low	Low	Low	Low	Low	Low	Low	None
De Oliveira Jr (2011)[33]	Low	Low	Low	Low	Low	Low	Low	None
Bagchi (2012)[31]	Low	Low	Low	Low	Low	Low	Low	Unclear
Ruangsin (2012)[36]	Low	Unclear	Low	Low	Low	Low	Low	None
Tabari (2013)[38]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear
Safavi (2014)[37]	Low	Unclear	Low	Low	Low	Low	Low	Unclear
Wijaya (2015)[41]	Low	Unclear	Low	Low	Low	Low	Low	Unclear
Areeruk (2016)[42]	Low	Low	Low	Low	Low	Low	High	Unclear
Cho (2016)[32]	Low	Low	Low	Low	Low	Low	Low	Unclear
Lee (2016)[30]	Low	Low	Unclear	Low	Low	Low	Low	None
Wang (2016)[40]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Lee (2017)[34]	Low	Low	Low	Low	Low	Low	Low	None
Manandhar (2018)[44]	Low	Low	Low	Low	Low	Low	Low	Unclear
Raikwar (2018)[43]	Low	Low	Low	Low	Low	Low	Low	None

postoperative sore throat (SMD, −1.06; 95% CI, −1.80 to −0.33; $P = 0.005$; df = 3; $I^2 = 91\%$; Fig. 3).

Adverse events

Four studies reported on adverse events. One study reported that the frequency of adverse events during 24 hr after surgery was comparable between the dexamethasone and control groups,[39] another noted that no adverse event was associated with dexamethasone,[35] the third reported that there were no differences in the incidence of local or systemic side effects between the dexamethasone and control groups,[37] and the fourth reported that there were no local or systemic adverse events, except one episode of vomiting in the non-analgesic control group.[43]

Secondary outcomes

Moderate and severe postoperative sore throat

Six studies involving 562 participants provided data on the incidence of moderate or severe sore throat at 24 hr after surgery/extubation.[30,31,36,40,43,44] Intravenous administration of dexamethasone was associated with a lower incidence of moderate or severe postoperative sore throat (RR, 0.10; 95% CI, 0.03 to 0.39; $P = 0.001$; df = 4; $I^2 = 0\%$; Fig. 4).

Postoperative cough

Three studies comprising 349 participants provided data on the incidence of cough at 24 hr after surgery/extubation.[30,31,33] Intravenous administration of dexamethasone was associated with a reduced incidence

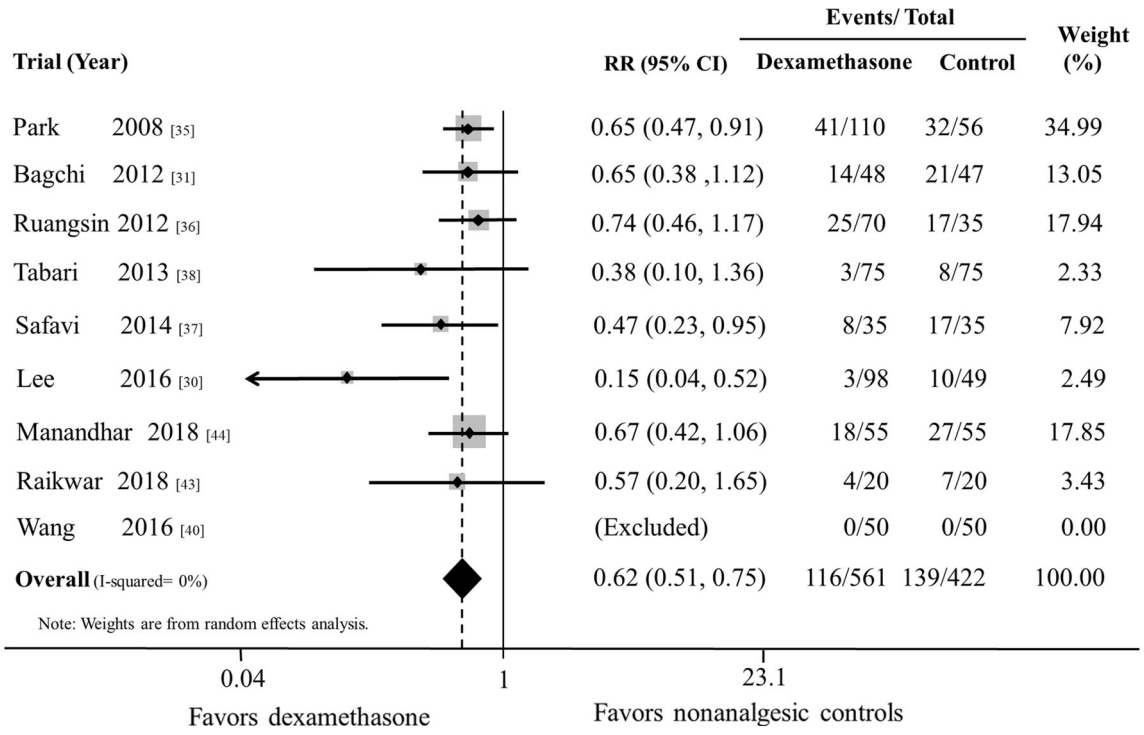

Fig. 2 Forest plot for the incidence of postoperative sore throat at 24 hr after surgery/extubation. The plot shows decreased incidence in patients treated with *iv* dexamethasone compared with non-analgesic control. RR = risk ratio

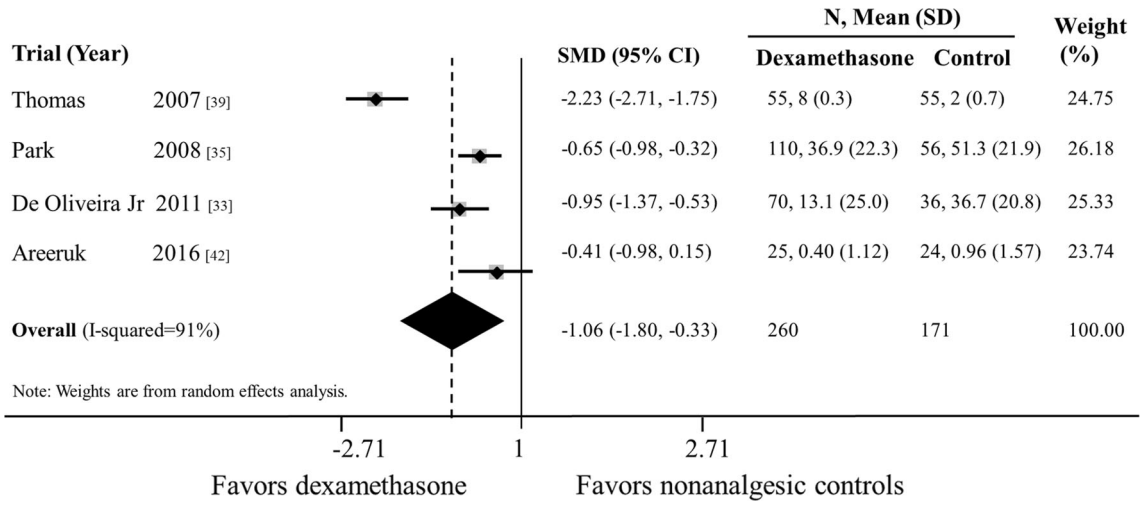

Fig. 3 Forest plot for the severity of postoperative sore throat at 24 hr after surgery/extubation. The plot shows decreased severity in patients treated with *iv* dexamethasone compared with non-analgesic controls. SD = standard deviation; SMD = standardized mean difference

of postoperative cough (RR, 0.66; 95% CI, 0.55 to 0.80; $P < 0.001$; df = 2; $I^2 = 0\%$; Fig. 5).

Postoperative hoarseness

Six studies including 621 participants provided information on the incidence of hoarseness at 24 hr after surgery/extubation.[30,31,33,35,37,43] Intravenous administration of dexamethasone was associated with a reduced incidence of postoperative hoarseness (RR, 0.47; 95% CI, 0.31 to 0.74; $P = 0.001$; df = 5; $I^2 = 61.0\%$; Fig. 6).

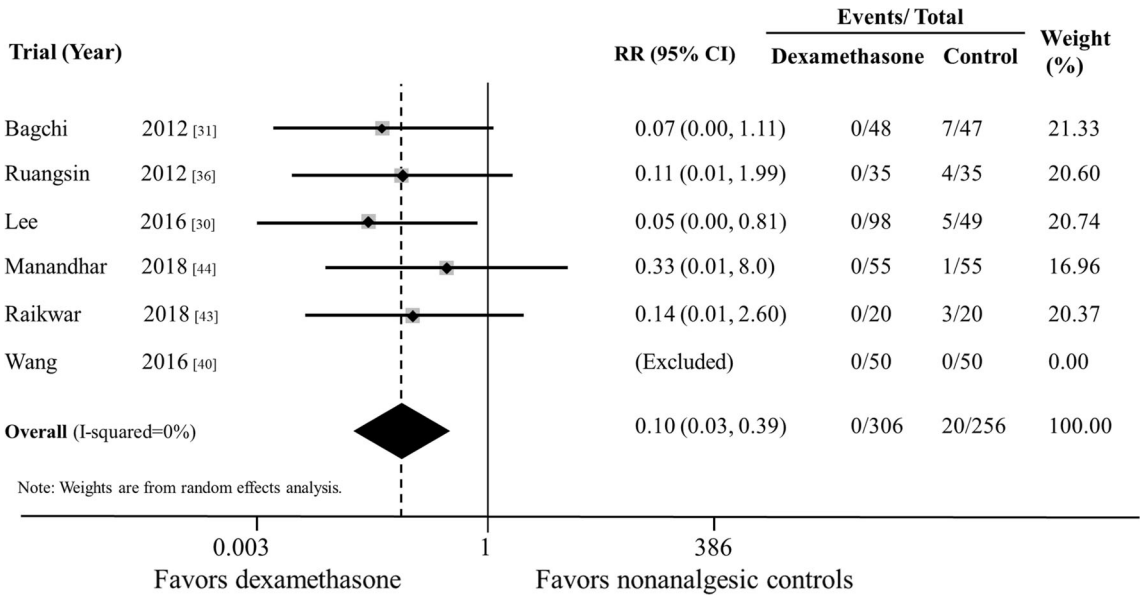

Fig. 4 Forest plot for the incidence of moderate or severe postoperative sore throat at 24 hr after surgery/extubation. The plot shows decreased incidence in patients treated with *iv* dexamethasone compared with non-analgesic controls. RR = risk ratio

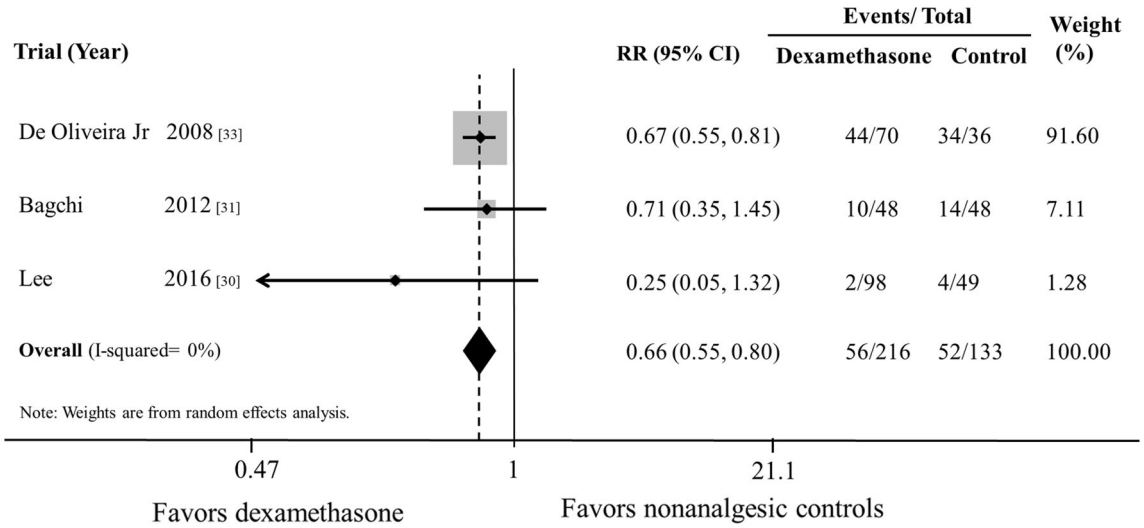

Fig. 5 Forest plot for the incidence of postoperative cough at 24 hr after surgery/extubation. The plot shows decreased incidence in patients treated with *iv* dexamethasone compared with non-analgesic controls. RR = risk ratio

Subgroup, sensitivity, and trial sequential analyses

There was no significant difference in the incidence of postoperative sore throat between subgroups created according to the type of comparator (P = 0.46; eTable, available as Electronic Supplementary Material). The results of sensitivity analyses excluding studies at an unclear or high risk of bias were consistent with those of primary analyses for all outcomes (eTable, available as Electronic Supplementary Material [ESM]). Trial sequential analysis suggested that the cumulative z curve crossed both the conventional and trial sequential monitoring boundaries for benefit before reaching the required information size (2,020 participants), which therefore supports the true positive efficacy of intravenous dexamethasone for preventing postoperative sore throat (Fig. 7).

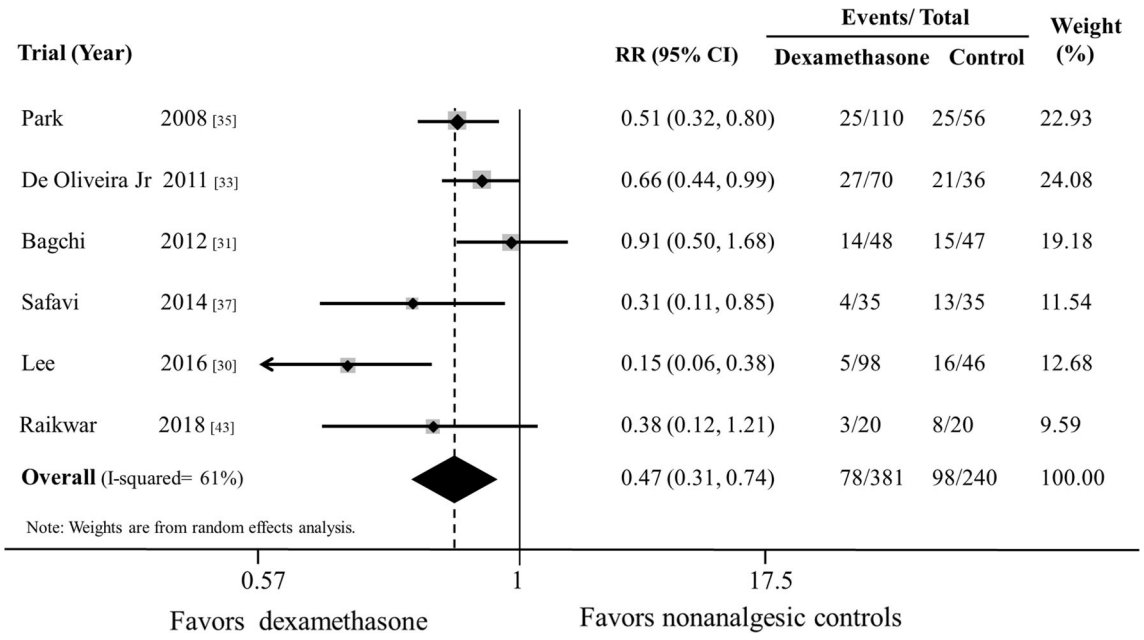

Fig. 6 Forest plot for the incidence of postoperative hoarseness at 24 hr after surgery/extubation. The plot shows decreased incidence in patients treated with *iv* dexamethasone compared with non-analgesic controls. RR = risk ratio

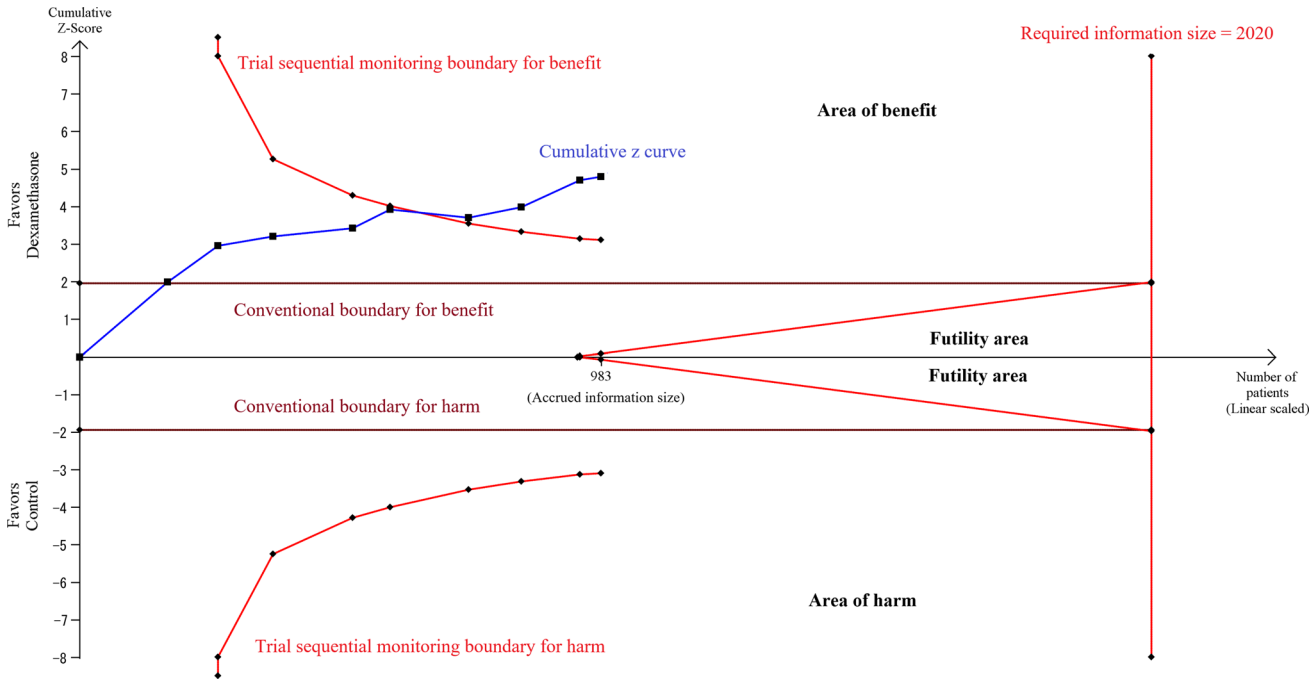

Fig. 7 Trial sequential analysis for the incidence of postoperative sore throat at 24 hr after surgery/extubation in patients treated with *iv* dexamethasone or non-analgesic controls. The cumulative z curve (blue line) crosses the conventional boundary for benefit (z score of 1.96; horizontal brown line) and the trial sequential monitoring boundary for benefit (red line), demonstrating true positive evidence to suggest that no further studies are required. A diversity-adjusted required information size of 2,020 patients (red vertical line) was calculated, using $\alpha = 0.05$ (two-sided) and $\beta = 0.20$ (power of 80%) and an anticipated relative risk reduction of 20%

We examined the relationship between the effect size (incidence of sore throat) and dexamethasone dose. Subgroup analysis found a similar effect size between groups that reported the dexamethasone dose (P = 0.61): low dose (RR, 0.62; 95% CI, 0.35 to 1.09; df = 2; I^2 = 42%) and intermediate dose (RR, 0.60; 95 % CI, 0.47 to 0.76; df = 6; I^2 = 0%). Meta-regression (P = 0.19) failed to find a dose-response relationship (eFigure, available as ESM).

Dexamethasone vs active controls

Five trials employed analgesic agents as comparators.[32,34,37,38,41] The comparators were corticosteroids applied to endotracheal tube cuffs in two trials,[38,41] ketamine gargles and intravenous dexamethasone in two trials,[37,43] ketamine gargles[37,43] in two trials, intravenous dexamethasone and intravenous lidocaine in one trial,[32] and intravenous dexamethasone and acetaminophen in one trial.[34]

With regard to the prevention of postoperative sore throat, intravenous dexamethasone administration was similar to corticosteroids applied to endotracheal tube cuffs[38,41] or ketamine gargles alone (RR, 0.80; 95% CI, 0.41 to 1.52),[37,43] or intravenous dexamethasone and acetaminophen,[34] while it was inferior to ketamine gargles and intravenous dexamethasone (RR, 2.25; 95% CI, 1.13 to 4.48)[37,43] or intravenous dexamethasone and intravenous lidocaine.[32] With regard to the prevention of postoperative hoarseness, intravenous dexamethasone was similar to ketamine gargles and intravenous dexamethasone (RR, 1.17; 95% CI, 0.42 to 3.26),[37,43] ketamine gargles alone (RR, 0.70; 95% CI, 0.29 to 1.71),[37,43] intravenous dexamethasone and intravenous lidocaine,[32] or intravenous dexamethasone and acetaminophen.[34]

Discussion

Our review suggests that, compared with non-analgesic controls, preoperative intravenous administration of dexamethasone was associated with a reduced incidence and severity of postoperative sore throat in adults undergoing elective surgery under anesthesia/endotracheal intubation. Our analysis indicates that the number of patients needed to treat with intravenous dexamethasone (to prevent one case of postoperative sore throat) is eight (95% CI, 5 to 20), which indicates a considerable prophylactic benefit. Intravenous dexamethasone administration also decreased the incidence of moderate or severe sore throat as well as hoarseness and cough after surgery. Limited available evidence suggests that intravenous dexamethasone administration is not associated with significant adverse events. Our findings were robust throughout the sensitivity analysis and TSA, providing strong evidence that preoperative intravenous dexamethasone administration effectively alleviates postoperative sore throat.

The presumed etiology underlying postoperative sore throat is mucosal inflammation around the tracheal tube cuff.[12] Previous studies suggest that topical and intravenous anti-inflammatory agents prevent postoperative sore throat in surgical patients,[16-18,45] thus supporting this explanation. Furthermore, intravenous corticosteroids administered to critical care patients prior to elective extubation decrease laryngeal edema and reduce post-extubation airway complications.[46] In line with this evidence, our study suggests that preoperative intravenous dexamethasone administration is associated with a reduced risk of postoperative sore throat.

Some studies have attempted to examine a dose-response relationship by testing two doses of dexamethasone. Our subgroup and meta-regression analyses suggest no association between the dose of dexamethasone and the effect size. We assumed a mean body weight of 60 kg because most studies were conducted outside North America. Re-analysis with an assumed body weight of 70 kg yielded similar findings. Although our findings do not elucidate the optimal dexamethasone dose for preventing postoperative sore throat, we believe that low-dose dexamethasone may be effective.

Previous studies have suggested that topical application of ketamine and corticosteroids help to prevent postoperative sore throat.[17,47] Our study suggests that intravenous dexamethasone is superior to topical ketamine, while topical corticosteroids and most analgesic agents combined with intravenous dexamethasone are no better than intravenous dexamethasone alone. Nevertheless, most of these comparisons were performed in single, small-sized trials and we believe that additional studies of this nature are warranted.

Our review could not adequately assess adverse events associated with intravenous dexamethasone. In 1996, The Consolidated Standards of Reporting Trials (CONSORT) statement recommended that trial investigators should report unintended effects related to interventions.[48] All studies that are included in our review were published after this statement. Nevertheless, only four studies reported adverse events and few details were provided. There is literature indicating that short-term, high-dose corticosteroids and single-dose intravenous dexamethasone are not associated with significant adverse events.[27,46] By analogy, we speculate that the prophylactic intravenous administration of dexamethasone to prevent sore throat is unlikely to be related to significant adverse events.

Two previous systematic reviews suggested that intravenous administration of dexamethasone helps to prevent postoperative sore throat.[19,20] Our findings are in agreement with these studies. Nevertheless, there are substantial differences between those reviews and the present one. First, the previous reviews included four and seven trials, respectively, whereas this report includes 15 studies, 13 of which included non-analgesic controls. Second, we pooled efficacy outcomes strictly at 24 hr after surgery/extubation. In contrast, the previous reviews pooled outcomes recorded over a wide range of time intervals because the original studies were few and inconsistent in reporting their outcomes; we excluded two such trials, which were included in the previous reviews. Third, we included two non-English language reports and studies involving comparisons with other analgesic agents; thus, our review was more comprehensive. Fourth, our TSA suggested true positive efficacy of intravenous dexamethasone administration to help prevent postoperative sore throat.

Additional strengths of our study include the comprehensive nature of the literature search, which identified 15 publications thus permitting sensitivity and meta-regression analyses. Moreover, we compared intravenous dexamethasone with topical corticosteroids and ketamine, which are known prophylactic measures to prevent postoperative sore throat. Finally, we complied with the Cochrane methodology. We contacted the original study authors to more accurately evaluate the risk of bias and requested necessary unpublished data. We also confirmed the robustness of our findings with sensitivity analysis and TSA.

Nevertheless, our review is not without limitations. First, the number of pooled studies for each outcome was relatively small even though the TSA provided strong evidence for the efficacy of preoperative intravenous dexamethasone. Second, there is a possibility of publication bias for each outcome. We were unable to test for publication bias given the limited number of studies available for each outcome, according to the recommendation of the Cochrane Collaboration. Third, there were potentially diverse, un-controlled confounding variables of the included trials. For example, operator inexperience, elevated cuff pressure, larger tracheal tubes, and a prolonged duration of intubation are known risk factors for postoperative sore throat. Unfortunately, we could not adjust for these variables because they were inconsistently reported.

In conclusion, our study suggests that preoperative intravenous dexamethasone administration alleviates postoperative sore throat more effectively than non-analgesic strategies.

Conflicts of interest None declared.

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