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## Review

## Critical review on the efficacy and safety of levobupivacaine peritonsillar infiltration

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## ABSTRACT

Levobupivacaine is a long-acting local anesthetic that is both safe and non-toxic. However, few researchers have examined the efficacy and safety of peritonsillar injections of levobupivacaine for postoperative pain relief. The goal of this study was to assess current randomized controlled trials that employed this strategy. A literature review was conducted using databases such as DELPHIS, PUBMED, COCHRANE, and SCOPUS. A total of fifteen randomized controlled trials were found and thoroughly reviewed. There were no fatalities reported. One study reported a case of nausea and vomiting. In most of the studies, levobupivacaine with magnesium, epinephrine, dexamethasone hydrochloride, tramadol, or levobupivacaine alone were compared to a placebo. Four trials employed different combinations of levobupivacaine and other medicines to recruit adults. Most of the studies had a modest sample size. As a result, larger research with more representative populations should be conducted. Despite certain flaws in the trial design, our findings suggest that levobupivacaine is safe and effective at reducing postoperative pain.

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## 1. Introduction

Tonsillectomy is a common pediatric surgical procedure that removes the tonsils; it can be performed with or without adenoidectomy. The procedure can be complete, whereby the surgeon

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dissects the peritonsillar space between the tonsil capsule and the muscular wall, or partial, whereby varying amounts of tonsillar tissue are removed (Akcan and Dündar, 2018). Bameshki et al. (2013) found that tonsillectomy is associated with moderate to severe pain and difficulty swallowing after surgery, despite advancements in surgical and anesthetic techniques. Undertreatment of pediatric pain has been widely researched and continues to be a concern for healthcare professionals and patients. Many therapeutic modalities have been used in children to treat post-tonsillectomy pain control, including non-steroidal anti-inflammatory agents (NSAIDs), systemic opioids, and local anesthetics (Hasnain et al., 2012). However, systemic opioids can cause respiratory depression, sedation, or nausea and vomiting, while NSAIDs may interfere with bleeding, although they cause less drowsiness, respiratory depression, and vomiting (Cho et al., 2014).

Guidelines related to post-tonsillectomy pain, such as those of the Scottish Intercollegiate Guidelines Network (<http://www.sign.ac.uk/guidelines/fulltext/117/>; Baugh et al., 2011) state that long-acting local anesthetics like bupivacaine and levobupivacaine show lower morbidity than systemic opioids and NSAIDs, but they should not be used as their safety is not yet proven in postoperative pain. In particular, the Scottish intercollegiate Guidelines Network (SIGN) guidelines state that few trials have shown significant evidence of benefits for managing post-tonsillectomy pain by injection of local anesthetic. These guidelines were based on 6 randomized control trials that were conducted in both adults and children (Hollis et al., 2000). A Cochrane review (Grainger and Saravanappa, 2008) involving 13 randomized controlled trials (RCTs) on both adults and children, assessed the effects of pre-operative and postoperative local anesthesia to treat post-tonsillectomy pain. Their findings suggest that the treatment did not produce effective pain relief. However, most of the studies included in that review applied local anesthetics topically or had old evidence. In China, a recent meta-analysis of 7 RCTs compared peritonsillar bupivacaine injection with normal saline in the treatment of post-tonsillectomy pain; one study used levobupivacaine exclusively (Sun et al., 2010). The meta-analysis found that bupivacaine infiltration is a safe and effective method for the relief of pediatric post-adenotonsillectomy pain (Sun et al., 2010). These conflicting results indicate the need for further reviews that verify and assess more recent RCTs that have focused on the efficacy and safety of local anesthetics to treat post-tonsillectomy pain.

Bupivacaine is a fast-acting local anesthetic that has been commonly used since its introduction in 1963. However, it can cause severe cardiovascular and central nervous system toxicity (Moore and Hersh, 2010). Levobupivacaine, introduced in 1999, is a racemic enantiomer of bupivacaine that is reportedly less toxic (Ozcan et al., 2014; Burlacu and Buggy, 2008). The present study aimed to explore the safety and efficacy of peritonsillar levobupivacaine infiltration to treat post-tonsillectomy pain.

Following an intensive literature search of the most popular databases, including MEDLINE and DelphiS, between 2000 and 2018, no specific systematic reviews or meta-analyses addressing the efficacy or safety of levobupivacaine alone on post-tonsillectomy pain relief were found. The present study aimed to verify and critically evaluate recent RCTs involving levobupivacaine (Chirocaine) injection into the peritonsillar space, as well as to apply the principles of evidence-based practice to enhance the safety and reduce the pain of tonsillectomy. The study focused on morbidities collateral to tonsillectomy, such as hemorrhage, toxicity, or mortality, in children and adults receiving peritonsillar levobupivacaine injections. The study provides a basis for future researchers to conduct meta-analyses or large systematic reviews.

## 2. Methodology and search strategy

The following keywords were used in the search: “Tonsil” and “Levobupivacaine”; these were linked using the Boolean operator “AND” to ensure that most results on the topic were found. To expand the search, other keywords relevant to the research question, such as “pain,” “random,” “local,” and “chirocaine” were searched using the OR operator. The search was conducted using the following medical and allied health databases:

- (1) DelphiS (<http://library.soton.ac.uk/delphis/>), which includes WebCat and many other databases, as well as the majority of online journal articles.
- (2) PubMed advanced search (<http://www.ncbi.nlm.nih.gov/books/NBK3827/>), which includes over 25 million citations from the MEDLINE biomedical literature, life science journals, and online books.
- (3) The Cochrane Library (<http://www.cochranelibrary.com/about/about-the-cochrane-library.html>), which includes six databases.
- (4) Scopus (Huber and Swogger, 2014), which covers the life sciences and health sciences.

To find the most recent articles, the search was limited to the past 14 years (2008 to October 2021). However, older articles were referred to if they were frequently cited. The literature review was limited to human studies since most of the previous studies were conducted in human healthcare facilities. Additionally, only articles published in English language publications were chosen. The present search included all age groups—both adults and children—to ensure the widest coverage of the present topic. As noted, most tonsillectomies are performed on children (Kasapoglu et al., 2013). So that the evidence could be properly evaluated, only full-text articles were included. Studies conducted using topical levobupivacaine were excluded as the present study was focused on peritonsillar injections and infiltrations. Low-hierarchy articles, such as reports, expert opinions, and letters to editors, were excluded. The present study aimed to generate level II evidence (RCT), according to the hierarchy of evidence illustrated by the Oxford Centre for Evidence-Based Medicine (<http://www.cebm.net/index.aspx?o=5653>).

## 3. Data analyses

The relevant articles were appraised in terms of the integrity of the methodology to determine scientific content, unbiased result analysis, and statistical tests used (Huber and Tu-Keefner, 2014). The Consolidated Standards of Reporting Trials (CONSORTa) guidelines were used, as detailed by Schulz et al. (2010), with worksheets and OCEBM (<http://www.cebm.net/index.aspx?o=5653>) framework tools for RCTs.

The most recent RCTs addressing levobupivacaine (Chirocaine) injection into the peritonsillar space were critically evaluated, contrasted, and compared. The RCTs used either levobupivacaine alone or levobupivacaine mixed with epinephrine, dexamethasone, or magnesium sulfate.

### 3.1. Peritonsillar injection of levobupivacaine and magnesium

The search yielded 3 articles on this topic, all of which involved children only (3–12 years old). Hashish and Diab (2011) and El-Anwar et al. (2015) used visual analogue scales (VASs) to compare the post-tonsillectomy analgesic effects of levobupivacaine alone and levobupivacaine plus magnesium in Saudi Arabia and Egypt,

respectively. Besides evaluating pain, these studies tested whether the addition of magnesium sulfate reduced the incidence of bronchospasm. El-Anwar et al. (2015) evaluated 40 patients in each group, whereas Hashish and Diab (2011) enrolled 30 patients in each group. They both found that the addition of magnesium is safe, that it significantly increased the analgesic effect of levobupivacaine, and that it significantly decreased the incidence of laryngospasm, without any major complications. Similarly, Karaaslan et al. (2008) conducted a double-blind RCT in Turkey. They recruited 25 patients each to the levobupivacaine, combined treatment, and control (normal saline injection) groups, and used the modified Children's Hospital of Eastern Ontario pain scale (mCHEOPS) to assess the analgesic effects of the treatment. Consistent with Hashish and Diab (2011) and El-Anwar et al., (2015), Karaaslan et al. (2008) discovered that the combination group required less analgesia and had fewer incidents of laryngospasm than the levobupivacaine (LP) alone group. However, the combination group yielded twice as many postoperative nausea and vomiting incidences compared to the control and levobupivacaine alone groups, suggesting that the treatment is less safe, and more well-designed studies must be carried out to confirm these outcome. However, none of the studies were blinded or followed randomized protocol as per the guidelines of CONSORT (Hashish and Diab, 2010).

Although the abstract by El-Anwar et al. (2015) provided a reasonable overview, it did not use sub-headings. Some of the results were published online. Hashish and Diab (2011) produced a long abstract that omitted the group allocations. Although the study by Karaaslan et al. (2008) was the oldest, it utilized the best design, randomizing the groups by using a sealed envelope technique to allocate patients on the operating theatre schedule. Furthermore, Karaaslan et al. (2008) used double blinding, but, like Hashish and Diab (2011), did not specify whether the surgeon was aware of the group allocations. However, they did mention that the drugs had been prepared by an anesthesiologist who was not involved in the postoperative VAS evaluation. This contrasts with the study by El-Anwar et al. (2015) which mentioned all the details of the double-blinding procedure.

No ethical committee approved the study by El-Anwar et al. (2015) although they did mention that they had conformed to the Helsinki Declaration, which is in line with the CONSORT guidelines. The other 2 studies were approved by ethical committees. Furthermore, El-Anwar et al. (2015) incorrectly cited Hashish and Diab (2011)'s study as having been published in the Asian Academy of Management Journal, when it had actually been published in the Al-Azhar Assiut Medical Journal, which shares the same acronym. More importantly, Hashish and Diab (2011) failed to mention whether ethical approval or consent was obtained from the patients' parents/guardians; this goes against the CONSORT and CEBM guidelines.

Although all 3 studies used validated pain scales, Karaaslan et al. (2008) used the mCHEOPS, which is well-established, consistent with child self-reports of pain during injections, and can be used with younger children (Cohen et al., 2008). For this reason, Karaaslan et al. (2008) could analyze children ranging in age from 1 to 13 years, and their sample was therefore more representative of children. In contrast, Stinson et al. (2006) reported that the VAS scale is the most appropriate for children over 8 years of age. El-Anwar et al. (2015) used the scale in patients aged 7–13 years, but they used a small sample, so it is unclear whether their study could be considered representative.

Finally, the results of Hashish and Diab 21 and El-Anwar et al. (2015) must be interpreted with caution, as the researchers' selected patients without randomization, which may have introduced a high risk of bias (Higgins and Altman, 2008). In addition,

in the study by Hashish and Diab (2011), the blinding process was unclear.

### 3.2. Peritonsillar pain relief with levobupivacaine plus epinephrine

In Turkey, Tas et al. (2010) conducted a double-blind RCT in 10 children to compare the effects of levobupivacaine plus epinephrine with those of saline in children who had undergone adenotonsillectomy. They used a VAS to assess pain in an intra-individual study, in which one side of the tonsils was injected with the drug and the other with saline. They concluded that levobupivacaine plus epinephrine decreased early postoperative pain and intra-operative blood loss. Kasapoglu et al. (2013) conducted an RCT comparing the effects of levobupivacaine plus epinephrine infiltration with those of no infiltration (control). They recruited 20 adult patients for each group and used a VAS to assess postoperative pain. They concluded that pre-incisional infiltration of levobupivacaine is a safe and reliable method for post-tonsillectomy pain reduction in adults. Another RCT by Kasapoglu et al. (2011) used the mCHEOPS to compare 3 groups of patients: 20 who were given peritonsillar infiltration of 0.25% levobupivacaine plus 1:200,000 epinephrine, 20 who were given 0.25% bupivacaine plus 1:200,000 epinephrine, and 20 who were given a placebo (normal saline). They concluded that combination of levobupivacaine/bupivacaine with epinephrine was more effective than saline in reducing early post-tonsillectomy pain, and the regimen required less analgesic treatment. Bupivacaine had a slightly longer effect than the placebo group.

Aysenur et al. (2014) performed a double-blind RCT comparing levobupivacaine plus epinephrine and levobupivacaine plus dexamethasone with a placebo (normal saline). They allocated 20 patients to each group and assessed pain using the McGrath's face scale (Fig. 1). They came to the same conclusion as Kasapoglu et al. (2011): levobupivacaine plus epinephrine was more effective than saline, and levobupivacaine plus dexamethasone was the most effective of all groups.

In Turkey, Cicekci et al. (2017) performed a double-blind RCT involving 90 children undergoing tonsillectomy. One group received an intratonsillar injection of levobupivacaine alone, and another received levobupivacaine plus epinephrine. They utilized the mCHEOPS (Table 1), as well as other comorbidities such as postoperative nausea and vomiting, to assess outcome. They concluded that *peri*-operative injection of levobupivacaine alone was a valid alternative to levobupivacaine plus epinephrine to treat pain after pediatric tonsillectomy.

The title of the study by Tas et al. (2010) did not indicate the study design, unlike those of Aysenur et al. (2014) and Kasapoglu et al. (2011) which clearly stated that the study was an RCT. Furthermore, Tas et al. (2010) included only 10 patients in each group, which casts doubt on whether it was sufficiently representative. In addition, although they recorded most hemodynamics and possible complications during the study, they failed to record any extra analgesic drugs given intra-operatively or postoperatively, unlike the other 2 studies. This important confounder may have affected the outcome. In addition, the intra-individual design they used made it difficult to assess pain, and cross-contamination of the agents may have occurred (Kasapoglu et al., 2011). Besides, it is generally accepted that evaluating pain in children is difficult, because children may be unwilling or unable to articulate their pain (Karaaslan et al., 2008). Nonetheless, all the authors used validated scales for pain assessment (Table 1 and Fig. 1).

Kasapoglu et al. (2011), Kasapoglu et al. (2013), Cicekci et al. (2017) and Tas et al., (2010) all mentioned sequence randomization using the sealed envelope technique, but Aysenur et al. (2014) did not. However, none of the studies included details of

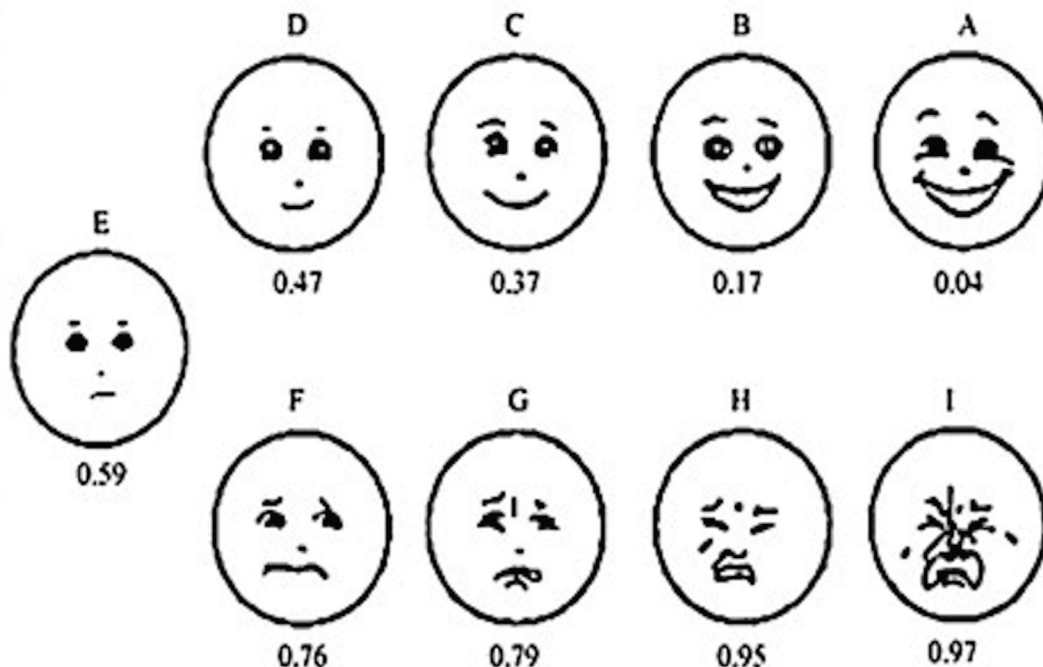


Fig. 1. McGrath's face scale (happy to sad, 9-face scale). Adopted from Aysenur et al. (2014).

**Table 1**  
Pain measures used by the majority of the studies. Ratings adopted from Cohen et al. (2008).

Measure	Brief Description	Age	Rating
(mCHEOPS, McGrath)	Observational measure of post-operative pain in children	1–12 years	Well-established
Pain intensity self-report	Self-report VAS for pain intensity	3–adult years	Well-established
VAS	Horizontal line with descriptive pain anchors at endpoints; intersecting line to indicate intensity		
Hannallah OPS	Observational measure of post-operative pain in children, including score of systolic blood pressure	8 months–13 years	Well-established
FLACC pain scale (Merkel et al., 1997)	OPS incorporating 5 categories of pain behavior	2 months–7 years	Well-established

FLACC, faces, leg, activity, cry, consolability; mCHEOPS, modified children's hospital of Eastern Ontario pain scale; OPS, objective pain scale; VAS, visual analog scale.

whether the sequence randomization was carried out by an independent observer who was not otherwise involved in the study.

All the studies were reported as double-blind. However, that by Tas et al. (2010) may actually have been single-blind, as it mentioned that the surgeons and other staff were unaware of the drug preparations, but there were no details of whether the physicians, nurses, or parents who assessed pain were also unaware. Similarly, neither Kasapoglu et al. (2011) nor Kasapoglu et al. (2013) mentioned whether the surgeon was unaware of the drug prepared.

Cicekci et al. (2017) showed rigorous study design, while the other studies showed design issues and relatively small sample sizes. In particular, the findings of Kasapoglu et al. (2011), Kasapoglu et al. (2011), Aysenur et al. (2014), and Tas et al. (2010) should be taken with caution, as the blinding method was unclear.

The findings were consistent across studies. Only Kasapoglu et al. (2013) utilized an adult sample, so further studies are needed with larger samples to confirm the outcome in adults.

### 3.3. Trials comparing dexamethasone hydrochloride to levobupivacaine

Aysenur et al. (2014) evaluated the effects of preemptive local infiltration using dexamethasone alone versus that using levobupivacaine plus epinephrine on postoperative pain and morbidity in 60 pediatric adenotonsillectomy patients. They concluded that peritonsillar dexamethasone infiltration was more effective than both levobupivacaine plus epinephrine and saline. In another study, Basuni et al. (2013) conducted a double-blind RCT comparing dexamethasone plus levobupivacaine infiltration with levobupivacaine infiltration plus intravenous (I.V) dexamethasone. There were 60 participants in each group, and the study assessed postoperative pain using a VAS. No significant differences occurred between the groups in terms of postoperative emesis, fever, and halitosis. The investigators concluded that infiltration of dexamethasone plus levobupivacaine hydrochloride had better postoperative analgesic effects than I.V. dexamethasone plus peritonsillar levobupivacaine hydrochloride infiltration.

Bayram et al. (2015) conducted a double-blind RCT comparing infiltration of levobupivacaine plus dexamethasone with infiltration of a placebo (normal saline). They recruited 20 adult patients to each group and used a VAS to assess postoperative pain. Despite the difference in sample age, they found similar outcomes to Basuni et al. (2013)—that peritonsillar infiltration of levobupivacaine hydrochloride plus dexamethasone provides pain reduction and decreases analgesic consumption immediately after tonsillectomy.

Among previous studies, Basuni et al. (2013) findings appeared to be clear and comprehensive; they had a clear title, subheadings, and an informative abstract, with recent literature in the introduction. In addition, they used the best randomization technique—

computer generation—and utilised the services of the independent bodies to analyze their data, as per the CONSORT and CEBM guidelines. Furthermore, the researchers confirmed that both the surgeon and the assessor of the VAS (outcome) had been double-blinded and that the drugs had been prepared by an independent observer who was not involved in postoperative pain assessment. However, they stated some inaccurate information in their discussion, suggesting that the VAS can be used in children younger than 3 years of age, which is against recommendations. Moreover, unlike Bayram et al. (2015) they did not mention the study duration, which is against the CONSORT guidelines. In fact, Bayram et al. (2015) were the only researchers to carry out dexamethasone trials using adult participants. Similar to most of the studies discussed, the title did not indicate the design, although the text did have an informative introduction. They used a sealed envelope technique for randomization, although they did not mention details about who performed this task. The state of double blinding in the study was unclear, as the authors did not mention whether the surgeon was unaware of which medication had been prepared, although they did affirm that the same surgeon had carried out all surgical procedures.

To summarize, Basuni et al. (2013) used a large sample to show that levobupivacaine plus dexamethasone can effectively reduce *peri*-operative pain. This was confirmed by Bayram et al. (2015), although their study was less rigorous. Considering the finding by Aysenur et al. (2014) using dexamethasone alone, we suggest that caution be exercised when interpreting these findings—further studies are needed to confirm the outcome.

### 3.4. Trials using tramadol with levobupivacaine injection

El Shafeii et al. (2006) were the only researchers identified to use tramadol alone. They conducted a double-blind RCT comparing 3 groups of 21 patients each—I.V. tramadol analgesic, levobupivacaine infiltration plus I.V. tramadol, and placebo infiltration (normal saline)—using a VAS and blood serum epinephrine levels to indicate postoperative pain. They concluded that the combination of I.V. tramadol and peritonsillar levobupivacaine resulted in better pain scores and fewer side effects than I.V. tramadol alone. Their title was unclear and did not indicate the study design; the abstract did not indicate the vital outcome assessment tool—namely, blood serum epinephrine levels—and the time scale for the study was missing. It is unclear whether ethical approval was obtained. Although they stated that randomization had taken place, they did not state the method used, indicated that the study was conducted by an independent observer, and that measures had been taken to avoid bias. The authors did not indicate whether the study was double-blind, nor did they state whether the surgeon was unaware of the group allocations, although they did affirm that the anesthesiologist and pain score assessor had been blinded to the groups. No record of any extra analgesia drugs given intra-operatively or postoperatively was recorded; this important confounder may have affected the outcome. Further studies with a better design and larger samples are needed to confirm the outcome.

### 3.5. Trials concerning peritonsillar infiltration of levobupivacaine alone

Özmen et al. (2011) conducted a double-blind RCT comparing 3 groups of 20 patients each: levobupivacaine, bupivacaine, and control placebo (normal saline). They used the McGrath's face scale to assess pain and concluded that local infiltration of levobupivacaine is a safe and effective method and is equivalent to bupivacaine in the treatment of post-tonsillectomy pain. Erdogan et al. (2014) conducted a controlled trial comparing peritonsillar levobupiva-

caine infiltration with saline injection—there were 22 adult patients in each group, and the investigators assessed postoperative pain using a VAS. They concluded that pre-incisional levobupivacaine infiltration is a safe and easily applied medication for postoperative pain control, and that it decreased the volume of blood loss in adult patients during tonsillectomy. Cakar Turhan et al. (2015) conducted an RCT comparing 2 concentrations of levobupivacaine (0.25% vs. 0.5%) with a placebo (normal saline). They recruited 24 patients in each group and evaluated pain using the “faces, leg, activity, cry, consolability” (FLACC) scale (Table 1). They concluded that the different concentrations of levobupivacaine were equally safe and effective during pre-incisional peritonsillar infiltration in children. Lastly, Ergil et al. (2012) performed a double-blind RCT comparing 3 groups of 30 patients each: peritonsillar infiltration of levobupivacaine, lidocaine plus epinephrine, and a placebo control (normal saline). They used the Hannallah pain score and concluded that levobupivacaine had a vasoconstrictive effect at 0.25% concentrations and a consistent analgesic effect; this may be beneficial in patients who have undergone tonsillectomy.

Erdogan et al. (2014) were the only investigators to recruit adults. They reported that ethical approval had been obtained and that consent had been received from patients. However, they did not explain whether they avoided bias by randomization or blinding. The demographic table revealed an unequal gender distribution between both groups, which goes against CEBM requirements, and they did not account for the extra analgesia medications given to patients—this confounder may have affected the outcome and precision of the results. Of the 4 studies, only Özmen et al. (2011) mentioned the timescale.

None of the 4 studies stated whether randomization or coding of medication had been carried out by an independent observer to avoid bias (Özmen et al., 2011, Erdogan et al., 2014, Cakar Turhan et al., 2015, Ergil et al., 2012). However, they did indicate the use of the sealed envelope technique for random sequence generation.

Although all the trials mentioned that double blinding had taken place, only Ergil et al. (2012) mentioned sufficient details. Unclear or single blinding was found in the study by Ozmen et al.34 who did not mention whether the anesthesiologist who had assessed pain was unaware of the group allocated. Similarly, Cakar Turhan et al. (2015) failed to mention whether the surgeon was aware of the group allocation.

Despite the comments by Erdogan et al. (2014), their findings in adult tonsillectomies must be confirmed by larger, well-designed studies. Regardless of any design issues, the other studies in pediatric tonsillectomy are consistent with their findings and show overwhelming evidence of the use of levobupivacaine in peritonsillar infiltration for postoperative pain relief.

## 4. Discussion

Most studies in this review were level II RCTs, and they varied in strength and rigour (Table 2). All 15 articles included a peritonsillar injection of levobupivacaine mixed with other medications or injected alone.

Basuni et al. (2013) who used dexamethasone plus levobupivacaine, seemed to conduct the most rigorous study, as they avoided design issues by expressly detailing randomization and blinding. Hashish and Diab (2011) and Erdogan et al. (2014), on the other hand, lacked rigour because they used unclear double-blinding and no randomization. In addition, Hashish and Diab (2011) failed to obtain informed consent from parents or indicate ethical approval.

**Table 2**  
Summary of articles included in the literature review.

Author	Sample	Level of evidence	Conclusion	Bias risk	Comments
Kasapoglu et al. (2013)	40 adults	II	Pre-incisional infiltration of levobupivacaine is a safe and reliable method for post-tonsillectomy pain reduction in adults.	Low	Unclear double blinding; unclear randomization sequence generation
Özmen et al. (2011)	60 children, 2–12 years old	II	Local infiltration of levobupivacaine is a safe and effective method equivalent to bupivacaine for post-tonsillectomy pain.	Low	Unclear double blinding; unclear randomization sequence generation
Ergil et al. (2012)	90 children, 2–10 years old	II	Levobupivacaine has a vasoconstrictive effect at 0.25% concentrations that may be beneficial in tonsillectomy patients; it also has a consistent analgesic effect.	Low	Unclear randomization sequence generation
Erdogan et al. (2014)	44 adult patients	II	Pre-incisional levobupivacaine infiltration is a safe and easily applied medication for post-operative pain control. It decreases the volume of intraoperative blood loss in adult patients after tonsillectomy.	High	No randomization; no blinding; confounders not considered (precision); unequal gender within groups
Cakar Turhan et al. (2015)	72 children, 3–12 years old	II	Different concentrations of levobupivacaine are equally safe and effective during pre-incisional peritonsillar infiltration in children.	Low	Unclear double blinding; unclear randomization sequence generation
Karaaslan et al. (2008)	75 children, 3–12 years old	II	Levobupivacaine and levobupivacaine plus magnesium infiltration decrease the post-tonsillectomy analgesic requirement.	Low	Unclear double blinding; small sample
Hashish and Diab (2011)	60 children, 8–12 years old	II	Addition of magnesium to local infiltration anesthetics into the peritonsillar fossa decreases pain after tonsillectomy.	Very high	No randomization; unclear double blinding; no informed consent taken from parents; no indication of ethical approval
El-Anwar et al. (2015)	80 children, 7–13 years old	II	Addition of magnesium to levobupivacaine local infiltration into the peritonsillar area is safe and significantly augments the analgesic effect of levobupivacaine after tonsillectomy in children.	High	No randomization
Tas et al. (2010)	20 children, 6–13 years old	II	Pre-incisional injection of levobupivacaine with epinephrine decreases early post-operative pain and intraoperative blood loss of tonsillectomy.	Low	Small sample; unclear randomization sequence generation; unclear double blinding
Kasapoglu et al. (2011)	60 children, around 6 years old	II	Pre-incisional peritonsillar infiltration with levobupivacaine combined with epinephrine or bupivacaine are more effective than placebo in reducing early post-tonsillectomy pain and reduce the requirement for analgesics. Bupivacaine had a slightly longer effect than placebo.	Low	Unclear randomization sequence generation; unclear double blinding; relatively small sample
Aysenur et al. (2014)	60 children, 3–14 years old	II	Peritonsillar dexamethasone infiltration was more effective than both levobupivacaine plus epinephrine and saline in reducing post-tonsillectomy pain.	High	Unclear methodology; unclear randomization sequence generation
Basuni et al. (2013)	120 children, 6–12 years old	II	Addition of dexamethasone to levobupivacaine for pre-operative peritonsillar infiltration has better post-operative analgesic effects than I.V. dexamethasone plus peritonsillar levobupivacaine infiltration in children.	Very low	No time scale
Bayram et al. (2015)	40 adults, 18–60 years old	II	Peritonsillar infiltration of levobupivacaine hydrochloride plus dexamethasone reduces pain and decreases analgesic consumption after tonsillectomy.	Low	Unclear randomization sequence generation; unclear double blinding; relatively small sample
El Shafeii et al. (2006)	42 adults, 16–30 years old	II	I.V. tramadol plus peritonsillar levobupivacaine has better pain scores and fewer side effects than I.V. tramadol alone.	High	Unclear whether ethical approval was obtained; unclear randomization sequence generation unclear double blinding
Cicekci et al. (2017)	90 pediatric 5–12 years old	II	Peri-operative levobupivacaine infiltration alone is a valid alternative to levobupivacaine plus epinephrine for peri-operative and post-operative pain relief after pediatric tonsillectomy.	Low	No time scale

Most of the studies involved children. Only Kasapoglu et al. (2013), Bayram et al. (2015), El Shafeii et al. (2006), and Erdogan et al. (2014) recruited adults and used different mixtures of medications with levobupivacaine via *peri*-tonsillar infiltration (Erdogan et al., 2014). The average sample size of these 4 studies was 20 patients per group. This confirms the need for larger, well-designed studies that are more representative to confirm outcomes.

Surgeons have used different techniques to perform tonsillectomy; the most conventional of these are cold steel and/or cautery dissection, as well as vessel sealing systems, harmonic scalpels, and coblation. However, no significant differences in postoperative

pain were found between the coblation and/or harmonic scalpel methods compared with the cold steel and/or cautery techniques (Oomen et al., 2012).

None of the studies reported any mortality. Morbidity was reported by El-Anwar et al. (2015) with an increase in nausea and vomiting.

Further studies must give detailed descriptions of their methodologies, and they need to show how they avoided bias through detailed randomization and blinding techniques. They must confirm that all confounders have been considered by declaring the incidence of extra narcotic use during and after surgery, as well as the dosage and timing of peritonsillar infiltration.

## 5. Conclusion

Finally, multi-centered RCTs with larger populations are needed. Despite weaknesses in the studies about pediatric peritonsillar injections, the overwhelming evidence shows that levobupivacaine is safe and reduces postoperative pain.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

Akcan, F.A., Dündar, Y., 2018. Posterior pillar mucosal suspension technique for posttonsillectomy pain and wound healing: a prospective, randomized, controlled trial. *Eur. Arch. Otorhinolaryngol.* 275 (11), 2879–2887.

Aysenur, D., Mine, C., Ozgur, Y., Ahmet, A.H., Fuat, E.A., Ilker, I., et al., 2014. Pre-emptive peritonsillar dexamethasone vs. levobupivacaine infiltration for relief of post-adenotonsillectomy pain in children: a controlled clinical study. *Int. J. Pediatr. Otorhinolaryngol.* 78 (9), 1467–1471.

Bameshki, A.R., Razban, M., Khadivi, E., Razavi, M., Bakhshae, M., 2013. The effect of local injection of epinephrine and bupivacaine on post-tonsillectomy pain and bleeding. *Iran J. Otorhinolaryngol.* 25, 209–214.

Basuni, A.S., Ezz, H.A.A., Albirmawy, O.A., 2013. Preoperative peritonsillar infiltration of dexamethasone and levobupivacaine reduces pediatric post-tonsillectomy pain: a double-blind prospective randomized clinical trial. *J. Anesth.* 27 (6), 844–849.

Baugh, R.F., Archer, S.M., Mitchell, R.B., Rosenfeld, R.M., Amin, R., Burns, J.J., Darrow, D.H., Giordano, T., Litman, R.S., Li, K.K., Mannix, M.E., Schwartz, R.H., Setzen, G., Wald, E.R., Wall, E., Sandberg, G., Patel, M.M., 2011. Clinical practice guideline: tonsillectomy in children. *Otolaryngol. Head Neck Surg.* 144 (1\_suppl), S1–S30.

Bayram, A., Dogan, M., Cihan, C., Karatas, D., Gokahmetoglu, G., Ozcan, I., 2015. The efficacy of levobupivacaine hydrochloride-dexamethasone infiltration for post-tonsillectomy pain in adults. *J. Craniofac. Surg.* 26, e651–e653.

Burlacu, C.L., Buggy, D.J., 2008. Update on local anesthetics: focus on levobupivacaine. *Therapeut. Clin. Risk Manage.* 4, 381–392.

Cakar Turhan, K.S., Salviz, E.A., Beton, S., Timuroglu, S.T., Catav, S., Ozatamer, O., 2015. Peritonsillar infiltration with levobupivacaine for posttonsillectomy pain relief: does concentration have any effect? A double-blind randomized controlled clinical study. *Eur. Rev. Med. Pharmacol. Sci.* 19, 1276–1284.

Cho, H.K., Kim, K.W., Jeong, Y.M., Lee, H.S., Lee, Y.J., Hwang, S.H., 2014. Efficacy of ketamine in improving pain after tonsillectomy in children: meta-analysis. *PLoS One* 9, e101259.

Cicekci, F., Sizer, C., Atici, S.S., Arican, S., Karabrahimoglu, A., Kara, I., 2017. Comparison of the perioperative and postoperative effects of levobupivacaine and of levobupivacaine + adrenaline in pediatric tonsillectomy: A double-blind randomized study. *Pain Res. Manage.* 2017, 1–7.

Cohen, L.L., Lemanek, K., Blount, R.L., Dahlquist, L.M., Lim, C.S., Palermo, T.M., McKenna, K.D., Weiss, K.E., 2008. Evidence-based assessment of pediatric pain. *J. Pediatr. Psychol.* 33 (9), 939–955.

El Shafeii, K., Mounir, A., Affi, M., 2006. Tramadol with and without peritonsillar levobupivacaine infiltration for effective pain control and patient satisfaction after tonsillectomy in adults. *Egypt J. Anaesth.* 22, 239–243.

El-Anwar, M.W., Mostafa, K., Elsamad, A., 2015. Levobupivacaine alone versus levobupivacaine plus magnesium infiltration for post-tonsillectomy analgesia. *Int. J. Pharmacol.* 11 (5), 490–495.

Erdogan, B.A., Aydin, S., Paksoy, M., Sanli, A., Sevim, S., 2014. Efficacy of preincisional levobupivacaine for adult tonsillectomy patients. *B-ENT* 10, 193–197.

Ergil, J., Akkaya, T., Gozaydin, O., Gunsoy, B., Alicura, S., Aladag, E., Gumus, H., Akin, I., 2012. Vasoconstrictive and analgesic efficacy of locally infiltrated levobupivacaine in tonsillectomy patients. *Int. J. Pediatr. Otorhinolaryngol.* 76 (10), 1429–1433.

Grainger, J., Saravanappa, N., 2008. Local anaesthetic for post-tonsillectomy pain: a systematic review and meta-analysis. *Clin. Otolaryngol.* 33 (5), 411–419.

Hashish, M., Diab, A., 2011. Levobupivacaine plus magnesium used for postoperative analgesia in pediatric tonsillectomy patients compared to levobupivacaine alone. *Al-Azhar Assiut. Med. J.* 9, 261–277.

Hasnain, F., Janbaz, K.H., Qureshi, M.A., 2012. Analgesic effect of ketamine and morphine after tonsillectomy in children. *Pak. J. Pharm. Sci.* 25, 599–606.

Higgins, J.P.T., Altman, D.G., 2008. Assessing risk of bias in included studies. In: Higgins, J.P.T., Green, S. (Eds.), *Cochrane handbook for systematic reviews of interventions: Cochrane book series*. The Cochrane Collaboration, London, England, pp. 187–241.

Hollis, L.J., Burton, M.J., Millar, J.M., 2000. Perioperative local anaesthesia for reducing pain following tonsillectomy. *Cochrane Database Syst. Rev.*, CD001874

Huber, J.T., Swogger, S. (Eds.), 2014. *Introduction to reference sources in the health sciences*. 6th edition. American Library Association, Philadelphia.

Huber, J.T., Tu-Keefner, F., editors, 2014. *Health Librarianship: An Introduction*. Santa Barbara: ABC-CLIO.

Karaaslan, K., Yilmaz, F., Gulcu, N., Sarpkaya, A., Colak, C., Kocoglu, H., 2008. The effects of levobupivacaine versus levobupivacaine plus magnesium infiltration on postoperative analgesia and laryngospasm in pediatric tonsillectomy patients. *Int. J. Pediatr. Otorhinolaryngol.* 72 (5), 675–681.

Kasapoglu, F., Demir, U.L., Kaya, F.N., Cetin, Y.S., Yavascaoglu, B., 2013. The effects of levobupivacaine infiltration on post-tonsillectomy pain relief in adults: a single-blinded, randomized, and controlled clinical study. *Eur. Arch. Otorhinolaryngol.* 270 (2), 761–766.

Kasapoglu, F., Kaya, F.N., Tuzemen, G., Ozmen, O.A., Kaya, A., Onart, S., 2011. Comparison of peritonsillar levobupivacaine and bupivacaine infiltration for post-tonsillectomy pain relief in children: placebo-controlled clinical study. *Int. J. Pediatr. Otorhinolaryngol.* 75 (3), 322–326.

Merkel, S.L., Voepel-Lewis, T., Shayevitz, J.R., Malviya, S., 1997. The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatr. Nurs.* 23, 293–297.

Moore, P.A., Hersh, E.V., 2010. Local anesthetics: pharmacology and toxicity. *Dent. Clin. North Am.* 54 (4), 587–599.

Oomen, K.P.Q., Modi, V.K., Stewart, M.G., 2012. Evidence-based practice: pediatric tonsillectomy. *Otolaryngol. Clin. North Am.* 45 (5), 1071–1081.

Ozcan, E., Izdes, S., Ozturk, L., Kanbak, O., 2014. Comparison of the efficacy of different concentrations and volumes of levobupivacaine in axillary brachial plexus blockade. *Minerva Anesthesiol.* 80, 330–336.

Özmen, S., Özmen, Ö.A., Kasapoğlu, F., 2011. Effects of levobupivacaine versus bupivacaine infiltration on postoperative analgesia in pediatric tonsillectomy patients: a randomized, double-blind, placebo-controlled study. *Ann. Otol. Rhinol. Laryngol.* 120 (7), 489–493.

Schulz, K.F., Altman, D.G., Moher, D., 2010. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 340 (mar23 1), c332.

Stinson, J.N., Kavanagh, T., Yamada, J., Gill, N., Stevens, B., 2006. Systematic review of the psychometric properties, interpretability and feasibility of self-report pain intensity measures for use in clinical trials in children and adolescents. *Pain* 125, 143–157.

Sun, J., Wu, X., Meng, Y., Jin, L., 2010. Bupivacaine versus normal saline for relief of post-adenotonsillectomy pain in children: a meta-analysis. *Int. J. Pediatr. Otorhinolaryngol.* 74 (4), 369–373.

Tas, E., Hanci, V., Ugur, M.B., Turan, I.O., Yigit, V.B., Cinar, F., 2010. Does preincisional injection of levobupivacaine with epinephrine have any benefits for children undergoing tonsillectomy? An intraindividual evaluation. *Int. J. Pediatr. Otorhinolaryngol.* 74 (10), 1171–1175.

## Further Reading

OCEBM Levels of Evidence Working Group, 2011. *The Oxford 2011 levels of evidence*. Oxford Centre for Evidence-Based Medicine. (2011). [Online] Available at: <http://www.cebm.net/index.aspx?o=5653> [Accessed 1.10. 2018].

Scottish Intercollegiate Guidelines Network (SIGN), 2010. *Guideline 117: Management of sore throat and indications for tonsillectomy*. [Online] Available at: <http://www.sign.ac.uk/guidelines/fulltext/117/> [Accessed 1.10. 2018].

Soton. Home - DelphiS - LibGuides@Southampton at University of Southampton Library. (2018). [Online] Available at: <http://library.soton.ac.uk/delphis> [Accessed 1.10. 2018].

The Cochrane Library, 2018. *About the Cochrane Library*. [Online] Available at: <http://www.cochranelibrary.com/about/about-the-cochrane-library.html> [Accessed 1.10. 2018].

U.S National Library of Medicine, 2015. *National Center for Biotechnology Information (US)*. [Online] Available at: <http://www.ncbi.nlm.nih.gov/books/NBK3827/> [Accessed 1.10. 2018].