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Review Article

PROSPECT guideline for tonsillectomy: systematic review and procedure-specific postoperative pain management recommendations

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Summary

Tonsillectomy is one of the most frequently performed surgical procedures; however, pain management remains challenging. Procedure-specific efficacy as well as specific risks of treatment options should guide selection of pain management protocols based on evidence and should optimise analgesia without harm. The aims of this systematic review were to evaluate the available literature and develop recommendations for optimal pain management after tonsillectomy. A systematic review utilising preferred reporting items for systematic reviews and meta-analysis guidelines with procedure-specific postoperative pain management (PROSPECT) methodology was undertaken. Randomised controlled trials published in the English language up to November 2019 assessing postoperative pain using analgesic, anaesthetic or surgical interventions were identified. Out of the 719 potentially eligible studies identified, 226 randomised controlled trials met the inclusion criteria, excluding the studies examining surgical techniques. Pre-operative and intra-operative interventions that improved postoperative pain were paracetamol; non-steroidal anti-inflammatory drugs; intravenous dexamethasone; ketamine (only assessed in children); gabapentinoids; dexmedetomidine; honey; and acupuncture. Inconsistent evidence was found for local anaesthetic infiltration; antibiotics; and magnesium sulphate. Limited evidence was found for clonidine. The analgesic regimen for tonsillectomy should include paracetamol; non-steroidal anti-inflammatory drugs; and intravenous dexamethasone, with opioids as rescue analgesics. Analgesic adjuncts such as intra-operative and postoperative acupuncture as well as postoperative honey are also recommended. Ketamine (only for children); dexmedetomidine; or gabapentinoids may be considered when some of the first-line analgesics are contra-indicated. Further randomised controlled trials are required to define risk and combination of drugs most effective for postoperative pain relief after tonsillectomy.

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Recommendations

1 The basic analgesic regimen should include paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) administered pre-operatively or intra-operatively and continued postoperatively.
2 A single dose of intravenous (i.v.) dexamethasone is recommended for its analgesic and anti-emetic effects.
3 Pre-operative gabapentinoids, intra-operative ketamine (only in children) and dexmedetomidine are recommended in patients with contra-indications to the basic analgesic regimen.
4 Analgesic adjuncts such as intra-operative and postoperative acupuncture and postoperative honey are recommended.
5 Opioids should be reserved as rescue analgesics in the postoperative period.

Why was this guideline developed?

Tonsillectomy is one of the most frequently performed surgical procedures and pain management remains challenging. The aim of this procedure-specific guideline is to provide clinicians with up-to-date evidence for optimal pain management in tonsillectomy, and recommendations made based on this evidence, adverse effects and considerations regarding risks of interventions. Although other guidelines for tonsillectomy pain management are available, none have used the procedure-specific postoperative pain management (PROSPECT) methodology to critically evaluate the available literature. This includes a systematic evidence-based approach, the inclusion of a basic analgesic regimen for efficacy evaluation, a balance between efficacy and safety and a Delphi process for the final recommendations with international surgeons and anaesthetists involved.

How does this guideline differ from other guidelines?

The French Oto-Rhino-Laryngology Head and Neck Surgery Society [1] and Ericsson et al. [2] published guidelines for post-tonsillectomy pain management in adults in 2014 and children in 2015, respectively. Both made recommendations based on expert consensus within the respective national societies based on published literature. These vary from the present guidelines in the process of our literature search, the use of a Delphi study to ratify our recommendations and we include contemporary studies from the last 5 years that are not included in previous guidelines. Moreover, previous guidelines do not highlight the importance of baseline analgesia. The PROSPECT approach to developing guidelines is unique such that the available evidence is critically assessed for current clinical relevance and the use of simple, non-opioid analgesic such as paracetamol and NSAIDs as basic analgesics are considered. This approach reports clinical effectiveness by balancing the invasiveness of the analgesic interventions and the degree of pain after surgery, as well as balancing efficacy and adverse effects.

Introduction

The management of post-tonsillectomy pain can be challenging and often inadequate. Tonsillectomy has been identified as one of the most painful surgical procedures [1], probably because pain remains poorly managed in clinical practice [1–3]. There are many reasons for undertreating pain after tonsillectomy, including clinicians underestimating the degree of pain associated with tonsillectomy surgery due to the fact that the surgical procedure is considered to be minimally invasive [1]. Moreover, despite numerous studies comparing and combining analgesics to find the most effective postoperative regimen, there is still no consensus on the best treatment strategy. Tonsillectomy is unique for several reasons including the type of tissue trauma, the exposure of the healing wound to movement of the pharynx during ingestion, the risk of bleeding and limitations in the choice of drugs, particularly in children. Thus, the ideal regimen providing adequate analgesia with few side-effects after tonsillectomy remains to be defined. Guidelines on pain management after tonsillectomy have previously been published [4, 5].

The PROSPECT Working Group is a collaboration of surgeons and anaesthetists working to formulate procedure-specific recommendations for pain management after common but potentially painful operations [6]. The recommendations are based on a procedure-specific systematic review of randomised controlled trials. The methodology considers clinical practice, efficacy and adverse effects of analgesic techniques [7].

The aim of this systematic review was to evaluate the available literature on the management of pain after tonsillectomy in both adults and children. Pain scores and analgesic requirements were the primary focus, but other recovery outcomes, including adverse effects, were also assessed when reported, and the limitations of the data were reviewed. The ultimate aim was to develop recommendations for pain management after tonsillectomy.

Methods

The methods of this review adhered to the PROSPECT methodology as previously reported [8]. Specific to this study, the Embase, MEDLINE, PubMed, OpenGrey, Web of

Science and Cochrane Databases (Cochrane Central Register of Controlled Trials; Cochrane Database of Abstracts or Reviews of Effects; Cochrane Database of Systematic Reviews) were searched for randomised controlled trials on 24 November 2019 with no time limitation. The search terms related to pain management or surgical interventions for tonsillectomy are in online Supporting Information Appendix S1. Studies that reported data pooled from patients undergoing mixed surgical procedures or procedures other than tonsillectomy or adenotonsillectomy were excluded, but we included studies in which a combination of tonsillectomy and adenotonsillectomy procedures was performed. We included studies of adults or paediatric patients (< 18 years of age).

Quality assessment, data extraction and data analysis adhered to the PROSPECT methodology [8]. Pain intensity scores were used as the primary outcome measure. In this study, we defined a change of more than 10 mm on the visual analogue scale or numerical rating score as clinically relevant. The aim was to qualitatively assess the data and not to perform a meta-analysis.

Recommendations were made according to PROSPECT methodology [8]. In brief, this involved a grading of A–D according to the overall level of evidence, as determined by the quality of studies included; consistency of evidence; and study design. The proposed recommendations were sent to the PROSPECT Working Group for review and comments and a modified Delphi approach was utilised as previously described. Once a consensus was achieved, the lead authors drafted the final document, which was ultimately approved by the Working Group.

Results

The systematic literature search identified 7851 records. After exclusion of duplicates and studies not fulfilling our predefined inclusion criteria, 226 studies were included in the qualitative analysis (Fig. 1). The results of the methodological quality assessments of are summarised in online Supporting Information Table S1. The characteristics of the included studies are shown in online Supporting Information Tables S2 and S3.

Among the 226 studies included in our analysis, 158 included paediatric patients, 40 included adult patients and 28 involved a mixed population. The definition of adult and paediatric age groups varied considerably among studies, where some of the studies included within the paediatric group participants up to the age of 20, 18 or 16. Our results pool paediatric and adult patients as 28 of the studies included both and we were unable to elucidate the age-groups patients in those studies. When results were different, or only studied in one population, we present specific analyses.

Paracetamol

Sixteen studies (two with a mixed population and 14 in children) involving 2058 patients were included. Paracetamol was administered intra-operatively in 10 studies, intra-operatively and postoperatively in four studies and postoperatively only in two studies. Two studies reported an analgesic benefit when compared with placebo [9, 10]; pain scores and morphine consumption were lower. In head-to-head comparisons with NSAIDs or dexamethasone, pain scores and morphine consumption were comparable [11, 12]. One study demonstrated that one dose of dexamethasone had a stronger analgesic effect than one dose of paracetamol when given intra-operatively in children [13]. One study reported a weak benefit (reduction of opioid consumption) of the combination of NSAIDs with paracetamol [10]. Finally, the rectal route was found less efficient than i.v. or oral routes in one study [14].

Non-steroidal anti-inflammatory drugs

Twenty-six studies (eight in adults; three with a mixed population; and 15 in children) including 2455 patients were considered for analysis. Pain was the primary outcome in all studies. Twenty studies supported the use of NSAIDs, showing an opioid-sparing effect and a reduction in pain scores when compared with placebo. In most studies showing an effect, NSAIDs were administered intravenously or orally, pre- or intra-operatively. Moreover, NSAIDs and cyclo-oxygenase-2 (COX-2) inhibitors showed similar efficacy.

Three studies showed that the opioid-sparing effect was associated with a reduction in postoperative nausea and vomiting [15–17]. As for complications associated with NSAIDS, there was no evidence for increased bleeding reported in the included studies. Two meta-analyses published in 2013 confirmed that NSAIDs administration during tonsillectomy is not associated with an increased risk of bleeding [18, 19].

Local anaesthetic infiltration and topical application

Out of the 51 studies retrieved, 21 compared bupivacaine with placebo (online Supporting Information Table S3). No studies included a basic analgesic regimen. Looking at the paediatric and adult studies separately, 7/10 (70%) of adult studies reported a reduction in pain scores after local anaesthetic infiltration, while 15/31 (48%) of paediatric

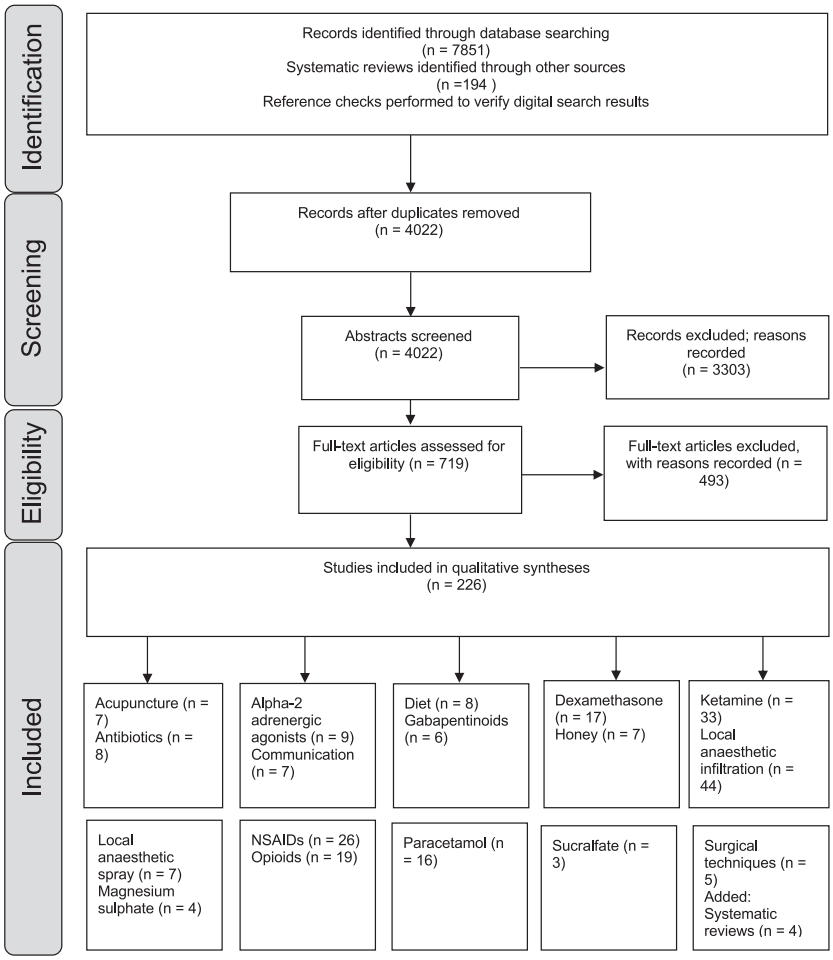

Figure 1 Diagram of included studies. NSAIDs, non-steroidal anti-inflammatory drugs.

studies and 10/10 (100%) of the mixed population studies were supportive of it.

However, the analgesic benefit reported in some studies was minor and limited to the very early postoperative period [20, 21]. No evidence favouring one local anaesthetic agent over another was found. The technique of infiltration itself was not standardised in the literature and systemic absorption of local anaesthetic was an associated risk. Indeed, three studies have reported complications [22–24] including arrhythmias; bleeding; intravascular injection; and sedation. In detail, Unal et al. [22] reported greater sedation scores with bupivacaine and ropivacaine infiltration compared with saline infiltration. Tolska et al. [23] found that bleeding requiring haemostasis under local anaesthesia was more common in the ropivacaine group (10/54 (18%)) than in the control group (4/47 (8%)). One patient out of the 54 patients included in the ropivacaine group sustained postoperative bilateral pneumonia requiring 5 days of hospitalisation. Junaid et al. [24] reported six transient cardiac arrhythmias out of the 30 enrolled patients in the bupivacaine infiltration group and concluded that there was an increased risk of complications. Bean-Lijewski et al. [25] described injection of 3–10 ml of bupivacaine 0.25–0.5% into each lateral pharyngeal space; the study was terminated after eight children had been enrolled because two out of four children receiving bupivacaine developed severe upper airway obstruction after tracheal extubation. This study concluded that bilateral local anaesthetic injection into the lateral pharyngeal space may induce an increased risk of severe upper airway obstruction and loss of protective reflexes.

Only one study [26] and one meta-analysis [27] have been published since 2007 on the efficacy of lidocaine spray on postoperative pain after tonsillectomy. Jahromi et al. [26] reported that lidocaine spray reduced pain scores for only 20 min after surgery when compared with saline or ketamine spray. The meta-analysis was inconclusive as the risk of bias was

high in most of the included trials and poor reporting quality and inadequate data did not permit comprehensive and reliable conclusions to be made.

Peripheral nerve block

Glossopharyngeal nerve block demonstrated advantages over normal saline injection or no injection in four studies involving 315 patients [28–31]. Two studies reported severe complications. Park et al. [29] described intravascular injection and tachycardia in 1 out of 25 patients while Debasish et al. [30] reported hypotension and bradycardia in 2 out of 32 patients (2/32).

Honey

The efficacy of postoperative honey as an analgesic adjuvant was tested in seven studies including a total of 547 patients. Only one study included adults exclusively; two studies included a mixed population; and the four other studies were performed in children. Three studies reported a reduction in pain scores and postoperative analgesic consumption when honey was administered on top of a basic analgesic regimen containing either paracetamol or NSAIDs [32–34] with no significant side-effects. The analgesic effect was minor and the sample size was small in most studies, varying from 42 to 111 patients per study, suggesting further research in the majority of reports. Two meta-analyses [35, 36] reported a benefit in terms of pain and a reduction in analgesic requirements, issuing low or very low-grade recommendations. An additional positive outcome in these meta-analyses was improved wound healing associated with the use of honey.

Opioids as rescue

Eleven out of 20 studies used tramadol administered either i.v. or via infiltration. Peritonsillar infiltration with tramadol may reduce pain and analgesic requirements when compared with placebo [37]. However, this may be a systemic effect and it cannot be recommended because of lack of data on safety of tramadol injection via this route. Intravenous tramadol had an analgesic effect postoperatively when administered once during surgery when compared with placebo [38]; however, no basic analgesic regimen was administered in this study. Other opioids have been less studied in recent years. Single studies are available for morphine infiltration [39], i.v. codeine [40], i.v. nalbuphine [41] and i.v. morphine [42]. Based on single studies for each opioid in recent years, recommendations are not possible. The risk of arterial oxygen desaturation associated with opioids in children with obstructive sleep apnoea has to be highlighted and assessed. The risk of postoperative nausea and vomiting needs to be prevented and the risk of respiratory depression needs to be evaluated in children with obstructive sleep apnoea.

Acupuncture

One meta-analysis [43] and seven studies involving 522 patients were included [44–50]. The majority reported a benefit with a reduction in pain and analgesic requirements if acupuncture was used. Four studies compared acupuncture with sham [46, 47, 49, 50] and two with usual analgesic treatment [44, 45]. No complications have been described. Time points of acupuncture were pre, intra- and postoperatively.

α-2 adrenergic agonists

Clonidine [51], and more recently, dexmedetomidine [52] have been studied peri-operatively to reduce pain. Nine studies were included using α-2 adrenergic agonist with 771 patients in total; the route of administration was either i.v. or by infiltrating the α-2-adrenergic agonist locally. A recent study documented no analgesic effect of clonidine 25 μg infiltration when a basic analgesic regimen was used [53]. There was no study assessing systemic clonidine in this setting. Clonidine is still included in some guidelines for analgesia after tonsillectomies in children based on efficacy in older studies [4]. However, these studies were mainly based on transferable results from other surgical procedures. Only two studies focused on tonsillectomy, and those did not show any additional analgesic effect of clonidine when used on top of adequate baseline medication after tonsillectomy.

From the eight studies concerning i.v. dexmedetomidine in paediatric patients, four documented an analgesic effect compared with placebo [54–57] or propofol [58] but only for 30 min after surgery, while two studies did not show any benefit on pain scores compared with placebo [59, 60]. One study compared dexmedetomidine with morphine showing an inferior analgesic effect but less respiratory depression, and one compared with fentanyl [61] showing improvement in analgesia with dexmedetomidine. None of these studies assessed the benefit of adding dexmedetomidine on top of a basic analgesic regimen. Dexmedetomidine was associated with less agitation after sevoflurane-based anaesthesia in two studies [55, 61]. In a meta-analysis of dexmedetomidine for tonsillectomies, the drug came out favourably when compared with placebo or opioids in terms of postoperative pain, without any delay in post-

operative care unit discharge [62], although more sedation in the early recovery phase was reported.

Gabapentinoids

Four studies assessing oral gabapentin (including two with children) [63–66] and two studies examining oral pregabalin in adults [67, 68] were included. All but one study [66] showed an analgesic effect of gabapentinoids when compared with placebo or when administered with paracetamol [68]. No study included a comparison with a combined basic analgesia regimen. Three studies reported side-effects of gabapentinoids. Mathiesen et al. [68] reported more dizziness with 300 mg pregabalin. There are no clear conclusions to be drawn on dosing level or whether the pre-operative dose should be repeated or not from these studies. However, data from meta-analyses report that at least 600 mg gabapentin or 150 mg pregabalin is needed in the otherwise healthy adult [69, 70].

Dexamethasone

The benefit of steroids in patients having tonsillectomy was investigated in 17 studies [13, 71–86] including 1943 patients; 14 studies examined dexamethasone. Dexamethasone showed a significant analgesic effect after tonsillectomy when administered alone or in combination with other analgesics. Dexamethasone consistently reduced the incidence of nausea and vomiting after tonsillectomy, being effective in low doses, that is, 2–4 mg i.v. There was no consistent evidence concerning the appropriate dose, or a dose-dependent effect for analgesia, but studies showing an analgesic effect in children use a dose of at least 0.15 $mg.kg^{-1}$, whereas the adult studies used a total of 8 mg or more. There was no evidence of an increase bleeding risk with dexamethasone, or other side-effects from the glucocorticoids, although none of the included studies have systematically addressed these effects. Known side-effects, such as increased blood glucose levels, increased alertness and restlessness during night, are not addressed in the studies reviewed. One study [81] suggested a more relevant and sustained effect on analgesia with peritonsillar infiltration of dexamethasone instead of i.v. or oral administration. Other glucocorticoids, for example, oral prednisolone [74], seem to perform similarly, but are less studied for this purpose. Four recent meta-analyses on the subject draw the same conclusions [87–90].

Ketamine

Ketamine was investigated in 33 studies (32 with paediatric patients and one with a mixed population) including 2546 patients. Thus, recommendations on the use of ketamine for tonsillectomies were only possible for children (online Supporting Information Table S2).

Thirteen studies examined i.v. ketamine after tonsillectomy [91–103]. Ten studies compared i.v. ketamine with placebo [93–95, 97–103]; out of these ten studies, nine showed reduced pain intensity ratings, five of which demonstrated a reduction in morphine consumption [93–95, 98–103] and one showed no significant effects [97]. In one study, i.v. ketamine improved the analgesic effect on top of paracetamol [99]. In all other studies comparing i.v. ketamine with placebo, baseline analgesia was not used or not mentioned. One study showed significantly better analgesia with ketamine plus i.v. dexamethasone compared with placebo or both drugs alone [96]. Another study showed better pain relief if i.v. ketamine was given pre-operatively compared with postoperatively [98]. By comparing i.v. ketamine vs. opioids, there was significant improvement of pain scores in one study [102], reduced opioid consumption in another study [95] and no difference in two studies [92, 94]. Finally, one study compared i.v. ketamine plus midazolam with midazolam alone with only a transient effect after surgery [91]. Altogether, these studies using i.v. ketamine showed analgesic benefits of a single bolus of i.v. ketamine but almost all studies were done without baseline analgesia. In addition, patients experienced more side-effects, predominantly sedation, with ketamine in four studies [93, 94, 97, 101].

There were 11 studies examining ketamine infiltration for tonsillectomy analgesia [93, 98108–116]. Nine of these studies compared ketamine infiltration with placebo, and eight of these studies showed a significant benefit to ketamine infiltration [93, 98, 109–115]. One study comparing peritonsillar ketamine infiltration with i.v. ketamine showed better pain relief with infiltration [98]. Another study compared peritonsillar ketamine infiltration with tramadol infiltration and showed benefit of tramadol compared with ketamine [115]. One study compared ketamine with bupivacaine infiltration, alone or in combination. The combination of both was associated with a superior analgesic effect when compared with each drug alone [116]. Another study compared peritonsillar infiltration of ketamine with or without bupivacaine and meperidine, without any difference between each group [108]. Altogether, ketamine infiltration was consistently effective in reducing pain and analgesic requirements after tonsillectomy in children.

Topical administration of ketamine was investigated in two studies of which one showed inferior analgesia with ketamine when compared with tramadol [117] and the other showed improved analgesia compared with placebo and

similar analgesia compared with i.v. morphine [118]. Intramuscular ketamine did not have analgesic efficacy [104] but subcutaneous ketamine was associated with similar analgesia to the i.v. route [100] and oral administration was less effective compared with infiltration [105,106]. One study evaluated the effects of peritonsillar, i.v. or rectal administration of ketamine in children undergoing tonsillectomy and found no differences between the groups [107].

Other therapies

Four studies (289 patients) examining the analgesic effect of magnesium sulphate with pain as the primary outcome were included. One study [119] showed a transient effect of topical magnesium sulphate, while two studies [120, 121] did not show any difference when intra-operative and postoperative i.v. magnesium sulphate was compared with placebo. One study [122] reported a reduction in pain scores when comparing oral postoperative magnesium sulphate with metamizol. Among the three meta-analyses [123–125] included, two concluded that there was no benefit of i.v. administration of magnesium sulphate and two concluded that there was a small effect when administered locally.

Eight eligible studies [126–133] reported inconclusive pain outcomes with the use of antibiotics. In studies reporting an analgesic effect, two tested antibiotic mouth wash. The analgesic effect lasted only one day and additional analgesic was still needed while the treatment was given for 3 to 7 days. One study reported more postoperative nausea and vomiting with the use of antibiotics [133].

Evidence from three small studies (188 patients) suggested a weak analgesic benefit when sucralfate was used as adjuvant with repeated applications over several days [134–136].

Six studies in children [137–142] and one in adults [143] examined different methods to improve communication with patients or parents for better compliance with analgesics. Although most studies were small and of poor quality, the majority of them recommend enhanced parental education and/or telephone follow-up to observe the need for analgesics at home and their side-effects.

Eight studies assessed the effects of different dietary protocols on post-tonsillectomy pain and complications. Six studies in children [144–149], one in adults [150] and one with mixed age population [151] were included. Four studies [147–149, 151] with 204 participants did not demonstrate any benefit of restricting postoperative diet to liquids or to cold diet when pain scores, nausea or vomiting or bleeding were compared. Ice lolly use was effective in reducing pain scores for 1 hour postoperatively [144]. Minimising fasting time to 4 hours for solids and 2 hours for liquids improved postoperative outcomes in terms of analgesic requirements and postoperative nausea and vomiting in two studies [145, 146]. Only one study [150], which was of poor quality and included 49 participants, suggested effective analgesia and improved wound healing with the administration of ginger capsules postoperatively.

There were numerous studies examining surgical techniques, but these usually focused on outcomes such as bleeding, infection recurrence, hospital stay and costs. For this reason and also due to the fact that recent systematic reviews covering publications until 2016 have been published, we decided to only include studies published between 2017 and 2019. Five randomised studies [152–156] and four systematic reviews [157–160] assessing the impact of surgical techniques on postoperative pain were included. There are two traditional methods of surgical removal of tonsils. The first is the original cold dissection approach, in which a dissector or a guillotine is used to mechanically remove the tonsils from adjacent tissue. The other method is electrocautery where electrical current is used to create burning heat and coagulation in the wound surface. In recent years, novel techniques have been introduced, including the laser evaporation technique, in which the tonsillar surface is treated with a laser beam and evaporates, and the coblation technique. Coblation involves the use of moderate heat to dissect the tonsils from the throat wall. The most recent is the vessel seal techniques, using ultrasound for the dissection. Compared with other techniques, laser tonsillotomy is less time consuming; does not require general anaesthesia; provides less bleeding and less pain but has a significant recurrence rate of tonsillitis. It is thus not considered as a method of complete tonsillectomy and not considered further for these recommendations. Coblation techniques have slightly less postoperative pain during the first day compared with cold dissection and electrocautery dissection techniques [155, 158–160], which seem to be similar in this aspect [154, 156, 160]. Vessel seal technology is new and promising, but remains understudied and results are inconclusive so far [157].

Discussion

Based on available evidence and the PROSPECT approach to providing recommendations, combinations of paracetamol and NSAIDs are recommended pre-operatively or intra-operatively, and continued into the postoperative period, unless there are contra-indications

Table 1 Overall recommendations for pain management in patients undergoing tonsillectomy.

Pre-operative and intra-operative
Paracetamol (Grade D)
Non-steroidal anti-inflammatory drugs (Grade A)
Dexamethasone intravenously (Grade A)
Pre-operative gabapentinoids, or intra-operative ketamine (for children), or intra-operative dexmedetomidine may be considered, when basic analgesic regimen is contra-indicated
Analgesic adjuncts: acupuncture (Grade B)
Postoperative
Paracetamol (Grade D)
Non-steroidal anti-inflammatory drugs (Grade A)
Opioid for rescue (Grade D)
Analgesic adjuncts
Acupuncture (Grade B)
Honey (Grade B)

Table 2 Analgesic interventions that are not recommended for pain management in patients undergoing tonsillectomy.

Intervention	Reason for not recommending
Pre-operative and intra-operative	
Peritonsillar infiltration or topical application of local anaesthetics	Evidence of a short-lasting effect but concerns of serious side-effects
Oral or topical ketamine	Limited procedure-specific evidence
Lidocaine spray	Lack of procedure-specific evidence
Magnesium sulphate	Lack of procedure-specific evidence
Tramadol infiltration	Lack of procedure-specific evidence
Postoperative	
Dexamethasone	Lack of procedure-specific evidence

(Table 1). In addition, a single intra-operative dose of i.v. dexamethasone is also recommended (Table 1). Several interventions are not recommended for analgesia after tonsillectomy (Table 2).

A systematic review [161] including 29 randomised controlled trials considered that single analgesics (e.g. paracetamol; NSAIDs; gabapentinoids; dextromethorphan; dexamethasone) provide only a weak to moderate benefit on post-tonsillectomy pain on the day of surgery. Thus, the authors recommend a multimodal analgesic approach. These findings are in line with our recommendations. Of note, the concerns regarding the potential bleeding risk with the use of NSAIDs are not substantiated in recent studies. Several meta-analyses did not report an increase in the risk of postoperative bleeding [18, 19]. Thus, most guidelines have been modified. Indeed, Swedish [4] and French [5] guidelines recommend NSAIDs as a first line treatment after tonsillectomy. Similar to NSAIDs, dexamethasone was once incriminated as increasing postoperative bleeding [162].

Intra-operative acupuncture and postoperative honey are also recommended as analgesic adjuncts as they have been shown to provide superior pain relief when combined with paracetamol, NSAIDs or oral opioids. Importantly, these approaches have no reported side-effects. However, intra-operative acupuncture is rarely provided as it requires specific training.

Whenever the basic analgesic regimen (i.e. paracetamol and NSAIDs) is contra-indicated or postoperative pain is expected to be greater than usual (e.g. patients consuming opioids pre-operatively), we recommend considering intra-operative i.v. ketamine or dexmedetomidine, and/or pre-operative gabapentinoids. Despite a significant analgesic effect vs. placebo, these medications are not in the first-line in our recommendations because of associated side-effects. Indeed, ketamine is associated with hallucinations, agitation and sedation, and it should be administered at the beginning of the surgical procedure and only as single i.v. dose. Ketamine infiltration is not recommended because of the risks of systemic side-effects after absorption [107, 163]. Gabapentinoids may cause sedation and dizziness at doses having an effect on pain scores or analgesic consumption [68]. Moreover, tonsillectomy is a procedure associated with risks of hypoxaemia, therefore adding gabapentinoids and opioids as rescue could increase the risk of respiratory depression [164]. A similar dilemma holds true for dexmedetomidine, which is associated with the risk of sedation, hypotension and bradycardia. Clonidine is recommended in some guidelines for analgesia after tonsillectomy in children based on efficacy in older studies and transferable results from studies other than tonsillectomy [4]. Of note, tonsillectomy is a short procedure and a single dose of one of these three medications can delay postoperative recovery.

Analgesia was reported with local anaesthesia infiltration when compared with placebo. However, this benefit was only short-lasting and was only demonstrated in studies that were not using a basic analgesic regimen with paracetamol and a NSAID combination. Moreover, studies have reported complications associated with the

technique. Indeed, tonsillar infiltration may not be as safe as other infiltration in other areas because of the neurovascular bundle in the vicinity that could explain high potential for side-effects.

We cannot recommend a specific surgical technique that would influence pain after tonsillectomy, because most studies have evaluated surgical technique with respect to issues of bleeding as well as cost efficacy rather than focusing on differences in postoperative pain.

Some of the limitations with this review are related to the limitations with the individual studies included. There was considerable heterogeneity between studies, such as variable dosing regimens, methods of administration control groups and time-points of pain assessments. The small sample size of most studies has the potential to overestimate effects. Also, the analgesic interventions were not always evaluated against a control group that included an optimised multimodal analgesic regimen. A significant proportion of the included studies assessed unimodal analgesic therapies rather than broader and more comprehensive analgesic techniques. Ideally, all patients should receive an optimised analgesic regimen, and the added procedure-specific benefit of individual interventions should then be tested against this baseline [165]. Also, there was significant heterogeneity in study designs with respect to the analgesic regimen. Moreover, as it is not part of our methodology, we did not weight the recommendations nor make dosage recommendations.

Future adequately powered studies should assess the effects of analgesic interventions not only on pain, opioid consumption, opioid-related adverse events and complications associated with the intervention, but also outcome measures such as time to ambulation, length of hospital stay and functional outcomes after discharge. Another important aspect will be to bring patient-specific risk-factors for postoperative pain into the studies.

In summary, this review has identified an analgesic regimen for optimal pain management after tonsillectomy (Table 1). A balance of evidence-based analgesic efficacy and potential risks of the analgesic intervention determine these recommendations. Peri-operative pain management for tonsillectomy surgery should include, unless contra-indicated, paracetamol, NSAIDs, dexamethasone, honey, acupuncture and opioid as rescue. As second-line treatment, gabapentinoids, ketamine or dexmedetomidine can be used.

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Appendix PROSPECT Working Group

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Search strategy used for this review.

Table S1. Quality assessment and level of evidence assigned to the randomised trials included in this review.

Table S2. Summary of key results from studies evaluating systemic analgesics, systemic analgesic adjuncts, regional analgesia and surgical procedures used to support the recommended interventions in patients after tonsillectomy.

Table S3. Summary of key results from studies evaluating systemic analgesics, regional analgesia, perineural analgesic adjuncts and surgical procedures used to support interventions that are not recommended for analgesic benefit in patients having tonsillectomy.