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META-ANALYSIS

Pharmacological Interventions for Post-operative Sore Throat (POST): A Network Meta-analysis

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Abstract

Background: To study the efficacy of current post-extubation pharmacologic treatments for postoperative sore throat (POST) prevention. **Method:** We searched nine databases for randomized controlled trials (RCTs) assessing the efficacy of post-extubation treatments in POST prevention. A network meta-analysis was used to pool the results. **Results:** Of the 124 records screened, we included 13 studies with 1820 patients. Ketorolac tromethamine was found to be the most effective with the lowest POST rates (P-score = 0.99), followed by ketamine (P-score = 0.68), amyl-m-cresol (P-score = 0.67), flurbiprofen (P-score = 0.66), benzydamine hydrochloride (P-score = 0.62), magnesium (P-score = 0.33), dexamethasone (P-score = 0.30), and lidocaine (P-score = 0.07). Moreover, the following treatments were found to be significantly effective in reducing POST in comparison to control/placebo treatment: ketorolac tromethamine (OR = 0.11; [95% CI=0.05 – 0.21]) followed by ketamine (OR = 0.32; [95% CI = 0.17 – 0.62]), amyl-m-cresol (OR = 0.32; [95% CI = 0.14 – 0.73]), flurbiprofen (OR = 0.33; [95% CI = 0.13 – 0.81]), and benzydamine hydrochloride (OR = 0.36; [95% CI = 0.24 – 0.54]). **Conclusion:** Ketorolac tromethamine, ketamine, amyl-m-cresol, flurbiprofen, and benzydamine hydrochloride were found to be significantly effective in reducing POST. Moreover, ketorolac tromethamine was the most effective and significantly better than all other treatments in reducing POST rates.

Keywords

Sore throat, Prevention, Systematic review

1. Introduction

Although general anesthesia is of extreme importance when performing many surgical procedures, various complications can be induced from the maneuver itself, ranging from mild to life-threatening complications [1]. Postoperative sore throat (POST) is a common complication following endotracheal intubation, affecting up to half of all patients [2]. Several risk factors have been identified for developing POST following endotracheal intubation, including obesity, female sex, size of the endotracheal tube, long operation time, multiple intubation attempts, long intubation times, and emergency intubation in the intensive care unit (ICU) [3]. The intubation technique results in pathological changes including epithelial loss, glottis hematoma, glottis edema, submucosal tears, and contact ulcer granuloma, which play an important role in POST development [4]. Laryngitis, tracheitis, hoarseness, cough, and dysphagia are commonly reported symptoms leading to a diagnosis of POST [5]. These symptoms interfere with the patient's routine activity and can progress to delayed wound healing, especially when causing difficulties in eating and drinking [6].

Preventive strategies and cautious intubation techniques remain the most effective approaches in reducing the incidence of POST. Adequate anesthesia time, using a smaller tracheal tube or an appropriately sized laryngeal mask airway, and decreasing intracuff pressure are widely used measures to prevent POST [4]. Nevertheless, several trials have discussed the role of some therapeutic agents in preventing POST. Shahani et al. showed a significant reduction in the severity of POST following ketamine treatment when compared to placebo [7]. In another clinical trial conducted by Borazan and colleagues, magnesium treatment led to a significant reduction in POST at 0, 2, 4, and 24 h after surgery when compared to a control group [8]. Additionally, the group allocated to benzydamine hydrochloride treatment had a significantly lower incidence of POST at 1, 6, and 24 h after surgery than that in the placebo group [9]. However, there is no conclusive evidence on the most effective therapeutic agent, or which has the least adverse events. In this systematic review and meta-analysis, we aimed to study the efficacy of the current pharmacologic treatments of POST.

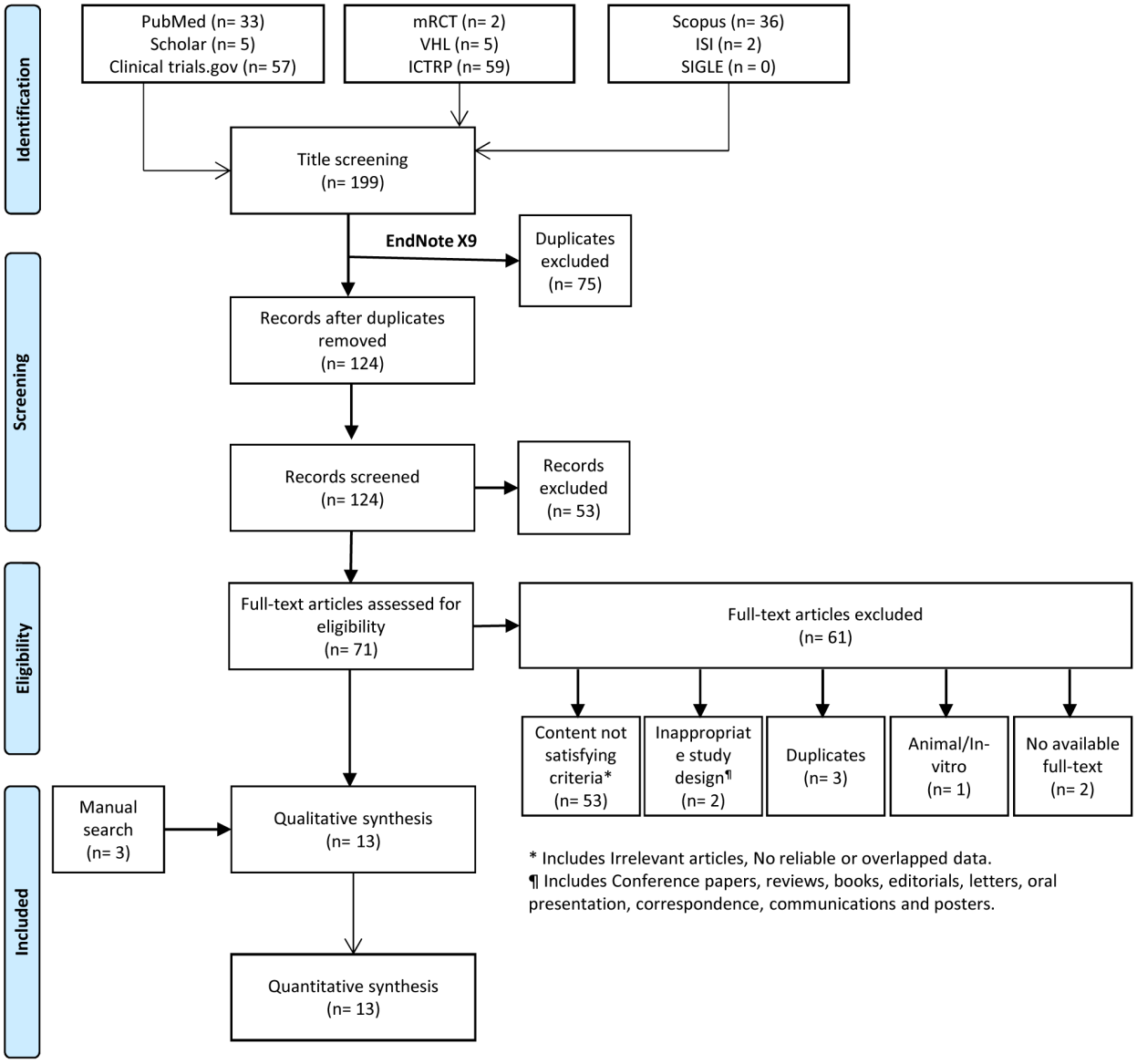


FIGURE 1. PRISMA flow diagram showing the process of the review.

2. Method

2.1 Search strategy and study selection

The study process was conducted following the accepted methodology recommendations of the PRISMA checklist for systematic reviews and meta-analyses, where registration of the protocol is not mandated [10]. We conducted a systematic electronic database search for suitable studies from inception until 10th April 2020 in nine databases: Google Scholar, System for Information on Grey Literature in Europe (SIGLE), Scopus, Web of Science (ISI), PubMed, Virtual Health Library (VHL), Clinicaltrials.gov, metaRegister of Controlled Trials (mRCT), and the World Health Organization International Clinical Trials Registry Platform (ICTRP) databases using the following search terms: (ketamine OR aspirin OR azulene OR benzydamine OR oral spray OR dexpanthenol OR amyl-m-cresol OR magnesium) AND (postoperative OR surg* OR operat*) AND (sore throat). Moreover, a manual search for grey literature was conducted to implement different searching strategies: (1) grey literature databases, (2) customized Google search engines, (3) targeted websites, and (4) consultation with contact experts.

We included randomized clinical trials (RCTs) reporting the efficacy of post-extubation treatments for sore throat prevention. There were no restrictions on study design, country, language, or publication date. Papers were excluded if they met any of the following exclusion criteria: 1) non-RCTs; 2) published before 2010; 3) *in vitro* or animal studies; 4) data duplication, overlapping or unreliably extracted or incomplete data; and 5) abstract only articles, reviews, theses, books, conference papers, or articles without available full texts (conferences, editorials, author response, letters, and comments). Three independent reviewers screened the titles and abstracts to initially select potentially eligible studies. Further full-text screening was performed to ensure the inclusion of relevant studies in our systematic review. Any disagreement was settled following discussion and consulting the senior member when necessary.

TABLE 1. Characteristics of the included studies.

The last name of 1st author/year published/country of patients	Drug	Sample size	Age (mean (SD))	Weight (mean (SD))	Male (event)	Overall Judgement
Shahani/2019/India	Ketamine	48	38.9 (14.9)	63.7 (8.5)	22	Low risk
	Placebo	48	35.2 (13.4)	66.3 (9.7)	22	
Aigbedia/2017/Nigeria	Ketamine	72	40.6 (10.5)	64.1 (9.1)	26	Low risk
	Lidocaine	68	37.2 (12.3)	71.7 (11)	17	
Borazan/2012/Turkey	Magnesium	35	38 (7)	58 (7)	11	Low risk
	Placebo	35	41 (9)	57 (8)	10	
Chang/2015/Korea	Benzydamine hydrochloride	46	55	62 (9)	31	Low risk
	Placebo	46	56	60 (10)	30	
Ebneshahidi/2010/Iran	Strepsils	73	29 (9)	58 (9)	43	High risk
	Placebo	72	31 (10)	57 (11)	40	
Huang/2010/China	Benzydamine hydrochloride	284	48.3 (1.5)	62.7 (1.8)	139	Low risk
	Placebo	94	45.5 (18)	62.7 (11.7)	44	
Mekhemar/2016/Egypt	Benzidamine hydrochloride gel	31	48.7 (6.2)	97.8 (10.6)	10	Low risk
	lidocaine hydrochloride gel 5%	31	49.6 (6.8)	97.3 (9.3)	13	
	lidocaine hydrochloride in spray 10%	31	48.4 (6.5)	93.9 (11.3)	12	
	Placebo	31	49.8 (6.1)	95.3 (8.9)	13	
Muderris/2019/Turkey	Flurbiprofen oral spray	46	38.9 (1.7)	73.3 (1.6)	23	High risk
	Benzydamine hydrochloride oral spray	45	34.5 (2)	70.8 (2.3)	22	
	Placebo	45	28.2 (1.9)	77.2 (1.9)	26	
Park/2015/Korea	Magnesium	73	51 (12)	67 (12)	41	Low risk
	Dexamethasone	73	51 (12)	67 (19)	42	
Thomas/2020/India	Ketamine	48	39.9 (14.6)	63.7 (6.5)	22	Low risk
	Placebo	48	35.2 (13.4)	66.3 (7.9)	22	
Mostafa/2010/Egypt	Ketamine	36	11.1 (2.7)	31.1 (5.5)	23	Low risk
	Magnesium	36	10.9 (2.4)	29.4 (4.1)	24	
	Dexamethasone	36	10 (2.6)	29.6 (6.2)	22	
Yang/2016/Taiwan	Ketorolac	95	53.7 (15.6)	NR	37	High risk
	Placebo	95	51.2 (15.8)	NR	39	
Kim/2019/Korea	Benzydamine hydrochloride	33	45 (16)	63 (11)	3	High risk
	lLdocaine spray	33	47 (12)	64 (15)	12	
	Placebo	33	46 (10)	66 (11)	9	

NR = not reported.

TABLE 2. Network meta-analysis of efficacy of different treatment on reducing post-operative sore throat rates.

Ketorolac Tromethamine							
0.33 (0.13 to 0.84)	**Ketamine**						
0.33 (0.12 to 0.96)	1.01 (0.35 to 2.90)	**Amyl-m-cresol**					
0.32 (0.10 to 0.99)	0.98 (0.32 to 2.96)	0.97 (0.28 to 3.31)	**Flurbiprofen**				
0.29 (0.14 to 0.64)	0.89 (0.43 to 1.86)	0.88 (0.35 to 2.23)	0.91 (0.36 to 2.31)	**Benzydamine Hydrochloride**			
0.15 (0.04 to 0.54)	0.45 (0.15 to 1.40)	0.45 (0.11 to 1.77)	0.46 (0.11 to 1.92)	0.51 (0.16 to 1.62)	**Magnesium**		
0.14 (0.04 to 0.56)	0.43 (0.13 to 1.43)	0.42 (0.10 to 1.81)	0.44 (0.10 to 1.96)	0.48 (0.14 to 1.68)	0.94 (0.50 to 1.76)	**Dexamethasone**	
0.08 (0.03 to 0.20)	**0.24 (0.13 to 0.43)**	**0.23 (0.08 to 0.68)**	**0.24 (0.08 to 0.74)**	**0.26 (0.13 to 0.55)**	0.52 (0.16 to 1.73)	0.55 (0.15 to 2.01)	**Lidocaine**
0.11 (0.05 to 0.21)	**0.32 (0.17 to 0.62)**	**0.32 (0.14 to 0.73)**	**0.33 (0.13 to 0.81)**	**0.36 (0.24 to 0.54)**	0.71 (0.24 to 2.12)	0.75 (0.23 to 2.50)	1.36 (0.68 to 2.71) **Control/Placebo**

** Treatments are reported in order of efficacy on reducing sore throat rates with ranking according to P-scores. Comparisons should be read from left to right. OR below 1 favors the row-defining treatment (lower risk of sore throat). Significant results are in bold font.*

2.2 Data extraction

The data extraction form was developed by two authors using a Microsoft Excel file. Three reviewers independently extracted data from the included studies using the Excel sheet. Data checking was performed by a fourth reviewer. All disagreements and discrepancies were resolved by discussion and consultation with a senior member when necessary.

2.3 Quality assessment

Three independent reviewers evaluated the risk of bias in the included studies. Due to the inclusion of RCTs only, we decided to use the Cochrane's revised quality assessment tool (RoB 2) [11]. Three investigators rated the quality of evidence according to several metrics: randomization bias, allocation bias, missing data bias, outcome bias, and selection bias [11]. Any discrepancy between the reviewers was solved by discussion.

2.4 Assessing confidence in the results

The evaluation of the credibility of results from a meta-analysis; for that, we evaluated the confidence in the results from network meta-analyses. It was done using the Confidence in Network Meta-Analysis (CINeMA) tool, which is based on the Grading of Recommendations Assessment (GRADE) approach of the ordinary meta-analysis [12, 13] (Supplementary material).

2.5 Statistical analysis

All analyses have been performed using R version 3.6.1 [14]. Frequentist network meta-analysis was conducted, using the "netmeta" package, to compare the difference in POST rate among different treatment groups by computing the pooled odds ratio (OR) and their corresponding 95% confidence intervals (CI) [13, 15]. In the case of different follow-up assessment points, we used the last follow up point to get the sustained long-lasting action.

A fixed-effects model network meta-analysis was adopted and heterogeneity which was assessed using Q-statistics with p-value < 0.05 considered significant. Whenever heterogeneity is present, the splitting of direct and indirect comparisons would be done to explore any possible sources [16]. Ranking of treatment was based on P-score, which is the frequentist approach analogue to surface under the cumulative ranking (SUCRA) [17]. To assess the risk of bias and small-study effects, comparison-adjusted funnel plots was developed [16]. Furthermore, funnel plot asymmetry has been assessed with three different tests; Egger's regression, Begg-Mazumdar, and Thompson-Sharp tests with p-value < 0.1 considered significant [18–20].

3. Results

3.1 Search results

The literature search yielded 124 records after the removal of 75 duplicates using endnote software. Title and abstract screening resulted in the inclusion of 71 records for full-text screening. The latter resulted in the inclusion of 10 studies. We found an additional 3 papers from a manual search of references. Finally, we included 13 RCTs for this systematic review and meta-analysis (Fig. 1, Table 1) [7–9, 21–30]. The inter-rater agreement between the four systematic reviewers, using the kappa statistic, was $\kappa = 0.62$.

3.2 Study characteristics and quality of the included studies

The total sample size was 1820 with a male prevalence of 46.7%. Regarding drugs used, five trials reported ketamine, four studies reported benzydamine hydrochloride, three studies used magnesium, three studies revealed lidocaine, dexamethasone, Strepsils®, flurbiprofen, ketorolac was used in one study each. All treatments were given orally, except for lidocaine which was applied locally as a spray. Three studies occurred in Korea, two in India, two in Egypt, two in Turkey, and one for each of the following countries, Nigeria, Iran, China, and Taiwan. Regarding the risk of bias, nine studies had a low risk of bias while four studies had a high risk of bias. The detailed review authors' judgments about each risk of bias item are presented in Fig. 2.

3.3 Post-extubation treatments for POST

A total of 13 studies with 1820 patients were included in the analysis of sore throat rates. Each arm of pairwise comparisons composed of different number of studies giving an asymmetrical network plot (Fig. 3A). Ketorolac tromethamine was found to be the most effective with the lowest POST rates (P-score = 0.99), followed by ketamine (P-score = 0.68), amyl-m-cresol (P-score = 0.67), flurbiprofen (P-score = 0.66), benzydamine hydrochloride (P-score = 0.62), magnesium (P-score = 0.33), dexamethasone (P-score = 0.30), and lidocaine (P-score = 0.07). Moreover, the following treatments were found to be significantly effective for reducing of POST in comparison to control/placebo: ketorolac tromethamine (OR = 0.11; [95% CI = 0.05 – 0.21]) followed by ketamine (OR = 0.32; [95% CI = 0.17 – 0.62]), amyl-m-cresol (OR = 0.32; [95% CI = 0.14 – 0.73]), flurbiprofen (OR = 0.33; [95% CI = 0.13 – 0.81]), and benzydamine hydrochloride (OR = 0.36; [95% CI = 0.24 – 0.54]) (Table 2) (Fig. 3B).

There was no risk of bias in assessing the asymmetry of comparison-adjusted funnel plot (Egger p-value = 0.933, Begg-Mazumdar p-value = 0.171, Thompson-Sharp p-value = 0.959) as shown in Fig. 4. Additionally, no significant heterogeneity or inconsistency were observed ($\tau^2 = 0.23$, $I^2 = 43\%$ and p-value = 0.080). Furthermore, the confidence in the results from the current network meta-analyses was "High" in all comparisons tested, whether in the mixed evidence (direct and indirect) or the indirect one.

4. Discussion

In the present study, we evaluated the effects of nine different treatments with anti-inflammatory action on the incidence of POST in 1820 patients who had undergone general anesthesia with endotracheal intubation. Five treatments were found to be significantly effective in reducing POST in comparison to control/placebo, namely, ketorolac tromethamine, ketamine,

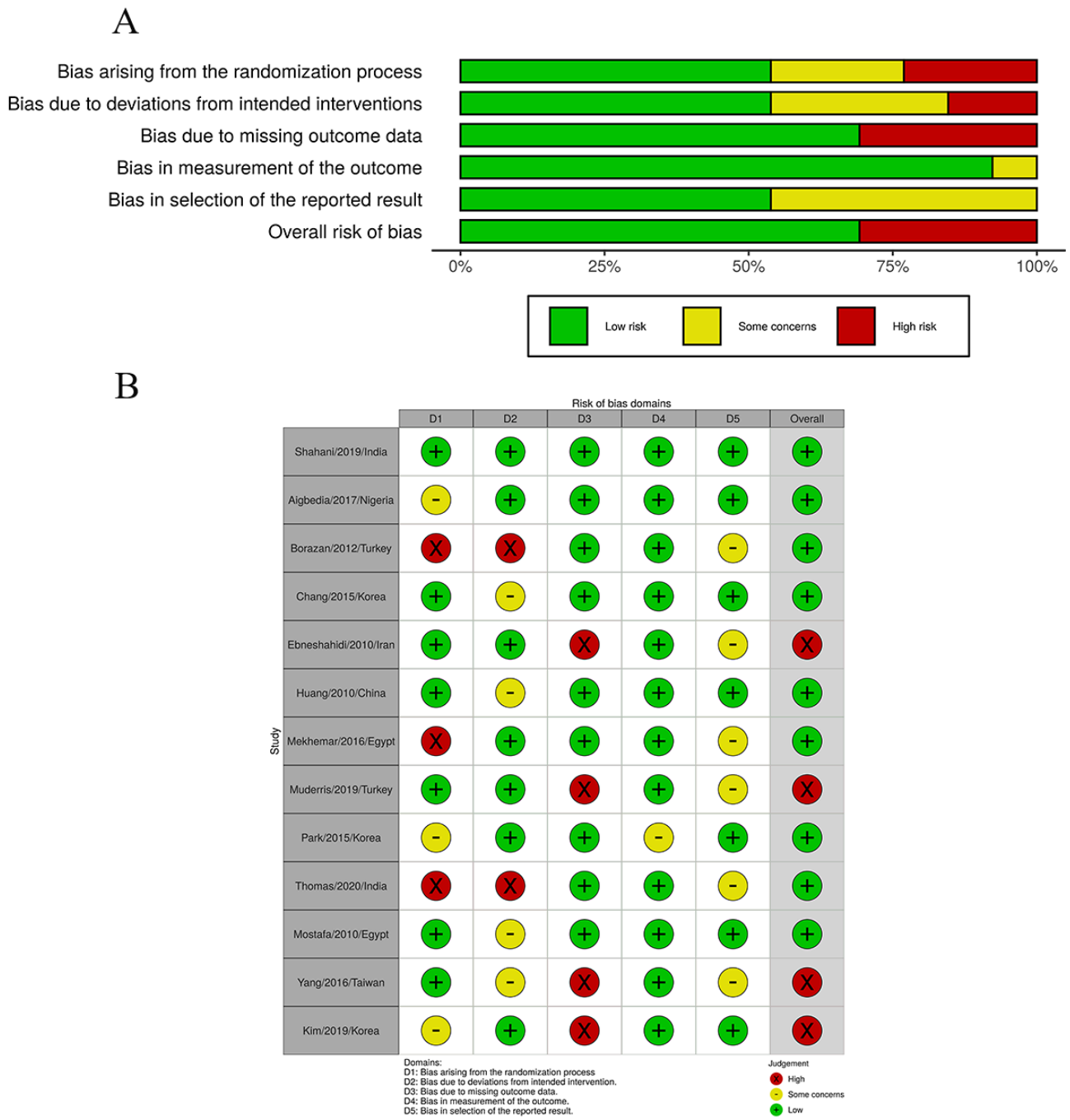


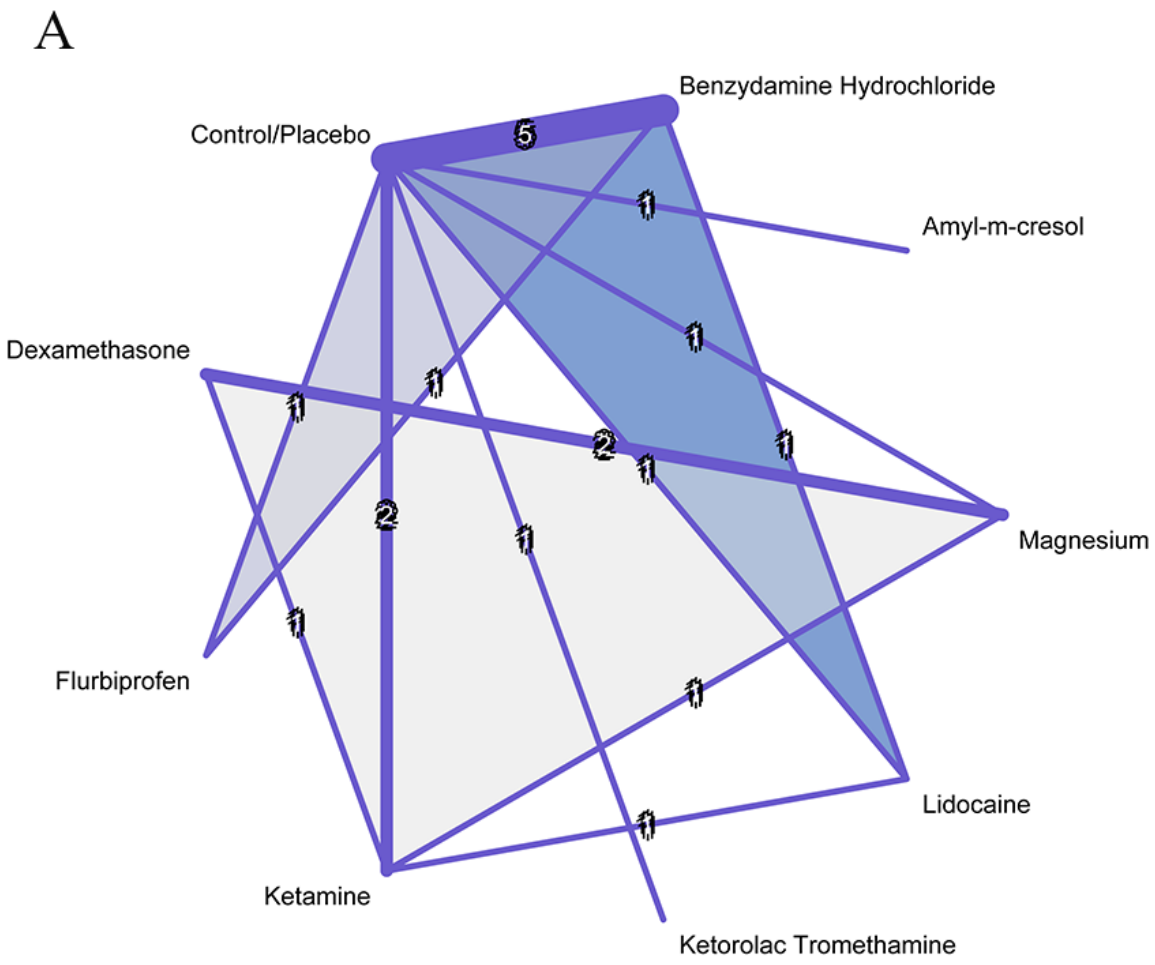
FIGURE 2. Quality of the included studies.

A: Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies; B: Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

amyl-m-cresol, flurbiprofen, and benzydamine hydrochloride. Ketorolac tromethamine was found to be the most effective and significantly better than all other treatments in reducing POST rates.

Multiple factors are involved in the pathogenesis of POST following endotracheal intubation, which is mainly caused by the inflammatory response to intubation and the presence of the endotracheal tube (ETT) [31, 32]. Furthermore, the localized inflammatory response could be aggravated by ETT motion induced by the neck hyperextension and manipulation during surgery [33, 34]. Accordingly, pharmacological treatments are mainly based on the anti-inflammatory mechanism of steroidal or non-steroidal treatments.

Ketorolac Tromethamine belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs) with having anti-inflammatory activity along with analgesic and antipyretic properties [35, 36]. This action is mainly mediated through the inhibition of cyclooxygenase, which, in turn, leads to inhibition of prostaglandin synthesis [35, 36]. One possible explanation for ketorolac having the greatest effect on subjective outcomes, such as sore throat, may be related to its reported analgesic effect; it has been used successfully alone



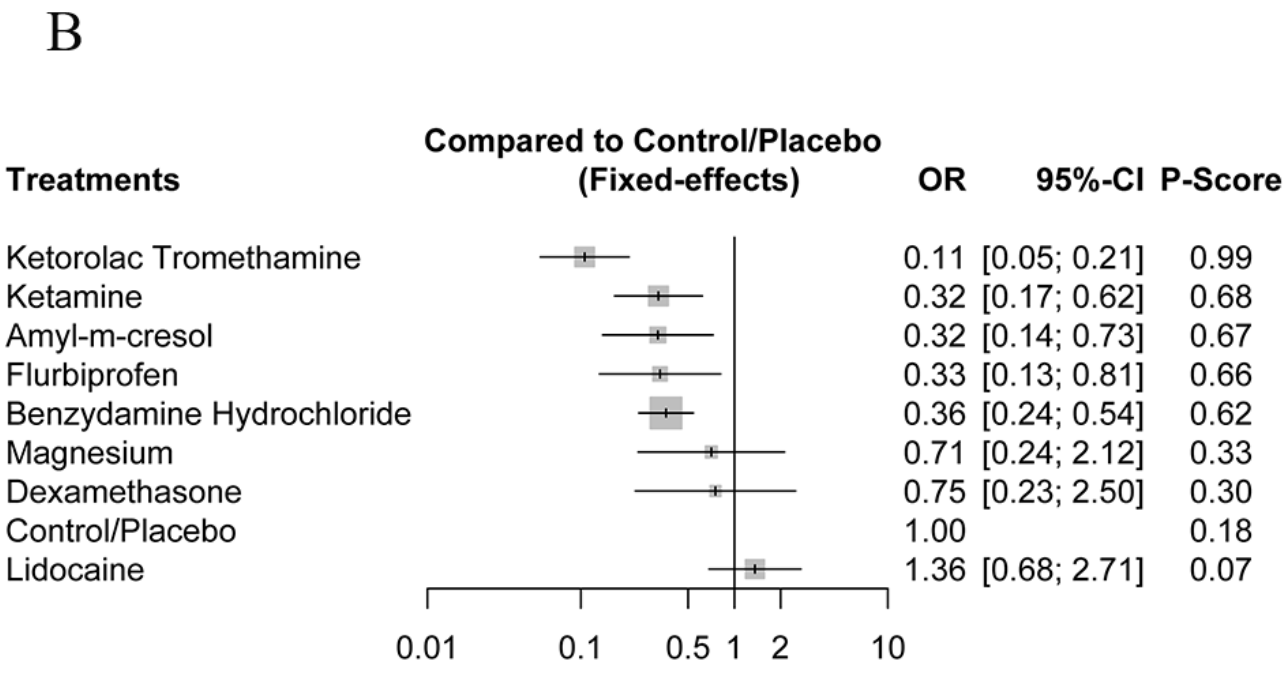


FIGURE 3. Network meta-analysis of the efficacy of different treatments on reducing postoperative sore throat rates. (A) Network plot; (B) Forest Plot (compared to control/placebo).

or complementary to opioids to relieve postoperative pain [37, 38]. Moreover, ketorolac was found to be as effective as dexamethasone in terms of its anti-inflammatory action in both topical and oral formulations, reducing acute swelling

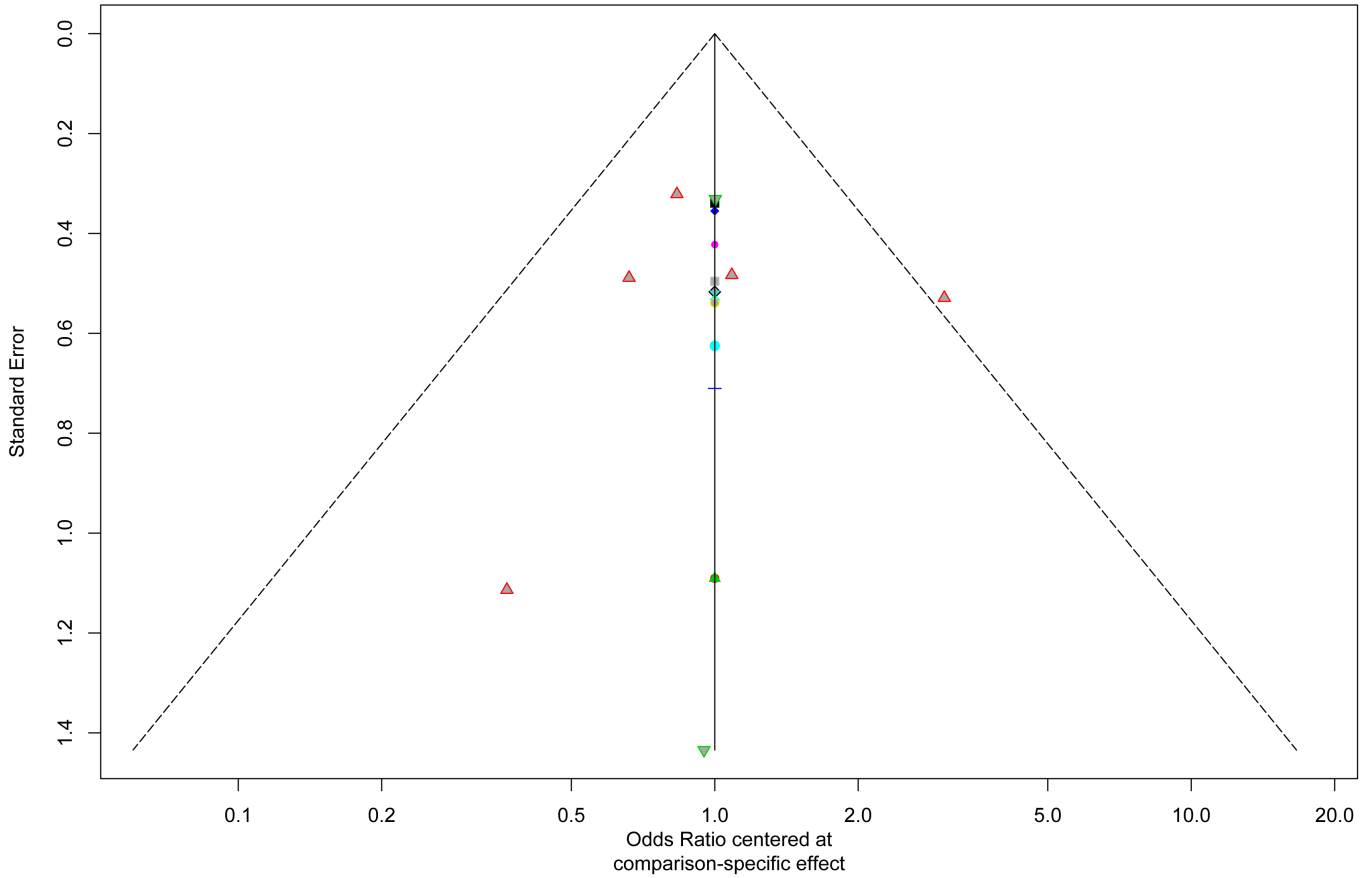


FIGURE 4. Comparison adjusted funnel plot for the network of sore throat rates.

and pain following different procedures [36–39].

Similar to our results, previous studies reported the efficacy of ketorolac tromethamine in reducing the intensity and rates of POST, with the alleviation of ETT-induced inflammation following general anesthesia [36, 40, 41]. It was proven that NSAIDs, including ketorolac, are effective in reducing the intensity and prevalence of POST. This was noted by the first hour following surgery, and the intensity was almost negligible by the end of the first postoperative day [42]. Ketorolac tromethamine is a particularly good therapeutic option because of its safety profile; it was reported to be absorbed through the nasal mucosa within only 20 min, leading to a good analgesic effect without the central effects or allergies associated with other similar drugs [43]. This effective pain-relieving action was also reported in low doses due to the good absorption through the mucosa, making it even a safer option [39, 44].

Although this study did not report significant bias or heterogeneity among the included studies, it has some limitations. The arms of the pairwise direct and indirect comparisons between different treatments were composed of only one study in most comparison arms. Moreover, the subjective nature of the assessed outcomes and other confounders (e.g., type of surgery, duration of surgery, and post-extubation cough or vomiting) were not accounted for in the synthesis of the current evidence. Thus, the results should be interpreted with caution.

5. Conclusion

Ketorolac tromethamine, ketamine, amyl-m-cresol, flurbiprofen, and benzydamine hydrochloride were found to be significantly effective for the reduction of POST. Moreover, ketorolac tromethamine was the most effective and significantly better than all other treatments in reducing POST rates, especially after emergency intubation in the ICU.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1326044543110266880/attachment/Supplementary%20material.xlsx

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