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How to Make Tonsillectomy a Safer Procedure: The Anaesthetist’s View

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Key Words
Tonsillectomy · Anaesthesia · Safety issues

Abstract
Anaesthetists use specific drugs peri-operatively to try to decrease the incidence and severity of postoperative pain and of postoperative nausea and vomiting. These drugs are usually administered pre-operatively with the premedication, or intra-operatively when the patient is still anaesthetised. The aim of this approach is to prevent the occurrence of intolerable pain or to avoid any nausea or vomiting symptoms which may be clearly unpleasant for the patient and which interfere with the patient’s well-being, recovery and satisfaction. However, since most of these drugs are given prophylactically, and since not all patients will actually be suffering from intolerable pain or severe nausea and vomiting symptoms postoperatively, many patients will receive these drugs unnecessarily. Thus, for the individual patient, the risk of suffering from drug-related adverse reactions without profiting from any benefit may be relevant. Perhaps a ‘wait-and-see’ approach should be considered; especially non-steroidal anti-inflammatory drugs or dexamethasone should not be given pre-operatively to all patients but should be provided exclusively to those in whom alternative analgesics (for instance, paracetamol combined with a weak opioid) or alternative anti-emetics (for instance, a setron or droperidol) have failed or are associated with unacceptable adverse effects. There is no evidence that prophylactic administration of an analgesic or an anti-emetic is more efficacious than the therapeutic administration. An interesting alternative to achieve satisfactory post-tonsillectomy analgesia may be with local anaesthesia swabs that are applied onto the wound.

Introduction

Tonsillectomy is among the most commonly performed operations in children worldwide. Tonsillectomy rates vary from country to country and from region to region [1, 2]. From the anaesthetist’s point of view, the most frequent problems after tonsillectomy are acute, post-
operative pain and nausea and vomiting. A less frequent complication is bleeding. Most often, pain and postoperative nausea and vomiting (PONV) are more of a nuisance than real medical problems, although pain may be severe enough to prevent a child from adequate oral intake during the first few days after surgery. PONV, although self-limiting, may be severe enough to prevent discharge of a patient after ambulatory surgery.

Posttonsillectomy bleeding is rare; however, contrary to pain or PONV, an increased risk of bleeding has major implications after tonsillectomy. Also, contrary to the risk and severity of pain and PONV, which both decrease overtime, bleeding may occur acutely (within the first 24 h) or in a delayed fashion (up to 10 days postoperatively). It is important in this context to distinguish between different bleeding end points. ‘Postoperative bleeding’, for instance, is not a useful end point as it may range from a subjective impression of an increased bleeding tendency during surgery, often rated by the surgeon on a 10-point scale, to the patient spitting a certain amount of blood postoperatively, or even the necessity of a blood transfusion. The most relevant end points in this context are the need for rehospitalisation due to bleeding or, even more importantly, the need for re-operation due to bleeding. Re-operation of an anaemic and hypovolaemic child with a stomach full of blood is clearly a high-risk situation due to an increased risk of cardiovascular collapse during the induction of anaesthesia and regurgitation of stomach contents with subsequent broncho-aspiration. Consequently, a rational care of patients undergoing tonsillectomy includes the administration of drugs that prevent pain and nausea and vomiting, without further increasing the risk of bleeding.

For pain treatment, anaesthetists tend to use non-opioid analgesics [for instance paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)] as first-line treatment. In cases of severe pain, weak opioids (tramadol, codeine) or even strong opioids (morphine) may become necessary. The combination of non-opioid and opioid analgesics (multimodal analgesia) is not uncommon.

Among the best documented and clearly effective anti-emetic drugs in the postoperative setting are 5-hydroxytryptamine 3 receptor antagonists (‘setrons’, for instance ondansetron), D2 antagonists (butyrophenons, for instance droperidol), and steroids (for instance dexamethasone) [3]. Again, combination of these treatments is not uncommon as anti-emetic efficacy may be improved [4].

In this context, the analgesics paracetamol, NSAIDs and codeine, and the anti-emetic dexamethasone deserve particular attention and shall be discussed in more detail. Paracetamol, for instance, although widely used in children undergoing surgery and considered to be a safe analgesic, is prone to toxicity, mainly hepatic toxicity. Also, there is evidence that in patients undergoing tonsillectomy, NSAIDs and dexamethasone may further increase the risk of postoperative haemorrhage. Finally, codeine, a popular prodrug of morphine, undergoes a specific hepatic metabolism and, in susceptible patients, may lead to respiratory depression.

**Paracetamol**

Paracetamol is a commonly used analgesic for acute postoperative pain worldwide. Paracetamol acts centrally through activation of descending serotonergic pathways, but the precise mechanism of action is not clear [5]. Paracetamol has the major advantage compared with NSAIDs not to interfere with platelet function. However, paracetamol is a weak analgesic only [6]. Given alone for the treatment of tonsillectomy pain, it is often insufficient at the recommended doses [7–9]. It should therefore be combined with other analgesics. The maximum daily dose in adults is 4 g and in children aged >3 months 60–90 mg · kg⁻¹. The conventional oral dosing for pain relief is 15–20 mg · kg⁻¹ 4- to 6-hourly. Further increasing
that dose does not improve analgesic efficacy but significantly increases the risk of hepatic toxicity [10]. It must be stressed that evidence of liver toxicity may be seen even in healthy subjects receiving normal daily doses of paracetamol [11].

Especially in children, the rectal route may constitute an alternative when oral administration is impossible, but has the disadvantage of slow onset and reduced bio-availability [12]. For this reason, a higher rectal loading dose should be given when the rectal route is chosen (40–60 mg · kg⁻¹) [13]. There are intravenous formulations of paracetamol available; however, there is no evidence of any advantage of the intravenous route over the oral or rectal route.

**Non-Steroidal Anti-Inflammatory Drugs**

NSAIDs have both analgesic and anti-inflammatory effects, and they have been shown to be potent analgesics for the treatment of acute, postoperative pain [6]. NSAIDs lack opioid-related adverse effects such as sedation, emesis, pruritus or respiratory depression. However, all non-selective NSAIDs inhibit cyclo-oxygenase type I and II to some extent. Thus, one of their well-known and well-documented adverse effects is the (reversible) inhibition of platelet aggregation. Through that mechanism, NSAIDs are expected to increase the risk of postoperative bleeding, and this has been well documented in large randomised trials and systematic reviews of randomised trials.

In a recent large randomised trial in patients undergoing surgery for hip replacement, an analgesic treatment with ibuprofen for 2 weeks postoperatively (1,200 mg daily) significantly increased the risk of postoperative bleeding from about 2 to 5% [14]. Whether this NSAID-related bleeding was of any clinical relevance after these orthopaedic surgeries remained unclear.

Several systematic reviews have addressed the additional risk of postoperative haemorrhage due to NSAIDs in children and adults undergoing tonsillectomy; they have sometimes reached conflicting results [15–18].

For instance, Krishna et al. [15] analysed 7 randomised and non-randomised trials that included data from 1,368 patients, children and adults, who received a variety of NSAIDs or aspirin. These authors concluded that there was an increased risk of posttonsillectomy haemorrhage with the use of aspirin but that there appeared to be no significantly increased risk of bleeding for non-aspirin NSAIDs. The increased bleeding risk with aspirin, which blocks cyclo-oxygenase irreversibly, is not surprising. The main conclusion from this systematic review is that aspirin must not be regarded as a valid analgesic to treat any acute, postoperative pain.

Marret et al. [16] analysed 7 randomised trials with data on 505 children undergoing tonsillectomy and receiving NSAIDs after, but not during, surgery. With NSAIDs, the risk of re-operation due to bleeding was significantly increased. In children who did not receive any NSAIDs, the average risk of re-operation due to bleeding was 0.8%; in children who were exposed to NSAIDs that incidence increased significantly to 4.2% (odds ratio 3.8; 95% confidence interval 1.3–11.5). These authors concluded that conventional NSAIDs such as ketorolac, ibuprofen or ketoprofen should not be used after tonsillectomy.

Møiniche et al. [17] analysed 25 randomised trials with data on 1,853 patients, adults and children, undergoing tonsillectomy and receiving NSAIDs before, during or after tonsillectomy. Similar to the analysis by Marret et al. [16], the risk of re-operation due to bleeding was significantly increased in patients receiving NSAIDs. Without NSAIDs, 1.1% of patients needed a re-operation compared with 2.7% of patients who were exposed to NSAIDs (odds ratio 2.33; 95% confidence interval 1.12–4.83). Interestingly, and similarly to the analysis by Marret et al. [16], the risk of haemorrhage was particularly increased when the NSAID treatment was started after surgery only. It has been speculated that pre- or intra-operative
NSAID administration may increase the bleeding tendency already intra-operatively and therefore the surgeons have to perform homeostasis more carefully. Subsequently, these patients may be less at risk of postoperative bleeding. An additional finding was that patients exposed to NSAIDs were consuming fewer opioids (which may be interpreted as an NSAID-related opioid-sparing effect), and, presumably through this mechanism, suffered less from PONV symptoms [17]. The conclusion of Møiniche et al. [17] was that there was evidence from randomised controlled trials that NSAIDs may increase the likelihood of re-operation due to bleeding, particularly when NSAIDs were given in the postoperative period.

Finally, in a Cochrane review, Cardwell et al. [18], analysed data from 13 randomised trials including 957 children undergoing tonsillectomy and receiving NSAIDs before, during or after tonsillectomy. The risk of re-operation due to bleeding in children receiving NSAIDs was increased, though not statistically significantly. The authors concluded that NSAIDs were safe in this context, and that they did not cause any increase in bleeding requiring a return to the operating theatre [18]. However, that conclusion needs to be interpreted cautiously for two reasons. Firstly, the analysis was based on a very limited number of bleeding events; only 6 of the 13 trials actually reported on any re-operation due to bleeding. Secondly, it appears that the authors accidentally extracted a wrong number of bleeding events from one included study [19].

Based on a convincing biological basis explaining the increased bleeding tendency in surgical patients receiving NSAIDs and evidence from carefully conducted randomised trials and meta-analyses, we may conclude that peri-operative NSAID administration increases the risk of bleeding after surgery and specifically after tonsillectomy. The reported absolute increase in the risk of re-operation after tonsillectomy appears to be about 2–3% [14, 16, 17]. This suggests that between 30 and 50 patients need to be treated with NSAIDs peri-operatively for 1 additional patient having a bleed that would not have occurred had they not received any NSAIDs. In a child undergoing tonsillectomy this may mean that the child has to return to the operating theatre for a re-operation due to the bleeding. In this specific setting, this degree of additional risk may be regarded as clinically relevant. It may be that the risk of bleeding is not increased when the patients are receiving the NSAID postoperatively only. Aspirin should not be regarded as a valid analgesic drug in surgical patients. Finally, there is strong evidence that NSAIDs decrease pain intensity after surgery, including after tonsillectomy, and that they may contribute to a decrease in the risk of PONV due to an ‘opioid-sparing effect’.

**Dexamethasone**

Dexamethasone has become a widely used drug in patients undergoing surgery. Dexamethasone is known to be an excellent anti-emetic drug, and it is also believed to have analgesic properties and to enhance postoperative recovery.

Various meta-analyses and large randomised controlled trials have demonstrated the efficacy of this steroid in reducing PONV in a variety of surgical settings [20, 21]. It has been suggested that, especially in children undergoing tonsillectomy, dexamethasone was extremely useful, not only for its anti-emetic, but also for its analgesic effects, and that it should be used routinely because adverse effects and cost appeared negligible [22, 23]. Indeed, dexamethasone has become standard care for tonsillectomy patients in many institutions around the world. For a long time, dose responsiveness of dexamethasone for the prevention of PONV in paediatric tonsillectomy has remained unknown, although variable doses up to 1 mg · kg⁻¹ and fixed doses up to 50 mg have been tested [24–27].

In a recent randomised trial including more than 200 children undergoing tonsillectomy, it was shown that dexamethasone, compared with placebo, significantly decreased the risk of PONV and that there was a significant dose responsiveness within a dose range of 0.05–0.5
mg · kg⁻¹; with the highest dose tested, 0.5 mg · kg⁻¹, the number needed to treat to prevent PONV compared with placebo was about 3 [28]. Dexamethasone also significantly decreased the need for supplemental ibuprofen in the postoperative period, suggesting that the steroid has additionally analgesic properties. However, that study had to be stopped prematurely since it appeared that children receiving dexamethasone had an increased risk of postoperative bleeding. In 8 children receiving dexamethasone, compared with 1 receiving placebo, an emergency re-operation was necessary. A clear dose response of the dexamethasone-related bleeding risk could not be established. It was suggested that this increased bleeding tendency after dexamethasone exposure may be related to steroid-related inhibition of wound healing [29, 30].

The increased risk of bleeding after tonsillectomy due to dexamethasone has remained controversial ever since. Numerous authors have tried to provide evidence, based on analyses from very different study protocols, that dexamethasone was safe in this context [31–33]. A recently published study concluded that the administration of peri-operative dexamethasone was not associated with bleeding requiring inpatient admission or re-operation [34]. However, this conclusion was based on a non-inferiority statistical design that tested the hypothesis that dexamethasone would not result in as much as 5% more bleeding events compared with placebo. This threshold is debatable though. An increase of up to 5% in the risk of any bleeding (for instance, spitting some blood) might not necessarily be of clinical relevance. However, an increase of 5% in bleeding needing a re-operation is quite different. It makes an important difference if 0.6% (as reported in the placebo group in that trial) or 5.6% of children need to be re-operated on; this difference in event rates corresponds to a number needed to harm of 20. Obviously, setting the inferiority margin at a lower level, for instance 1.5%, would have required a much higher number of patients to be randomised. The trial by Gallagher et al. [34] does therefore not further our understanding of the role of dexamethasone in children undergoing tonsillectomy. Other recently published analyses have confirmed an increased risk of posttonsillectomy bleeding in patients receiving dexamethasone [35, 36].

Interestingly, and contrary to the use of NSAIDs, where both anaesthetists and ENT surgeons seem to be willing to do without them in favour of, for instance, paracetamol or weak opioids, dexamethasone has now a reputation of indispensability, especially in children undergoing tonsillectomy. It is widely believed that postoperative recovery after tonsillectomy, including pain relief and oral intake, is significantly improved with dexamethasone although this has never been formally shown in high-quality clinical trials. Perhaps, doctors dealing with these children should remember that tonsillectomy may perfectly well be performed with alternative anti-emetics and more powerful, classic, analgesics. Also, the usual doses of dexamethasone that are used in this setting must be challenged. For instance, the anti-emetic efficacy of this steroid is quite remarkable with doses as low as 0.25 mg · kg⁻¹ [28]. Doses up to 0.5 or even 1 mg · kg⁻¹ (corresponding to 35–70 mg in an adult) should be discouraged. Also, for improved anti-emetic efficacy, anti-emetic drugs, including dexamethasone, setrons and droperidol, should be combined anyway.

**Codeine**

Codeine is probably the most commonly prescribed analgesic for mild to moderate pain worldwide. It is marketed as both a single-ingredient drug and in combination with paracetamol or NSAIDs. There is evidence that these combinations provide greater pain relief than either drug alone. The main problem with codeine is its metabolism. Codeine is considered to be a prodrug to morphine, since its analgesic effect is due in large part to its O-demethylation to morphine. The conversion of codeine to morphine occurs in the liver and is catalysed by the cytochrome P450 enzyme CYP2D6. However, there is extensive polymorphism in its gene with
poor, extensive and ultrarapid metaboliser phenotypes. In the general population only about 10% of the dose is O-demethylated to morphine [37]. Consequently, the ratio codeine:morphine is about 10:1; thus, the equivalent of a usual paracetamol-codeine tablet (which contains 500 mg of paracetamol and 30 mg of codeine) correspond to about 3 mg of morphine. In poor metabolisers, almost no morphine is produced and in ultrarapid metabolisers, a functional gene duplication results in high amounts of codeine converted to morphine. Ultrarapid metabolisers can produce 50–75% more morphine, and these patients are at risk of morphine overdosing and respiratory arrest [38]. There is an increasing number of reports of lethal respiratory depression in children treated with codeine after tonsillectomy [39, 40]. Most of these children were ultrarapid metabolisers and had tonsillectomy for obstructive sleep apnoea. It might be argued that codeine and other opioids that use the CYP2D6 pathway are not safe analgesics in this context. Indeed, several other opioids are metabolised, at least in part, by CYP2D6. Tramadol, hydrocodone and oxycodone are O-demethylated by CYP2D6 to O-desmethyltramadol, hydromorphone and oxymorphone, respectively. To avoid treatment complications, opioids that are not metabolised by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone and hydromorphone, along with non-opioid analgesics, may be considered as alternative. Finally, although the CYP2D6 ultrarapid metaboliser status can be found in 1–10% of individuals of European descent, this is the case in up to 30% of North African descendants [41].

Local Anaesthetic Infiltration – An Alternative?

As there are potential adverse effects with most systemic analgesic treatments, there is an increasing interest in alternative analgesic methods. A popular pharmacological strategy to reduce post-tonsillectomy pain is the use of local anaesthetics, either by topical application in the tonsillar fossa or by infiltration, before or after tonsillectomy. However, an early meta-analysis of randomised trials concluded that there was no evidence that the use of peri-operative local anaesthetics improved postoperative pain after tonsillectomy [42]. That analysis was based on a limited number of studies that were published before 1998. A more recent meta-analysis included data from 13 studies and 371 patients [43]. These authors concluded that overall, local anaesthetics provided a modest but statistically significant reduction in posttonsillectomy pain; the decrease in pain intensity was about –0.7 cm on a 10-cm scale at 4–6 h postoperatively and –0.3 cm on the 10-cm scale 24 h after surgery. This degree of analgesic is weak compared with, for instance, NSAIDs [6]. In a subgroup of studies that reported on a longer follow-up, the use of local anaesthetics resulted in an average decrease in pain intensity of almost 1 cm on the 10-cm scale on day 5. That analgesic technique should be carefully considered given the uncommon but potentially serious adverse events that have been reported including intravascular injection with subsequent convulsion [43], vocal cord paralysis [44], osteomyelitis [45], intravascular injection [46] or deep cervical abscess [47].

Topical swabs that are impregnated with a local anaesthetic solution appear to provide a similar degree of analgesia to that of infiltration without the potential adverse effects of the infiltration. Swabs, rather than infiltration, may therefore be regarded as the method of choice of local anaesthetic application in patients undergoing tonsillectomy.

Conclusion

Anaesthetists are using specific drugs peri-operatively to try to decrease the severity of postoperative pain and the incidence and severity of PONV. These drugs are usually administered prophylactically, i.e. pre-operatively with the premedication, or intra-operatively...
when the patient is still anaesthetised. The aim of this approach is to prevent the occurrence of intolerable pain or to avoid any nausea or vomiting symptoms which may be clearly unpleasant for the patient and which interfere with the patient's well-being, recovery and satisfaction. However, since most of these drugs are given prophylactically, and since not all patients will actually be suffering from intolerable pain or severe nausea and vomiting symptoms postoperatively, many patients will receive these drugs unnecessarily. Thus, for the individual patient, the risk of suffering from drug-related adverse reactions without profiting from any benefit may be relevant. Perhaps a 'wait-and-see' approach should be considered; especially NSAIDs or dexamethasone should not be given pre-operatively to all patients but should be provided exclusively to those in whom alternative analgesics (for instance paracetamol combined with a weak opioid) or alternative antiemetics (for instance a setron or droperidol) have failed or are associated with unacceptable adverse effects (for instance opioid-related adverse effects). There is no evidence that prophylactic administration of an analgesic or an anti-emetic is more efficacious than the therapeutic administration. An interesting alternative to achieve satisfactory posttonsillectomy analgesia may be with local anaesthesia swabs that are applied onto the wound.

References


