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Review Article

Pharmacologic management of post-tonsillectomy pain in children

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Abstract Tonsillectomy is a very common procedure in children, often performed on an outpatient basis. Severe postoperative pain is common, and can be prolonged. Despite a large number of available analgesic medications, often employed in combination, achieving adequate pain control remains a persistent challenge. Research suggests a tendency among caregivers to undertreat pain, and a need for detailed care instructions and education to ensure adequate pain management. Furthermore, ongoing questions regarding the safety and efficacy of the most commonly used medications have led to wide variance in practice patterns and continuous reassessment through research that yields sometimes conflicting results. This review summarizes the current state of the literature and presents a management approach which attempts to maximize pain control while minimizing potential harm with combinations of medications and modification based on patient-specific factors.

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Introduction

Tonsillectomy is one of the most commonly performed surgical procedures in children and is often performed on

an outpatient basis in otherwise healthy children. This means that responsibility for pain management after surgery falls almost exclusively on the child's parent or guardian. Yet pain after tonsillectomy can be substantial and prolonged.

Despite the often severe pain experienced by children after tonsillectomy, under-treatment of pain has been consistently demonstrated. One prospective study showed that despite high prevalence of severe pain by parental report, over 40% of children received 2 or fewer doses of pain medication on postoperative day 1 after tonsillectomy, and over 60% received 2 or fewer doses on postoperative

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day 2.¹ Caregivers also frequently find themselves struggling to adequately manage their child's pain, and will often turn to their primary care provider or emergency departments for help.^{2,3} Recognition of the twin problems of under-treatment of pain by caregivers and sometimes inadequate education by Otolaryngologists led the American Academy of Otolaryngology-Head & Neck Surgery to include in its 2019 update to the *Clinical Practice Guideline: Tonsillectomy in Children* a recommendation specifically advising providers to "counsel patients and caregivers regarding the importance of managing post-tonsillectomy pain as part of the perioperative education process and should reinforce this counseling at the time of surgery with reminders about the need to anticipate, reassess, and adequately treat pain after surgery."⁴

While many adjunctive and alternative measures have been investigated, some of which show some promise (e.g. honey, acupuncture, etc.), pain control in this setting is currently primarily accomplished through pharmacologic measures.⁵ A number of medication options exist for treatment of post-tonsillectomy pain, and the literature investigating these options and various combinations and schedules is extensive, yet still in many ways woefully incomplete. Controversy regarding best practices continues, as the relative efficacy and safety of the many options is continually reassessed, sometimes with conflicting results. This review will discuss the literature regarding the most commonly used analgesic medications for post-tonsillectomy pain.

Acetaminophen

Acetaminophen is likely the most commonly administered analgesic medication after tonsillectomy but is considered by many to be inadequate on its own and is therefore frequently used in combination with other medications.⁶ Side effects are generally minimal, however massive overdose can lead to significant hepatic injury and even death.⁷ In 2011, the FDA restricted prescription combination medications to 325 mg maximum dose of acetaminophen and required addition of a boxed warning to these products highlighting the potential for severe liver injury.⁸ Intravenous dosing at time of surgery has been investigated with hopes of improving perioperative pain control and reducing narcotic usage with mixed but overall disappointing results.^{9–11} The American Academy of Otolaryngology-Head & Neck Surgery recommends dosing acetaminophen 10–15 mg/kg/dose every 4–6 h, with maximum dose being the lower of 75 mg/(kg·d) or 4000 mg.⁴

Non-steroidal anti-inflammatory drugs (NSAIDs)

Once avoided by many Otolaryngologists, NSAIDs (specifically Ibuprofen) have been widely adopted and accepted as safe. Indeed, the current American Academy of Otolaryngology-Head & Neck Surgery Clinical Practice Guideline calls ibuprofen "safe and effective", and issued a "strong recommendation" to support its use.⁴ Objections to NSAID use in this setting primarily involve concerns that the anti-

platelet effects of NSAIDs through COX-1 inhibition might lead to increased rates of postoperative hemorrhage.¹² A growing body of evidence supports the safety of ibuprofen after tonsillectomy.^{13–15} Mudd et al¹⁶ reviewed outcomes from 6710 tonsillectomies at their institution over a 3 year period. While age >12 years and history of recurrent tonsillitis were associated with increased bleeding risk, ibuprofen showed no effect on rates of hemorrhage. However, patients experiencing hemorrhage were significantly more likely to require transfusion if receiving ibuprofen (OR 3.16, CI 1.01–9.91), though the overall rate of transfusion in the study was 0.2%. Not all existing evidence points to a null effect on bleeding for ibuprofen, however. A recent randomized double-blind trial by Diercks et al¹⁷ enrolled over 700 patients at 4 facilities, randomizing patients to receive either acetaminophen or ibuprofen. In the same study, 1.2% of patients in the acetaminophen group required operative control of postoperative hemorrhage, compared to 2.9% in the ibuprofen group, and non-inferiority could not be established.

Ibuprofen has been shown to be effective for post-tonsillectomy pain control. A randomized trial by Kelly et al¹⁸ published in *Pediatrics* in 2015 demonstrated no difference in analgesic efficacy between ibuprofen and morphine, while ibuprofen demonstrated a significantly better safety profile, specifically with regard to incidence of postoperative oxygen desaturations. Ibuprofen and Acetaminophen have also been studied in combination in several studies. An older study by Pickering et al¹⁹ demonstrated significant improvement of perioperative analgesia by pre-medicating with both medications versus acetaminophen alone. Interestingly, in the same study, rofecoxib did not demonstrate the same improvements in pain as did ibuprofen. Conversely, a randomized trial by Merry et al²⁰ did not detect any difference in analgesic efficacy of combination therapy over either medication alone. Though lacking a comparison group, a study by Liu et al²¹ demonstrated 9.6% of patients reported inadequate pain control. Because this was a retrospective study, the risk for bias from under-reporting is significant, and it is possible that the true rate of poor pain control may be higher.

The American Academy of Otolaryngology-Head & Neck Surgery recommends dosing ibuprofen at 5–10 mg/kg/dose every 6–8 h. A recent investigation by Mast et al²² examined the effect of different dosing frequencies (alternating doses at 3 or 4 h intervals) of combination ibuprofen/acetaminophen therapy on phone call rate, postoperative hemorrhage, and ER visits for reasons other than bleeding. They found a lower bleeding rate with every-4-hour alternate dosing, with no increase in ER visits or calls about pain.

Intravenous ibuprofen was introduced to the market in the U.S. in 2015. Evidence regarding intraoperative intravenous ibuprofen with tonsillectomy is limited. A 2014 randomized trial demonstrated significant reductions in postoperative fentanyl usage and reduced vomiting, with no demonstrated increase in intra-operative or postoperative hemorrhage.²³ A recent retrospective study did not find a statistically significant difference in postoperative bleeding requiring return to ED or.²⁴ Patients receiving intravenous ibuprofen in that study were less likely to receive narcotic in the OR, but more likely to

receive narcotic in the recovery room, and intravenous ibuprofen did not affect rates of return to the ED for dehydration or uncontrolled pain.

While ibuprofen has gained wide acceptance in the post-tonsillectomy setting, other NSAIDs remain somewhat more controversial. Ketorolac is a powerful intravenous NSAID used for analgesia in a large number of settings. Nevertheless, concerns regarding bleeding risk with ketorolac have persisted, and the 2011 version of the American Academy of Otolaryngology-Head & Neck Surgery's *Clinical Practice Guideline: Tonsillectomy in Children* concluded that on this basis "ketorolac use should be avoided."²⁵ A subsequent meta-analysis demonstrated greater than 5 fold relative risk for bleeding in adults after administration of ketorolac, but no statistical effect in children.²⁶ Nevertheless, the authors acknowledged insufficient power to conclusively demonstrate non-effect, and reported relative risk of 1.39 (CI 0.84–2.30), suggesting the possibility of an actual effect on bleeding risk (anywhere from no effect to greater than 2 times risk), though less than that seen in adults. A recent retrospective study by Rabbani et al²⁷ demonstrated no impact of ketorolac administration on hemorrhage rates, while the ketorolac group used less opioid medication. The study is notable for its size, including over 650 children in each group. Interestingly, a recent study in adults also demonstrated no effect on bleeding from ketorolac usage over a 5 year period, further calling in to question the actual impact of ketorolac in this setting.²⁸ The 2019 update of the American Academy of Otolaryngology-Head & Neck Surgery's *Clinical Practice Guideline: Tonsillectomy in Children* softened its prior recommendation against ketorolac, stating "Ketorolac use with tonsillectomy remains controversial and dependent on provider preference."⁴

Opioids

Opioid analgesics have been used by humans for several thousand years. Indeed, opium is referenced numerous times for various uses in the texts of Hippocrates.²⁹ Historically, codeine (a derivative of opium) was a mainstay of analgesic regimens in the pediatric post-tonsillectomy setting. However, doubts about its efficacy led to a clinical trial in 2000 which demonstrated no analgesic benefit for acetaminophen/codeine over acetaminophen alone, with significantly worse oral intake, likely secondary to nausea and other gastrointestinal side effects of codeine.³⁰

Serious safety concerns regarding codeine were raised as case reports began to accumulate in prominent journals of severe adverse respiratory events in young children after exposure to codeine, including one small case series of children given codeine after tonsillectomy that included 2 deaths.^{31–33} An FDA safety review identified 13 reported severe adverse events between 1969 and 2012, including 10 deaths and 3 occurrences of severe respiratory depression.³⁴ Of these 13 events, 8 occurred post-tonsillectomy, and dosing was generally felt to have been appropriate. Also notable, The FDA issued a requirement for a "Boxed Warning" contraindicating codeine-containing products "in post-operative pain management in children following

tonsillectomy and/or adenoidectomy".³⁴ Subsequent FDA guidance designated both codeine and tramadol as contraindicated for treatment of pain in children under 12, and further designated tramadol as contraindicated for use after tonsillectomy and/or adenoidectomy in children under age 18.³⁵

Hydrocodone, another opioid frequently prescribed for post-tonsillectomy analgesia, has also had some restrictions placed on its use in children by the FDA in recent years. While hydrocodone has not received the same contraindication for pediatric post-surgical use, the FDA issued guidance that "prescription opioid cough and cold medicines that include codeine or hydrocodone should not be used in children" under 18 years of age.³⁶

Individual variations in drug metabolism are a key component in the variability of clinical responses to opioid analgesics. Enzymatic metabolism in the liver through a number of cytochrome P450 enzymes, most notably CYP2D6 in the case of several opioids, produces drug metabolites of varying activity levels. The level of activity of CYP2D6 within the liver is genetically controlled and highly variable. Thus, the speed with which the drug is metabolized may lead to variable concentrations of metabolites and dramatic differences in clinical responses, including efficacy, duration, and, crucially, side effects.³⁷ For instance, codeine is a pro-drug and itself not clinically active, but morphine is one of its major metabolites, via CYP2D6 metabolism. Individuals with very high levels of CYP2D6, known as "ultra-rapid metabolizers", are at risk for a sudden flood of metabolites, leading to adverse reactions such as respiratory suppression and even death. Rates of ultra-rapid metabolizers are variable among different ethnicities, with reports indicating very low prevalence among Asians, 1%–7% among Caucasians and African-Americans, up to 20% among those of Middle Eastern descent, and as high as 29% among those of African/Ethiopian heritage.^{38,39} While hydrocodone and tramadol are both themselves clinically active and not entirely dependent on metabolites for activity, CYP2D6 variability may affect individual responses to these drugs in similar ways.^{39,40}

Unlike codeine, oxycodone is an active drug, and is primarily metabolized via CYP3A4, producing inactive metabolites. There has been some support for oxycodone as an alternative to codeine on the grounds that it may therefore not be subject to the same metabolic heterogeneity seen with codeine. Some CYP2D6 metabolism does occur, however, producing the active metabolite noroxymorphone.³⁹ Additionally, pharmacokinetic studies have shown a wide range of absorption and bioavailability of oxycodone, as well as peak plasma levels of both oxycodone and the active metabolite noroxymorphone.^{39,41}

Morphine is metabolized by an entirely different pathway (glucuronidation), yet the potential for serious respiratory suppression with morphine is well-known. A randomized trial comparing morphine versus ibuprofen as primary analgesic in the post-tonsillectomy setting for children with sleep-disordered breathing demonstrated similar analgesic efficacy on the first night postoperatively, but substantially higher rates of oxygen desaturations among children receiving morphine, and the authors recommended against routine use of morphine in this setting.¹⁸

Adverse reactions to opioids can also be influenced by a host of other factors, including accidental overdose, drug–drug interactions, and individual hypersensitivity related to obstructive sleep apnea or other factors.⁶ Both the CYP2D6 and especially CYP3A4 enzymes are subject to a large number of important drug–drug interactions that can either enhance or inhibit enzymatic activity and thereby influence drug side effects, sometimes in dramatic and dangerous ways.⁴² Finally, and apart from potential adverse effects arising from use as intended, the potential for abuse, diversion, addiction, or accidental use (especially by young children) by other household members bears serious consideration in light of the opioid crisis currently raging.

As safety considerations surrounding opioids mount, evidence to support or refute the available opioids as providing superior analgesia over acetaminophen and/or ibuprofen alone is sparse. Oremule et al⁴³ found in a prospective non-randomized trial that rescue morphine did not enhance pain control or rates of postoperative healthcare contact when added to a regimen of acetaminophen and ibuprofen, and that a majority of caregivers in both groups felt that pain control was inadequate. Adler et al⁴⁴ reported no difference in parental satisfaction with pain control comparing regimens of ibuprofen/acetaminophen with or without hydrocodone, with less than 10% reporting unsatisfactory pain control in each group. As a note of caution, there was significant heterogeneity between groups with respect to age (the hydrocodone group was older on average), and surgical technique. Two additional studies have suggested no increase in ER visits for pain or dehydration in the absence of opioids, though the narcotic comparison group for Bedwell et al consisted of acetaminophen with codeine, limiting generalizability for currently available opioids.^{45,46} In another study 13% of patients initially prescribed ibuprofen and acetaminophen were subsequently prescribed an opioid because of uncontrolled pain.⁴⁷ This group was older on average than the study group as a whole. Contrastingly, Persino et al⁴⁸ surveyed parents after tonsillectomy to assess satisfaction with a regimen of acetaminophen and ibuprofen, with hydrocodone/acetaminophen available for rescue. In that study, nearly 80% of respondents indicated that acetaminophen/ibuprofen was not sufficient and used hydrocodone at least once. Of note, nearly 60% of patients in the study did not take both acetaminophen and ibuprofen regularly, and only 8% of patients in the study used all three medications as prescribed. This suggests the possibility that insufficient education/compliance with regard to acetaminophen and ibuprofen may have significantly influenced results. Of note, even among those who never used the hydrocodone, 70% felt it was useful to have had the prescription.

Apart from guidance contraindicating both codeine and tramadol, and given the scarcity and poor quality of available evidence, providers are ultimately left to their own judgment when considering the inclusion of opioid analgesics in a post-tonsillectomy pain regimen. We believe caution is warranted, however, particularly among children who may be at increased risk for adverse events, such as the very young and individuals with known severe obstructive sleep apnea, obesity, or other significant comorbidities.

Corticosteroids

In recent years, corticosteroids have seen an evolution in practice in the setting of pediatric tonsillectomy similar in some ways to NSAIDs. Because corticosteroids have long been known to have potential adverse effects on wound healing, steroid use during or after tonsillectomy has been controversial in the past. Czarnetzki et al⁴⁹ found an increase in bleeding risk after a single intraoperative dose of dexamethasone. However, that finding has not been replicated in other studies, including several meta-analyses.^{50–53} One meta-analysis did find increased incidence of operative intervention for bleeding (3% vs 1.5%) while not finding an increase in overall bleeding rate, however this finding was not seen when including only studies at low risk of bias, and no dose effect was seen.⁵⁴

A single intraoperative dose of dexamethasone has been shown to have significant benefits for alleviating postoperative nausea, vomiting, and pain, as well as improving time to oral intake, and on that basis the American Academy of Otolaryngology-Head and Neck Surgery has reiterated its strong recommendation to administer a single dose of dexamethasone at time of surgery.^{4,25,55} In a meta-analysis of randomized trials, Afman et al⁵⁶ showed an average 1 point decrease in pain scores on a 10 point visual analog scale in the first 24 h, a finding which was supported in a subsequent Systematic review by Steward et al⁵⁷ for the Cochrane library. Positive clinical results from intravenous dexamethasone, combined with efforts to move away from opioids, has increased interest in a potential role for oral steroids in the postoperative period. A study by Redmann et al⁵⁸ examined the effect of adding dexamethasone (0.5 mg/kg, maximum dose 20 mg, every other day for 3 doses) to a regimen of scheduled acetaminophen and ibuprofen, along with rescue oxycodone for patients age 6 and over. They found a significant reduction in phone calls for pain and lower incidence of bleeding, and no incidents of steroid-related complications.

Caregiver guidance

Even as advances are made in understanding the safety and efficacy of various analgesics for pediatric tonsillectomy patients, it remains true that the safety and efficacy of any medication depends on correct administration. Several studies have demonstrated wide variations in caregiver appreciation and accuracy of perception of the extent of patient pain after tonsillectomy and a corresponding tendency to sometimes significantly undertreat. One small prospective study showed significant underdosing of medication even with a very simple regimen including only acetaminophen while another showed over 40% of children received 2 or fewer doses of pain medication on postoperative day 1, and 60% received 2 or fewer doses on postoperative day 2.^{1,59} This, despite parental report of nearly 80% of children in significant pain on postoperative day 2. Of note, this same study showed nearly 50% still experiencing significant pain on postoperative day 7. A more recent study by Alm et al⁶⁰ similarly showed high levels of child pain with roughly 20% of parents underestimating their child's pain, and only about half of

patients receiving the recommended number of scheduled doses of acetaminophen each day on days 1–3, and only one third receiving the prescribed number of doses of ibuprofen.

The American Academy of Otolaryngology-Head and Neck Surgery has taken an active interest in the question of appropriate parental pain management. The 2011 guideline included a recommendation that clinicians “advocate for pain management and educate caregivers about the importance of managing and reassessing pain”.²⁵ This was expanded in the 2019 update to include a recommendation to “reinforce this counseling at the time of surgery”.⁴ Scheduling medication doses instead of given “as needed” has been advocated to improve pain control and eliminate variability in caregiver perceptions of patient pain as a barrier, but studies in children to date have not shown clear benefit.⁶¹ Nevertheless, with an increasing trend toward multi-medication pain control strategies, caregivers can easily become confused or overwhelmed. Schedule dosing for non-opioid analgesics along with instructions and provided resources to keep a log may help facilitate better caregiver pain management. We also advocate for explicit instructions for safeguarding access to medications to only the caregivers administering the medications. Similarly, we advocate for clear instructions regarding potential opioid side effects, and we recommend against scheduled dosing of opioids in this setting.

Other medications and alternatives?

Our purpose is not to review the evidence for all medications that are used or have been studied for use after tonsillectomy. Nevertheless, a few others merit mention here. Clonidine has been used enthusiastically in parts of Europe for some time, and was adopted nationally in Sweden in 2015 as first line treatment for patients not adequately treated with ibuprofen/acetaminophen, preferred over opioids because of significantly less risk for respiratory suppression or GI disturbance.⁶² A Systematic Review by the Cochrane Library suggested beneficial effects for postoperative pain with minimal side effects.⁶³ On the other hand, Blackburn et al⁶⁴ found in a prospective study that clonidine administered preoperatively prolonged emergence from anesthesia in a dose-dependent manner, with the highest dose (4 mcg/hr) increasing emergence by nearly 1 h. We found no studies examining the effect of oral clonidine on postoperative analgesia in this setting.

Gabapentin has demonstrated potential as an adjunct for pain management in a number of settings and has been investigated to a limited extent for post-tonsillectomy pain. A meta-analysis performed by Hwang et al⁶⁵ in 2016 suggested the possibility of analgesic benefit for a preoperative dose of gabapentin or pregabalin, with no reports of significant side effects, however no firm conclusions could be made. A subsequent randomized trial in adults suggested higher pain scores and analgesic consumption in patients receiving gabapentin.⁶⁶ Several studies have been published on the subject from Iran, including a randomized trial of patients aged 10–25 years, which demonstrated improved postoperative pain for patients receiving either gabapentin or diclofenac compared with placebo.⁶⁷

Finally, honey has been studied for a wide variety of uses, including wound healing, improving lipid profiles, cough suppression, and pain control, among others. Two meta-analyses supported a role for honey as an analgesic in this setting with minimal risk, but also acknowledged significant limitations of existing evidence and called for more robust trials.^{68,69} Interestingly, there is potential for substantial heterogeneity of biological activity of different varieties of honey, and it is unclear whether this may impact the efficacy of honey in this setting.⁷⁰

Our approach

In the wake of safety concerns regarding codeine, and increasing confidence in the safety of ibuprofen, our institution undertook a review and standardization of post-tonsillectomy analgesia five years ago. This and additional subsequent reviews resulted in an institutional standard for dosing and frequency of medications, along with some common exclusions (Table 1). While alternating Q3H dosing of acetaminophen and ibuprofen is very common after tonsillectomy, we decided upon Q4H dosing of acetaminophen and Q8H dosing of ibuprofen (administered concurrently with every other acetaminophen dose) in order to reduce the administrative burden on caregivers, and also thereby slightly decrease the dosing of ibuprofen, as a nod to persistent concerns regarding bleeding risk among some within our group. Oxycodone is preferred when an opioid is used, and codeine and tramadol are universally avoided. Guidance is given to parents regarding potential side effects of narcotics. Parents are also instructed to keep a log of pain medication doses given, to avoid confusion and to maintain proper dosing intervals. Since adoption of this standard at our institution, data supporting the efficacy of postoperative dexamethasone have led to inclusion of oral dexamethasone, though so far in a somewhat more limited

Table 1 An institutional standard for dosing and frequency of medications with some common exclusions.

Medication	Dosing	Exclusions
Acetaminophen	10 mg/kg q4h scheduled round-the-clock	Liver transplant
Ibuprofen ^a	10 mg/kg q8h p.r.n.	Bleeding disorders, kidney disease
Oxycodone ^a	0.1 mg/kg q4h p.r.n.	Age <5 years, severe OSA. Caution if obesity, micrognathia, other sedating medications.
Dexamethasone	0.5 mg/kg every other day × 3 doses, starting pod 1 or 2	Currently used for older patients not eligible for oxycodone, or for any patient failing analgesic regimen.

^a Note: some providers elect to prioritize ibuprofen before oxycodone, while others prioritize oxycodone, based on provider assessment of relative risks of each medication.

capacity than that described by Redmann et al.⁵⁸ The rapidly evolving state of the art, as evidenced by the research highlighted in this review, call for periodic reassessment of practice patterns, and further adjustments will undoubtedly occur in the future.

Conclusions

Controlling pain after tonsillectomy in children is often difficult, and many children suffer from poorly controlled pain for a week or more after surgery, despite our best efforts. A combination of multiple medications is typically needed for adequate pain control, and efforts to define an optimal regimen are ongoing. Acetaminophen and ibuprofen are widely supported. Steroids are also advocated preoperatively, and there is promising evidence regarding their use postoperatively. Opioids remain part of the analgesic armamentarium, but a detailed understanding of their potential risks is essential, and codeine and tramadol should be strictly avoided. Clonidine may also be considered as an opioid alternative, though there is very little evidence regarding its use for outpatient pain control. Regardless of the specific regimen employed, no medication is effective if not properly administered. Careful and comprehensive counseling and instructions must be provided to caregivers to facilitate safe, correct, and timely administration of pain medications.

Declaration of competing interest

None.

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