Efficacy of bupivacaine infiltration for controlling post-tonsillectomy pain, duration of surgery and post-operative morbidities: A systematic review and meta-analysis

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Received June 22, 2020; Accepted October 8, 2020

DOI: 10.3892/etm.2021.9631

Abstract. The objective of the present review and meta-analysis was to evaluate the efficacy of bupivacaine during tonsillectomy in terms of reducing the mean operative procedure duration, post-operative pain and the onset of post-operative morbidities. The Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines were followed to perform a systematic literature search using the MEDLINE, Scopus, EMBASE and CENTRAL databases. The present meta-analysis sought to evaluate the efficacy of bupivacaine administered during tonsillectomy as compared to the administration of normal saline. The efficacy of the intervention was evaluated based on pain scores using the visual analogue scale, the duration of the operation and the occurrence of post-operative morbidities. Out of 1,427 records, 15 articles with 729 participants (mean age, 10.2±6.7 years) were included in the study. The present systematic review supported the use of bupivacaine during tonsillectomy at a level of evidence of 1b and confirmed beneficial effects of bupivacaine intervention by demonstrating small to large effect reductions in the visual analog scale score (Hedge's g, -1.48), the mean duration of the operative procedure (Hedge's g, -1.35) and the incidence of post-operative morbidity (Hedge's g, -0.23) in comparison to the placebo groups treated with normal saline. Based on these results, the administration of bupivacaine is recommended during tonsillectomies to reduce the perceived level of pain, the duration of the operation and the post-operative morbidity.

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Key words: anesthesia, tonsillectomy, adenotonsillectomy, bupivacaine, pain

Introduction

Tonsillectomy is a common surgical intervention (1-3). It involves the complete or partial removal of the palatine tonsils primarily to prevent recurring infections and inflammation (4,5). However, the surgical site is a highly vascularized zone and complications are frequent due to unintended trauma during the procedure (6,7). For instance, tonsillectomy is associated with large amounts of blood loss during the operation (8,9) and with subsequent inflammatory responses due to tissue trauma that causes high levels of pain and post-operative morbidities (due to the accumulation of local tissue exudates around the surgical site) (10-12). A high level of edema within 24 h of the operation in the uvula and the palatopharyngeal and palatoglossal areas may interfere with optimal healing and is associated with increased post-operative morbidities (13). In addition, tonsillectomy causes collateral damage to the pharyngeal muscles and exposes nerve endings (tonsillar glossopharyngeal, maxillary trigeminal and lesser palatine nerve branches) (14), leading to post-operative complications such as severe pain, difficulty swallowing or breathing, as well as vomiting and otalgia (13,15,16).

These complications may be reduced with local anesthetic agents such as bupivacaine (17,18). The application of bupivacaine may decrease the onset of post-operative pain by blocking afferent nerve endings through inhibition of voltage-gated Na^+ channels (19). Furthermore, the anesthetic agent inhibits synaptic N-methyl-D-aspartate receptors (19,20) and has anti-inflammatory properties (21,22). In 2013, Block *et al* (21) also reported that bupivacaine reduces inflammatory activity by inhibiting Ca^{2+} ion signaling and the release of interleukin-1β in astrocytes, and by interacting with 5-hydroxytryptamine, opioid and glutamate receptors. Similarly, the reduction of vascular permeability by bupivacaine has also been reported to help reduce intra-operative and post-operative complications (23,24). Bupivacaine has been deemed superior to other anesthetic agents such as lidocaine and ropivacaine due to its sustained effects, higher potency and lower toxicity profile (25-27).

Despite the enhanced effectiveness demonstrated by bupivacaine, there is still no consensus regarding its application

during tonsillectomy to reduce intra-operative and post-operative complications. Certain studies have recommended the administration of bupivacaine during rhinoplasty due to its ability to prevent intra-operative and post-operative complications (28-31). Previous studies, particularly meta-analyses (18), have failed to provide conclusive evidence to support bupivacaine application during tonsillectomies. This lack of agreement has delayed the adoption of a standard protocol for optimal drug interventions during tonsillectomy. The present review includes, for the first time, a detailed analysis of the isolated efficacy of bupivacaine to improve intra-operative factors associated with tonsillectomy such as the duration of the operative procedure. Since the publication of the last meta-analysis on this subject, several high-quality randomized controlled trials (RCTs) have been published, evaluating the efficacy of bupivacaine to improve intra-operative and post-operative morbidities associated with tonsillectomy (28-34,34-36).

The present systematic review and meta-analysis aimed to provide an updated evaluation of the effects of bupivacaine on operative and post-operative outcomes associated with tonsillectomy. Endpoints included the mean perceived level of pain based on the visual analogue scale score, the mean operative procedure duration and the incidence of post-operative morbidities. The present results should help otolaryngologists to make optimal decisions about the best approach to minimize morbidities associated with tonsillectomy procedures.

Materials and methods

Data search strategy. The Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines were followed (35). A total of four academic databases (MEDLINE, CENTRAL, EMBASE and Scopus) were searched from inception until April 2020 using the following MeSH key words: 'Tonsillectomy', 'Bupivacaine', '1-Butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide', 'Bupivacain janapharm', 'Bupivacain-RPR', 'Bupivacaina braun', 'Bupivacaine anhydrous', 'Bupivacaine carbonate', 'Bupivacaine hydrochloride', 'Bupivacaine monohydrochloride', 'Bupivacaine monohydrate', 'Buvacaina', 'Carbostesin', 'Dolanaest', 'Marcain', 'Marcaine', 'Sensorcaine', 'Svedocain sin vasoconstr', 'anesthesia', 'anesthetics', 'visual analog scale', 'Children's Hospital of Eastern Ontario pain scale', 'morbidity', 'complications', 'blood loss' and 'post-operative morbidity'. The bibliography of the included studies was subsequently searched for any additional relevant studies. The inclusion criteria for studies were defined as follows: a) Studies that assessed and stated outcomes in a post-operative follow-up assessment; b) studies that were either RCTs, quasi-RCTs, controlled clinical trials, prospective observational trials with established control groups or retrospective trials; c) studies in peer-reviewed scientific journals or conference proceedings; d) studies written in English. To avoid any bias, two reviewers (NW and FG) independently replicated the selection process. The data extracted from the selected studies included the authors' names, patient information (age, sex), variables assessed, country, follow-up duration and outcome measures. Appropriate attempts to contact corresponding authors of relevant articles with incomplete quantitative outcome data were made to obtain additional data.

Quality assessment. The Cochrane risk of bias assessment tool for RCTs was used to evaluate the risk of bias (36). A total of two independent reviewers (NW and FG) appraised the selected studies critically on the basis of their methodology. The reviewers also analyzed each selected study for inadequate randomizations, allocations, selection outcome reports and distributions of allocation as a potential source of bias (37). Data ambiguity was resolved by discussions between the reviewers and a level of evidence analysis was included based on the guidelines of the Centre for Evidence-Based Medicine (38).

Data analysis. Statistical meta-analysis of the encompassed studies was performed using the Comprehensive Meta-analysis version 2.0 software (39). Data for relevant variables were extracted from the selected studies for analysis and mean values were compared between the groups of patients treated with either bupivacaine or normal saline. The statistical meta-analysis was based on the random-effects model (40), in which effect sizes are reported as weighted Hedge's g values. Results for weighted effect sizes were categorized as small (≤0.2), medium (0.2-0.8) or large (≥0.8) (41). I^2 statistics were computed to assess heterogeneity, which was classified as either insignificant (0-25%), modest (25-75%) or considerable (≥75%) (42). Sensitivity analysis was performed for studies with considerable sources of heterogeneity (43). Certain results were excluded due to insufficient randomization methods in the studies. For each statistic, 95% confidence intervals (CIs) and the level of heterogeneity were calculated and Duval and Tweedie's trim and fill process and the Egger's test of intercept were used to assess publication bias (44). The number of missing studies that may exist and the possible consequences for the present meta-analysis were estimated. Imputation of asymmetric studies was performed to define an unbiased overall effect. Subsequently, these trimmed effects were refilled in a plot and the combined effect was recalculated. The alpha level was set at 5%.

Results

Study selection. Initial examination of databases resulted in a total of 1,417 studies. After review of the bibliography of relevant studies, 10 additional studies were selected (Fig. 1). After removing duplicate references and applying selection criteria, 15 RCT studies were retained (17,28-34,45-51). The included studies compared the perceived level of pain after tonsillectomy between bupivacaine and normal saline groups (14,17,28-34,45-47,49-51) (12 studies evaluated the perceived level of pain with visual analog scale scores (17,28-31,33,34,47-51) and 2 with the Children's Hospital of Eastern Ontario pain scale scores (45,46). In terms of pain levels, 9 studies (17,28-34,46) reported a significant ($P<0.05$) reduction and 2 (45,49) an insignificant reduction ($P>0.05$) with the use of bupivacaine as compared with the use of normal saline during tonsillectomy. Furthermore, three studies reported no differences in the perceived level of pain between the groups (47,50,51). In addition, five of the included studies reported on the incidence of post-operative morbidity after tonsillectomy in both groups, of which 3 studies reported a significant ($P<0.05$) reduction (33,46,49), 1 reported an insignificant ($P>0.05$) reduction (34) and one an insignificant increase in the onset of post-tonsillectomy morbidity (for example, adverse

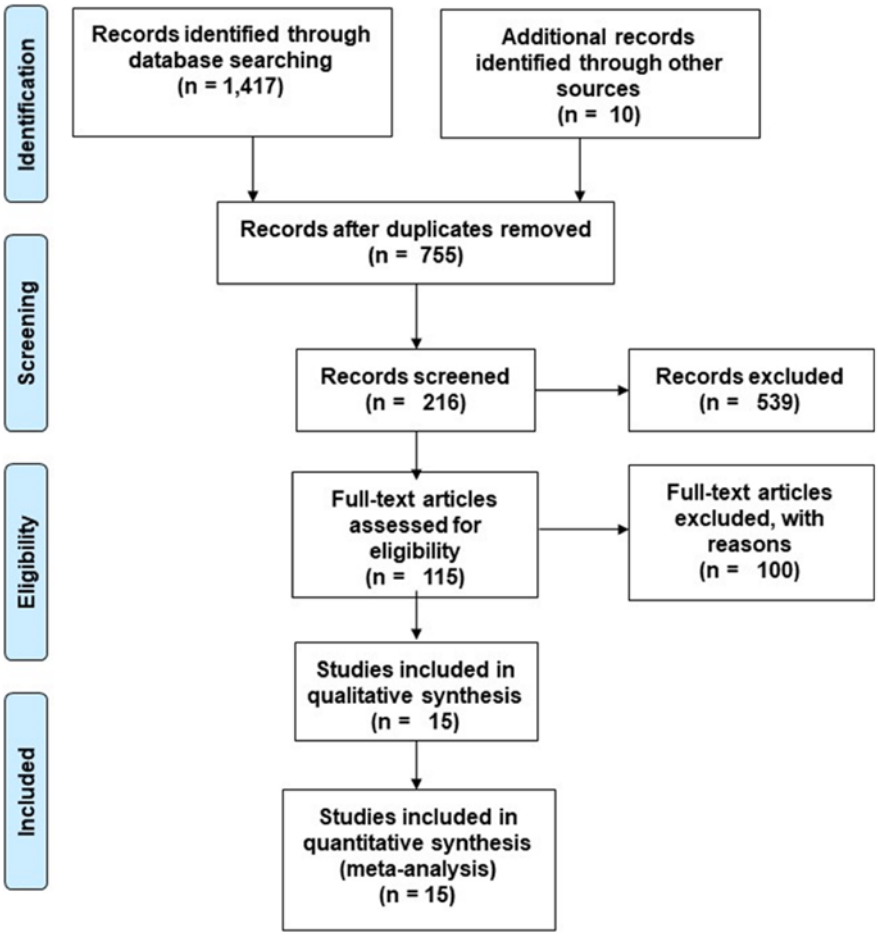

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flow chart for the included studies.

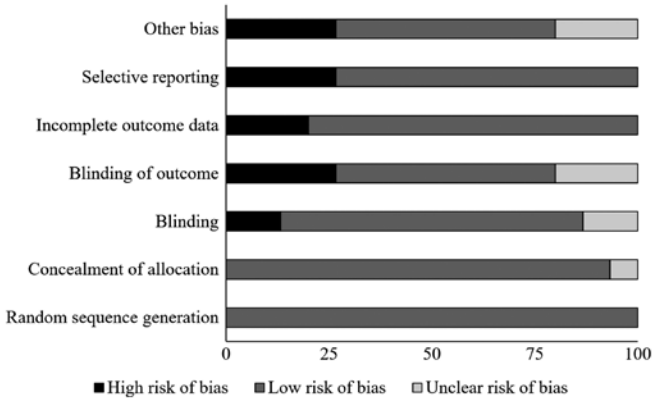

Figure 2. Risk of bias (%) within studies according to the Cochrane risk of bias assessment tool for randomized controlled trials.

effects of the operative procedure) (32,33,45,46,49) in patients receiving bupivacaine as compared to those in the placebo group. Finally, four studies compared the mean duration of the tonsillectomy procedure between the bupivacaine and normal saline groups (17,29,31,34) and reported a significant reduction in the mean duration of the procedure for the group receiving bupivacaine as compared to the placebo group.

Risk of bias. Table I and Fig. 2 present the results of Cochrane's risk of bias assessment for the selected RCTs. The general bias risk in the studies included was rated as low. The highest risk of bias was due to selective reporting and insufficient blinding. A 1b level of evidence was determined for all of the studies based on their described experimental design.

Publication bias. No missing studies on either side of the mean result were identified after applying the trim and fill technique (Fig. 3). The studies that fall out of the funnel area indicate the possibility of bias. In this case, it can be presumed that the asymmetry in our funnel plot is possibly as a result of heterogeneity arising due to differences between study results and methodology (52,53) had earlier stated that heterogeneity can lead to funnel plot asymmetry if it induces a correlation between study sizes and intervention effects. Nevertheless, in the current analysis the random-effects model indicated overall point estimates and 95% CIs for the evaluated strictures as -1.44 (-1.95 to -0.93), respectively. According to the trim and fill procedure report, these values remained unchanged. These values represent the overall effect size of all the parameters in the included studies before the assessment of publication bias. Furthermore, the intercept, i.e. the captured bias according to the Egger's test was B0: -7.46, 95% CI: -14.51 to -0.41 ($P<0.05$).

Participant information. Data from 710 patients from the studies included in the present analysis were assessed (Table II). Of these, 379 patients (122 females and 167 males) received bupivacaine and 331 patients (130

Table I. Quality of the analyzed studies according to the Cochrane risk of bias assessment tool for randomized controlled trials.

Study	Random sequence generation	Concealment of allocation	Blinding	Blinding of outcome	Incomplete outcome data	Selective reporting	Other biases	Level of evidence	Ref.
Junaid *et al* (2020)	+	+	+	?	-	+	-	1b	(30)
Abdel Raheem and Farouk (2019)	+	+	-	-	+	+	-	1b	(28)
Tuhanioglu and Erkan (2018)	+	+	+	+	-	-	?	1b	(34)
Haksever *et al* (2014)	+	+	+	+	+	+	+	1b	(32)
Ergil *et al* (2012)	+	+	+	+	+	+	+	1b	(29)
Özkiriş *et al* (2012)	+	+	?	-	+	+	+	1b	(31)
Özmen and Özmen (2011)	+	+	+	+	+	+	+	1b	(33)
Nikandish *et al* (2008)	+	+	+	+	+	+	+	1b	(17)
Karaaslan *et al* (2008)	+	+	+	-	+	+	+	1b	(45)
Unal *et al* (2007)	+	+	+	+	+	-	?	1b	(51)
Akoglu *et al* (2006)	+	+	+	?	+	+	+	1b	(46)
Kaygusuz and Susaman (2003)	+	+	-	-	+	+	-	1b	(49)
Johansen *et al* (1996)	+	+	+	+	+	+	-	1b	(48)
Stuart *et al* (1994)	+	+	+	+	+	-	+	1b	(50)
Jebeles *et al* (1992)	+	?	?	?	-	-	?	1b	(47)

-, High risk of bias; +, low risk of bias; ?, unclear risk of bias.

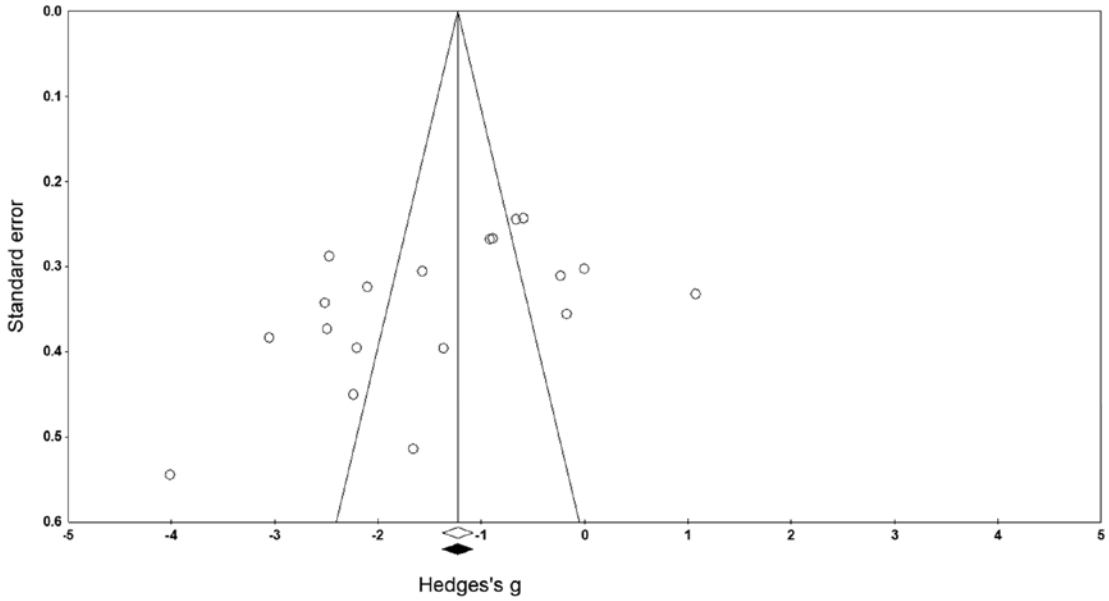

Figure 3. Publication bias funnel plot generated by the Duval and Tweedie trim and fill procedure. Each of the analyzed effects is denoted by a circle in the plot. The boundaries of the plot mark the area where 95% of all the effects would reside in the absence of publication bias. The vertical midline denotes the mean standardized effect of zero. The white and black diamond represent the overall effect size, and the adjusted effect size, respectively.

females and 141 males) received normal saline (control group). Furthermore, two studies did not define or mention the patients' sex distributions (28,30). The mean age of all the patients was 9.1±5.6 years. The mean age of the patients in the bupivacaine and the control group was 9.1±6.4 and 8.8±4.9 years, respectively. However, two studies reported only the overall mean age of their sample (28,30).

Post-operative pain. Of the included studies, 15 studies compared the effects on the perceived levels of pain of patients after receiving tonsillectomy between the bupivacaine and the placebo groups (17,28-34,45-51). An across-group random-effects analysis (Fig. 4) revealed a large negative and significant effect of bupivacaine to reduce the perceived level of pain after tonsillectomy as compared to the effect of normal saline (g, -1.48; 95% CI, -2.08 to -0.87; P<0.01) with negligible heterogeneity (I^2, 14.8%).

Duration of operation. A total of four studies compared the mean duration of the tonsillectomy procedure between the bupivacaine and control groups (17,29,31,34). An across-group random-effect analysis (Fig. 5) revealed a large negative and significant effect of bupivacaine to reduce the mean duration

Table II. Characteristics of the studies included.

Author, year, (ref.)	Patient age (years)	Sample size (n)	Country	Assessment	Follow-up (hours)	Outcomes
Junaid *et al*, 2020 (30)	14.5±7.4 BP: NA NS: NA	180 (83 F, 97 M) BP: 60 (F, M) NS: 30 (F, M)	Pakistan	Visual analog scale	4, 8, 12, 16	Significant reduction in visual analog scale scores in BP as compared to NS.
Abdel and Farouk 2019 (28)	Mean: 8.7 BP: NA NS: NA	60 (31 F, 29 M) BP: 30 (F, M) NS: 30 (F, M)	Egypt	Visual analog scale	1, 4, 8, 24	Significant reduction in visual analog scale scores in BP as compared to NS.
Tuhanioglu and Erkan, 2018 (34)	BP: 30±6 NS: 25±6	BP: 15 (9 F, 6 M) NS: 15 (8 F, 7 M)	Pakistan	Visual analog scale, operating time	0.25, 6, 12, 24, 168	Significant reductions in visual analog scale scores and operating time in BP as compared to NS.
Haksever *et al*, 2014 (32)	BP: 6.0±2.9 NS: 6.7±3.6	BP: 40 (20 F, 20 M) NS: 20 (10 F, 10 M)	Turkey	Visual analog scale, postoperative morbidity	1, 5, 13, 17, 21, 24, 48, 72, 96, 120, 144	Significant reduction in visual analog scale scores in BP as compared to NS. Reduced morbidities related to BP as compared to NS.
Ergil *et al*, 2012 (29)	BP: 6±2 NS: 6±2	BP: 30 (14 F, 16 M) NS: 30 (15 F, 15 M)	Turkey	Visual analog scale, operation duration	0, 0.15, 0.5, 6, 12, 24	Significant reductions in visual analog scale scores and operating time scores in BP as compared to NS.
Özkiriş *et al*, 2012 (31)	BP: 8.1±4.2 NS: 8.1±4.2	BP: 29 (13 F, 16 M) NS: 29 (12 F, 17 M)	Turkey	Visual analog scale, operation duration	1, 4, 8, 16, 24, 48, 72, 96, 120, 144, 168	Significant reduction in visual analog scale scores and operating time scores in BP as compared to NS.
Özmen and Özmen, 2011 (33)	BP: 6.0±3.7 NS: 6.7±3.6	BP: 20 (10 F, 10 M) NS: 20 (11 F, 9 M)	Turkey	Visual analog scale, post-operative morbidity	1, 5, 13, 17, 21, 24, 48, 72, 96, 120, 144	Significant reduction in visual analog scale scores and comorbidities in BP as compared to NS.
Nikandish *et al*, 2008 (17)	BP: 10±2.4 NS: 10±2.3	BP: 33 (14 F, 19M) NS: 36 (17 F, 19 M)	Iran	Visual analog scale, operation duration	1, 2, 4, 6, 8, 12	Significant reduction in visual analog scale scores, operating time score in BP as compared to NS.
Karaaslan *et al*, 2008 (45)	BP: 7.0±0.5 NS: 7.4±0.5	BP: 25 (11 F, 14M) NS: 25 (17 F, 8 M)	Turkey	Children's Hospital of Eastern Ontario pain scale, post-operative morbidity	0.25, 1, 4, 8, 16, 24	Reduction in Children's Hospital of Eastern Ontario pain scale scores in BP as compared to NS. Increased co-morbidities in BP as compared to NS.
Unal *et al*, 2007 (51)	BP: 7.5±3.1 NS: 8.2±2.9	BP: 20 (2 F, 18 M) NS: 20 (4 F, 16 M)	Turkey	Visual analog scale	0, 0.08, 0.16, 0.25, 0.5, 1, 2, 6, 12, 24	No difference in visual analog scale score between BP and NS.
Akoglu *et al*, 2006 (46)	BP: 6.0±2.5 NS: 6.1±1.6	BP: 16 (6 F, 10M) NS: 15 (6 F, 9 M)	Turkey	Children's Hospital of Eastern Ontario pain scale, post-operative morbidity	0.25, 1, 4, 12, 16, 24	Significant reduction in Children's Hospital of Eastern Ontario pain scale scores and comorbidities in BP as compared to NS.
Kaygusuz and Susaman, 2003 (49)	BP: 9±2.7 NS: 8±2.6	BP: 20 (7 F, 13 M) NS: 20 (9 F, 11 M)	Turkey	Visual analogscale, post-operative morbidity	1, 3, 7	Reductions in visual analog scale scores and morbidities in BP as compared to NS.
Johansen *et al*, 1996 (48)	BP: 25 NS: 23	BP: 9 (5 F, 4 M) NS: 10 (6 F, 4 M)	Denmark	Visual analog scale	0, 24, 48, 72, 96, 120, 144, 168, 192, 226, 240	Significant reduction in visual analog scale scores in BP as compared to NS.
Stuart *et al*, 1994 (50)	BP: 6.4 NS: 6.0	BP: 21 (9 F, 12 M) NS: 21 (12 F, 9 M)	UK	Visual analog scale	0, 0.16, 1, 4, 24	No difference in visual analog scale scores between BP and NS.
Jebeles *et al*, 1992 (47)	BP: 7.5±3.1 NS: 8.2±2.9	BP: 20 (7 F, 13 M) NS: 20 (9 F, 11 M)	USA	Visual analog scale	0, 24, 48, 72, 96, 120	No difference in visual analog scale scores between BP and NS.

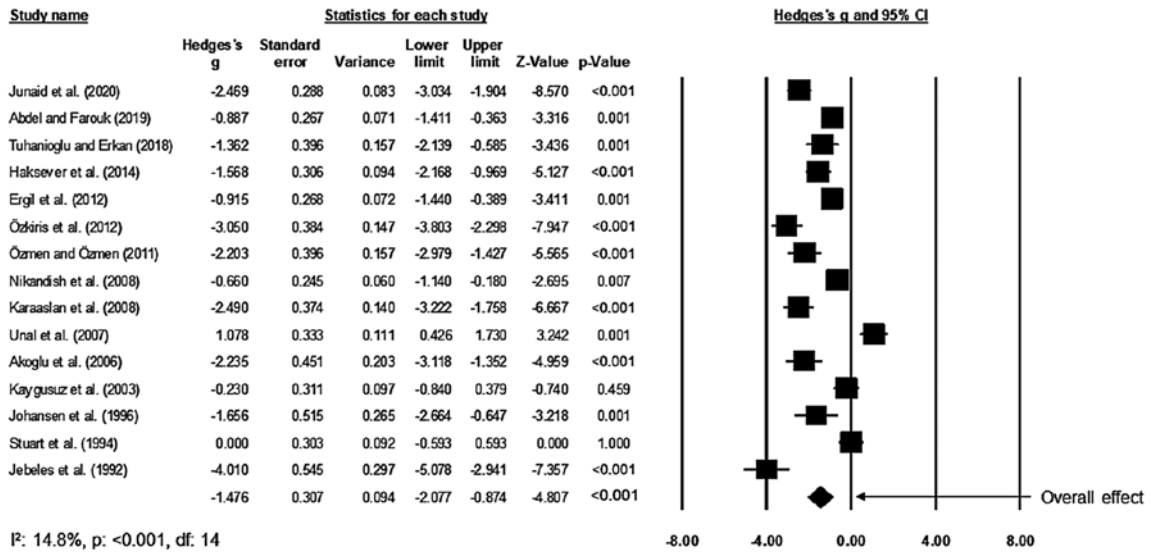

Figure 4. Forest plot for studies evaluating the perceived level of pain between groups receiving either bupivacaine or normal saline 24 h post-tonsillectomy. The weighted effect size is presented as boxes and 95% CIs are presented as horizontal lines. A negative effect represents a reduction in the perceived level of pain for patients receiving bupivacaine during tonsillectomy; a positive effect represents a reduction in the perceived level of pain for patients in the placebo group receiving normal saline during tonsillectomy.

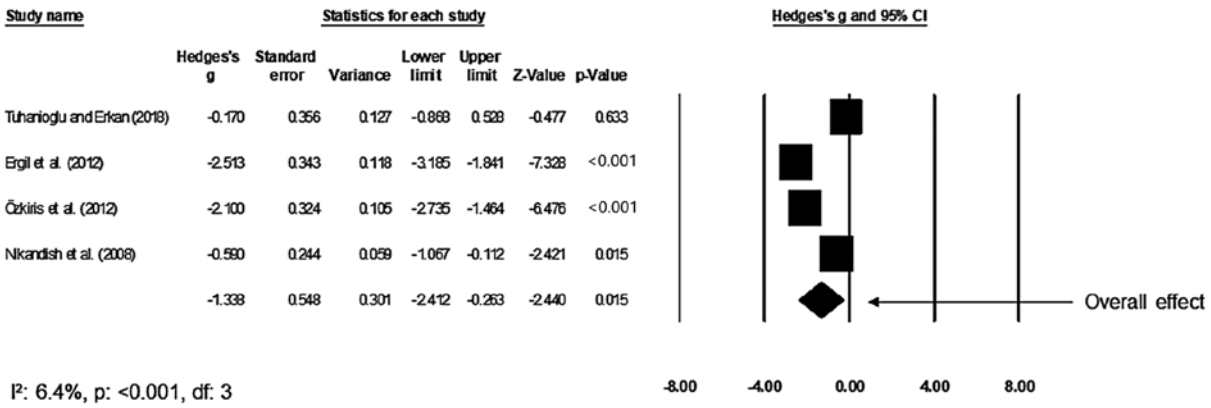

Figure 5. Forest plot for studies evaluating the mean duration of the tonsillectomy procedure between groups receiving either bupivacaine or normal saline. The weighted effect size is presented as boxes and the 95% CIs are presented as horizontal lines. A negative effect represents a reduced duration of the tonsillectomy procedure for patients receiving bupivacaine; a positive effect represents a reduced duration of the tonsillectomy procedure for patients in the placebo group receiving normal saline.

of the tonsillectomy procedure as compared to the effect of normal saline (g, -1.36; 95% CI, -2.44 to -0.27; P=0.01) with negligible heterogeneity (I^2, 6.4%).

Post-operative morbidity. A total of 5 studies compared post-operative morbidity of patients receiving tonsillectomy between the bupivacaine and control groups (32,33,45,46,49). An across-group random-effects analysis (Fig. 6) revealed a small negative and insignificant effect of bupivacaine to reduce post-operative morbidity as compared with that in the normal saline group (g, -0.23; 95% CI, -0.65 to 0.19; P=0.3) with no heterogeneity (I^2, 0%).

Discussion

The present review provided a comprehensive update on intra-operative and post-operative outcomes after administration of bupivacaine. It was demonstrated that the bupivacaine administration during tonsillectomy was associated with a reduction of the perceived level of pain, shorter mean duration of the operation and a decrease in the incidence of post-operative morbidities as compared to the effects of normal saline application.

Due to the complex anatomy of the pharyngeal segments and their prominent vasculature, tonsillectomy represents a challenge for otolaryngologists worldwide (54,55). The traumatic nature of the procedure increases the likelihood of widespread intra-operative and post-operative morbidities (18,30,31,33). To counteract these side effects, bupivacaine has been increasingly recommended during tonsillectomies due to its superior antinociceptive properties and its ability to reduce vascular permeability and inflammation (22-24,48). A review from 1978 by Babst and Gilling (56) suggested that bupivacaine has a high affinity towards neural tissue and acts by inhibiting the onset of action potentials by obstructing Na^+ ion transmission through the neural membrane, and by binding Ca^{2+} ion sites in the

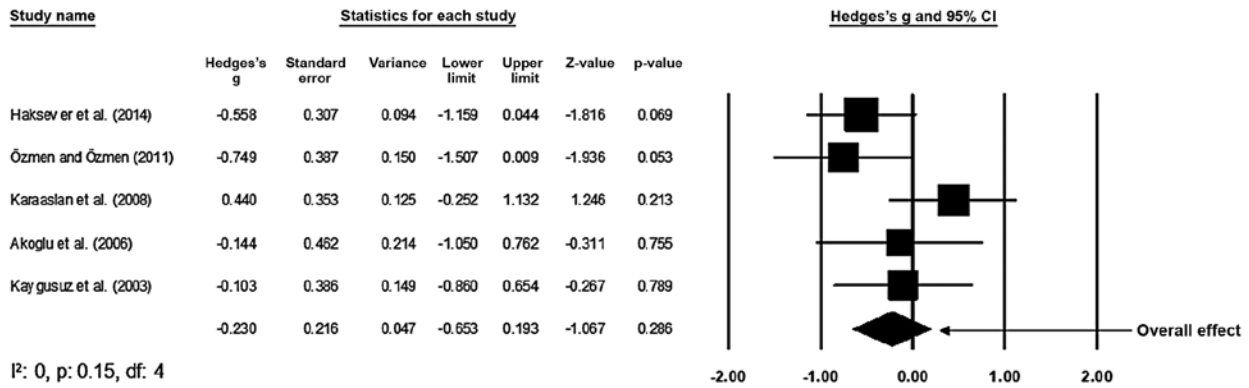

Figure 6. Forest plot for studies evaluating the post-operative morbidity rate between groups receiving either bupivacaine or normal saline during tonsillectomy. The weighted effect size is presented as boxes and 95% CIs are presented as horizontal lines. A negative effect represents a reduced incidence of post-operative morbidity for patients receiving bupivacaine during tonsillectomy; a positive effect represents an increased incidence of post-operative morbidity for patients in the placebo group receiving normal saline during tonsillectomy.

external lipid layer to interfere with the mobility of phosphate groups. Other studies have indicated that the vascular permeability reduction and vasodilation properties of bupivacaine may help prevent the post-operative morbidity associated with tonsillectomy (57,58). In agreement with these studies, the present meta-analysis also suggested that bupivacaine use is associated with beneficial effects after tonsillectomy. Haksever *et al* (32) compared the effects of adjunct administration of 0.5% topical bupivacaine hydrochloride with the administration of normal saline during tonsillectomy and observed a significant reduction in the perceived level of pain from five hours post-surgery till the sixth day of follow-up, and a substantial reduction in the incidence of post-operative morbidities such as trismus, nausea, vomiting and otalgia until the fourth day of follow-up post-tonsillectomy. Similarly, another study reported a significant reduction in the levels of post-tonsillectomy morbidity, including halitosis, fever, nausea, vomiting and otalgia, for the group receiving bupivacaine hydrochloride as compared to the rates in the placebo group (33). The study also indicated that post-operative morbidities were significantly lower during the first, second and the fourth days of follow-up, and a significant reduction in the perceived level of pain between groups from five hours post-tonsillectomy until the sixth day of follow-up was achieved (33). Comparison of the efficacy of bupivacaine and lidocaine suggested that bupivacaine was associated with a significant reduction in post-tonsillectomy morbidities (33). In accordance with the above, the results of the present meta-analysis further confirmed the efficacy of bupivacaine, and a large and significant effect size reduction in the perceived level of post-tonsillectomy pain (Hedge's g, -1.48) was determined in the bupivacaine vs. the placebo group. Furthermore, a small effect size reduction in the onset of post-operative morbidities (-0.23) was obtained in the bupivacaine vs. the control group.

The present analysis also indicated that the use of bupivacaine reduced the incidence of intra-operative complications associated with tonsillectomy. A large effect size reduction in the mean duration of the tonsillectomy operation (-1.36) was observed with the use of bupivacaine as compared to the use of normal saline. In the published literature, a proportional association exists between the duration of an operative procedure and the amount of intra-operative blood loss (59,60), which eventually leads to post-operative morbidities and prolongs the post-surgery recovery period. Collateral incisional damage to palatine, pharyngeal and tonsillar branches of the facial arteries are common during tonsillectomies due to the vascular organization of the tonsillar and the peri-tonsillar arch (61). These accidental incisions may increase the volume of intra-operative hemorrhages, prolong the recovery time after tonsillectomy and result in post-operative complications (61,62). Under such circumstances, the use of bupivacaine may limit intra-operative blood loss, thereby reducing the onset of post-operative morbidities.

Previous studies reported that the use of bupivacaine was associated with an improvement of the hematological outcomes, such as hemoglobin levels. A study included in our review reported an elevation in the level of hemoglobin in a pediatric population undergoing tonsillectomy with bupivacaine (12.1±0.6 mg/dl) as compared to the level in the placebo group (10.8±0.6 mg/dl) (29). The authors concluded that the improvement of hematological outcomes reflects the vasoconstrictive properties of bupivacaine, and at the same time, provides a prophylactic benefit against intra-operative and post-operative hemorrhagic complications, which may require blood transfusions in the pediatric population (63).

Of note, the present review and meta-analysis had certain limitations. First, the systematic review was not registered in a prospective registry such as PROSPERO and this may raise questions regarding the validity of the review (64). Furthermore, no subgroup analyses were performed on the specific doses of bupivacaine used in the studies, which may potentially impact the development of efficient otolaryngologic care guidelines for the optimal use of bupivacaine during tonsillectomies. Future studies should address this issue by performing meta regression-based analyses associating the effects of different dosages of bupivacaine during tonsillectomies. In addition, due to the paucity of the available data, the effectiveness of bupivacaine was not compared between pediatric and adult populations and the results cannot provide recommendations for specific populations. For the same reason, the patients' well-being outcomes, such as patient comfort and quality of life, were not assessed. Hence, further studies addressing these issues are required. The results will assist in developing robust

decision-making models for otolaryngologists to be able to choose ideal interventions and provide high-quality care for their patients.

In conclusion, the present systematic review and meta-analysis provided evidence at the level 1b supporting the use of bupivacaine during tonsillectomy to shorten the duration of the procedure. In addition, bupivacaine reduced the level of post-operative pain and the incidence of associated morbidities. The present results have implications for developing best-practice otolaryngologic care strategies for performing tonsillectomy operations.

Acknowledgements

Not applicable.

Funding

No funding received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JW conceived and designed the study. NW and FG collected the data and performed the analysis and the interpretation of the data. JW was involved in the writing of the manuscript. All authors approved the final manuscript for publication, and agreed to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable

Patient consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

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