Chapter 1

NSAIDs and Tonsillectomy

Introduction and historical background

Tonsillectomy is one of the most commonly performed surgeries in North America, particularly in children, with over 500 000 surgeries taking place in the US alone.[1] With careful patient selection, it is a safe and effective procedure, with minimal morbidity. Though many techniques for performing tonsillectomy exist, the ultimate goal is excising the lymphoid tissue residing in the oropharynx, alleviating symptoms of airway obstruction, as well as minimizing the frequency of strep throat.

First described by Celsus (25 BC – 50 AD), a Roman aristocrat, the procedure has evolved significantly, while still retaining the simple element of dissecting the tonsil capsule to detach the tonsil from the tonsillar bed. In its original description by Celsus, it involved blunt digital dissection, which then evolved to the use of a snare as described by Galen (AD 121-201). It is believed that the procedure remained common until the Dark Ages, when it was lost, but was reintroduced in the 1600's by Peter Lowe, the founder of the Royal Faculty of Physicians, though evolving beliefs caused a shift in technique, since their complete excision was thought to lead to alterations in "mucous flow". In 1861, Borelli revived the digital enucleation technique described by Celsus, which became the norm for tonsillectomy due to recurrence of symptoms with partial resection.[2] Since then, the introduction of the guillotine tonsillectomy and later electrocautery and coblation dissection have further refined the technique and

allowed to minimize surgical complications such as intraoperative and postoperative pain and bleeding.[3]

Definitions

Tonsillectomy

According to the AAO HNS, *tonsillectomy* is defined as a procedure that "completely removes the tonsil, by dissecting the capsule off the muscular wall. This procedure is commonly performed in association with adenoidectomy."[4] This procedure is performed using a variety of techniques, including electrocautery, coblation, cold dissection (eg: snare), laser, harmonic scalpel and thermal welding. All these techniques are described below. The ultimate goal of tonsillectomy is the removal of the tonsillar tissue, which is also known as the palatine tonsil. It belongs to the lymphatic aggregate known as Waldeyer's ring.

Waldeyer's ring is a network of lymphoid tissue that surrounds the oropharynx. It is mainly formed by the pharyngeal, palatine and lingual tonsils. The pharyngeal tonsils (or adenoids), which sit in the nasopharynx at the base of skull. The adenoids sit between the eustachian tube openings, which are found in the lateral nasopharynx, and are bordered by the tubal tonsils of Gerlach, a subset of the pharyngeal tonsils. The role of the eustachian tube is to ventilate the middle ear, allowing the later to drain the fluid its mucosa produces into the nasopharynx. When adenoidal hypertrophy becomes excessive, the eustachian tube opening becomes obstructed, fluid begins to accumulate in the middle ear, and predisposes to acute otitis media (AOM), the most common type of ear

infection in children. The tubal tonsils of Gerlach connect to the lateral pharyngeal bands of lymphoid tissue, which then connect to the palatine tonsils. The palatine tonsils lie within a capsule and sit within the space formed between the anterior and posterior pharyngeal pillars. Other areas of lymphoid aggregates composing Waldeyer's ring include the pharyngeal granulations and the lymphoid tissue within the laryngeal ventricles.

Adenoidectomy

Adenoidectomy is defined as the removal of the adenoid pad from the nasopharyngeal wall. The indication for this procedure includes sleep disordered breathing or sleep apnea, recurrent AOM, persistent otitis media with effusion [5] with hearing loss, and pediatric sinusitis. This procedure can be performed using several techniques, including the cold technique, which employs a curette to avulse the adenoid tissue from the pharyngeal wall, or a hot technique, which typically utilizes a suction electrocautery for the same purpose. Other techniques include use of a laser, coblator, microdebrider and other.

Indications for Tonsillectomy

Recurrent tonsillitis

Throat infection occurs when microorganisms, usually viruses or bacteria, infect the pharynx and/or the palatine tonsils. Group A Streptoccocus is a commonly cultured pathogen and causes a common condition known as strep throat. Such an infection is also associated with a constellation of symptoms such as sore throat, absence of cough, fever, lymphadenopathy, and is common in

children under the age of 15 years old. This constellation is quantified using the McIsaac score,[6] which offers a scoring system for calculating the probability of a patient presenting with a sore throat having strep throat and requiring antibiotics (insert figure). In fact, since sore throats are a prevalent condition, it is important to differentiate viral infections from bacterial ones, as the latter require antibacterial therapies. Overuse of antibiotics has led to the development of resistant bacterial strains, and therefore there is increased emphasis on tailoring therapies to specific microorganisms has taken precedence. The McIsaac score formulates an algorithm for work up sore throat, where it is suggested patients presenting with more than one of the above mentioned criteria received a throat swab and culture, and patients meeting more than three of these criteria have the option of receiving antibiotics upon assessment with the physician, or waiting for a culture.

In certain cases, patients experience multiple episodes of tonsillitis in a year, and this can be burdensome on them or their caregivers. Examples of such situations include lost parental work time, missed attendance to school, tonsillar hypertrophy and sleep disordered breathing, airway obstruction, weight loss, dehydration, failure to thrive, spread of infection to adjacent and distant structures, as is the case in peritonsillar abscesses, deep neck space infections, Lemmiere's syndrome, and sepsis.

The AAO HNS published a guideline[1] of admissibility criteria for tonsillectomy. In the case of recurrent tonsillitis, indications for tonsillectomy

include 7 episodes of tonsillitis in one year, 5 episodes of tonsillitis per year for two consecutive years, or 3 episodes per year for 3 consecutive years. Exceptions to these criteria, and indications for a less conservative approach to surgical candidacy, are patients suffering complications of tonsillitis, including history of febrile seizures, which can be precipitated by acute tonsillitis, patients known for or with a family history of periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA), as well as history of multiple antibiotic allergies or intolerances. History of peritonsillar abscess is also considered as an indication for tonsillectomy, as well as history of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS),[7,8] tonsillitis induced nephropathy,[9] and in certain cases, rheumatic fever.[10]

Adenotonsillar hypertrophy and Obstructive sleep apnea (OSA) /obstructive sleep apnea syndrome (OSAS)

Tonsils and adenoids are quite small at birth and progressively grow in children as their immune system develops along with exposure to viral and bacterial pathogens.[11] In certain cases, they can grow to a point where they cause obstruction of the airway passages. Obstructive sleep apnea syndrome or OSAS results when an individual does not consistently achieve adequate airflow during sleep. This is a common disorder that occurs in 2% of children[12,13] and results from a partial obstruction of the airway during sleep. It manifests itself in a range of symptoms including daytime sleepiness, decreased performance in daytime activities,[14] or alternatively as hyperactivity and lack of attention, or

breathing difficulties such as mouth breathing, snoring and pauses in breathing or apneas at night.[5] The severity of OSAS can vary from mild sleep disturbances to frank sleep apnea. Sleep apnea is classified as either obstructive or central. Obstructive sleep apnea (OSA)[5] is defined as a decrease in airflow due to a complete obstruction in the path of airflow despite respiratory efforts, whereas central sleep apnea is a decrease or cessation of airflow due to a failure of respiratory drive occurring during sleep.

Several anatomical and congenital factors can predispose to sleep apnea. Pediatric patients are different than adult patients in the nature of the cause of the obstruction. Common causes of obstruction in children include hypertrophy of the adenoids and tonsils, and less commonly the lingual tonsils. Adults present with a combination of factors including obesity, which affects neck circumference, lingual tonsillar hypertrophy, increased prominence of the tongue, and other contributory factors such as alcohol intake, causing relaxation of the muscles of the pharynx. Factors that can contribute to both pediatric and adult obstructive sleep apnea include jaw abnormalities such as retrognathia and other craniofacial abnormalities.

Polysomnography (PSG) is a special medical test that is considered the gold standard for establishing the diagnosis of sleep apnea and other disorders of sleep. It is a composite of various electrographical recordings measuring various factors relating to the sleep including limb movement, oxygenation, brain activity and sleep stages, respiratory effort and airflow.[15]

There are significant challenges that exist in determining the diagnosis of OSA or OSAS in children. PSG, although the gold standard for diagnosis, presents practical and financial limitations to its use. To perform PSG children must sleep in a testing center with several monitoring devices. This is impractical and can be troubling for children. Furthermore, PSG is an expensive test, and can delay treatment of OSAS or OSA. The latter point is one of particular significance, since waiting time for PSG can be in the order of months, and children with such conditions often experience daytime sleepiness and decreased performance in school. This is further coupled with surgical waiting lists which are routinely 3-6months. Moreover, the high incidence of respiratory symptoms in children due to repeated upper respiratory tract infections and strep throat exacerbates these conditions, rendering PSG of little added value given the time delay to surgical intervention.

As well, obstructive sleep apnea can cause and/or worsen health conditions that can have severe health consequences. Namely, in severe cases, it can cause “neurocognitive impairment and behavioral problems, failure to thrive and cor pulmonale,”[5] the latter of which is a severe cardiopulmonary condition caused by periods of cyanosis and carbon dioxide retention which results in pulmonary hypertension.

Other indications for tonsillectomy

Though the most common indications are listed above, there are special circumstances that also qualify patients for tonsillectomy, and in some cases a

more urgent tonsillectomy. For example, in rare cases, tonsillitis can cause hemorrhage within the oropharynx, which can lead to acute airway decompensation, as well as hemorrhage and anemia. In these circumstances, tonsillectomy is performed as an urgent procedure at the time of presentations. As well, in certain cases where tonsils are clearly causing airway obstruction, these may have to be removed acutely. This circumstance is sometimes found in association with an acute infection, particularly Epstein barr virus (EBV) in a condition known as mononucleosis. This condition is characterized by severe bacterial tonsillitis and adenotonsillar hypertrophy. Malignancy is also a concern in the setting of tonsillar hypertrophy, namely when it is asymmetric. Urgent tonsillectomy is performed in that setting to rule out malignant conditions, most commonly lymphoma in the pediatric setting.

Certain conditions when associated with adenotonsillar hypertrophy would prompt surgery without meeting criteria for recurrent tonsillitis or OSAS, for example when tonsillitis is associated with febrile seizure. In this setting the potential side effects of a seizure outweigh the possible complications of tonsillectomy. Finally in the setting of cardiac disease being exacerbated by sleep disordered breathing, or instances of failure to thrive or cor pulmonale are all diagnoses that would prompt immediate action.

Epidemiology of tonsillectomy and consequences of guidelines

There have been several recent reports of changes in incidence of tonsillectomy. In the early 20th century tonsillectomy was the most commonly

performed ambulatory surgery, but since the 1970's rates have significantly decreased.[4] As well, there has been a further decrease of 50% in incidence of tonsillectomy between 1977 and 1989.[16] These changes have been in part attributed to changes in indications for tonsillectomy with a more conservative approach to tonsillectomy for recurrent tonsillitis, causing a shift with an increased rate of tonsillectomy of sleep disordered breathing.[17] This is reinforced by reports that between 1996 and 2006 there has been an increase in the rate of tonsillectomy, but an overall decrease in the rate of tonsillitis.[18] Altogether, tonsillectomy has remained an extremely common procedure with over 500 000 tonsillectomies being performed yearly in the United States alone.[4,17,18]

There is no doubt that tonsillectomy is a common surgery, and guidelines have been successful in changing practices in surgical candidacy for children. However, the guidelines also have many limitations with regards to the care surrounding this procedure. In fact, aside from surgical candidacy criteria, the only further directions discussed in the guidelines with regards to medication use include a strong recommendation against the use of antibiotics, and a recommendation for the intraoperative use of dexamethasone to decrease post-operative vomiting. An important factor is pain control following tonsillectomy, and the guideline provides little guidance for this issue. It does provide the recommendation to "advocate for pain management after tonsillectomy and educate caregivers about the importance of managing and reassessing pain."[4]

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Chapter 2 – Mechanisms of pain and analgesia with NSAIDs

Background

There are numerous NSAIDs that currently exist on the market including the commonly used Ibuprofen, marketed as Advil® by Pfizer. Other commonly used and prescribed NSAIDs include diclofenac (Voltaren®), ketorolac (Toradol®), ketoprofen (Orudis®), rofecoxib (Vioxx®), celecoxib (Celebrex®), naproxen (Naprosyn®). NSAIDs are used as over-the-counter or prescription analgesics. They have commonly been used to treat musculoskeletal pain, including musculoskeletal trauma, but also chronic inflammatory conditions such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis[2]. They are also effective in treating gynecological pain including menstrual cramps, and are often used in treating migraine. They also have anti-pyretic properties and are therefore used to treat fevers in the setting of upper respiratory tract infections and pharyngitis. To understand the mechanism of action of NSAIDs and other analgesics in the setting of post-operative pain it is important to begin with an investigation of the pathways involved in this setting.

Mechanism of pain and wound healing post-tonsillectomy

To understand the processes that lead to pain following operative procedures such as tonsillectomy, it is important to discuss the mechanisms of wound healing. There is very little research investigating the precise mechanisms involved in pain post-tonsillectomy, therefore much of our understanding is derived from the basic concepts of wound healing which have been studies in other settings such as burns.[3]

A review of the steps of wound healing are well described in an article by Broughton et al, and is summarized here.[4] Wound healing is divided into 3 stages: inflammation, proliferation and maturation. Upon tissue injury, the body controls bleeding and achieves

hemostasis by causing contraction of vascular endothelial cells and activating coagulation pathways. The clot that forms is composed of collagen, platelets, fibrin and fibronectin. As platelets are recruited to form a clot, they release various compounds, including growth factors (transforming growth factor β, or TGF-β), inflammatory mediators such as thromboxane, and cytokines (Interleukin-1 or IL-1; tumor necrosis factor-α, or TNF- α) that result in neutrophils and fibroblasts being attracted to the wound. As well, platelets play an essential role in wound healing since they mediate pathways that result not only in coagulation, but they also participate in cellular scaffolding, cell adhesion and antimicrobial activity. After a short delay, endothelial cells then release products of the COX-2 enzyme: prostaglandins, which cause vasodilation and platelet disaggregation, and leukotrienes, which increase vascular permeability, chemotaxis and leukocyte adhesion. Due to increased vascular permeability, there is increased concentration of protein in the tissue surrounding blood vessels, resulting in edema of injured tissues. Prostaglandins and leukotrienes are important mediators of pain following tissue injury and act by directly and indirectly stimulating pain neurons in the affected areas.[5] Neutrophils, which increase in concentration at the site of injury as a result of platelet activity, play a key role in antimicrobial activity and the healing process by clearing extracellular matrix. As well, as a result of platelet and neutrophil accumulation, mediators are released to turn off destructive inflammatory processes. Neutrophils then begin to go through apoptosis and are replaced by macrophages and fibroblasts, which promote cellular proliferation through the release of growth factors. Macrophages are important to the transition into the proliferative phase, and they act to remove dead or apoptotic neutrophils, debris and bacteria. Fibroblasts, on the

other hand, promote proliferation by attracting keratinocytes, which act by depositing collagen in place of temporary extracellular matrix components such as fibronectin and proteoglycans. Macrophages and fibroblasts also stimulate the formation of new blood vessels at the site of injury, and promote the presence of myofibroblasts, causing contraction of the wound, and allowing it to close. The process of wound maturation then takes over, starting at 1 to 2 weeks following the injury, and is promoted by the presence of TGF-β which is released by keratinocytes, as well as a results of macrophage and fibroblast activity. By this process, type 1 collagen replaces the immature extracellular matrix and strengthens the wound.

Moreover, in the setting of tonsillectomy, pain results from several steps of the procedure that inflict tissue damage. First, the mouth retractor (eg: Boyle-Davis mouth gag), which is used to keep the mouth open and access the tonsils, can cause venous congestion of the tongue, stress on the temporomandibular joint and damage to sensory nerves in the oral cavity. As well, the dissection of the tonsillar capsule causes inflammation and edema, and leaving behind an open wound with exposed nerve fibers. This makes the operated pharynx vulnerable to mechanical trauma during swallowing saliva, fluids and food, and enhancing pain. Although the inflammatory mechanisms and mediators involved are unknown to this day, inflammation and infection of the wound manifests as a thick white fibrin layer forming on the tonsillar bed within 24h of surgery.[6] Signs of inflammation increase in intensity until the third and fourth post-operative days, and at about one week post-op, the fibrin coating begins to peel off allowing mucosa and granulation tissue to fill the surgical site. This healing period is particularly prone to secondary bleeding due to the

predominance of granulation tissue and the possibility of exposing a blood vessel as the fibrin layer peels off. As of the second post-operative week, pain decreases as the surgical site completely epithelializes, although small amounts of pain may persist beyond that time.

Mechanism of action – NSAIDs

The main action of NSAIDs is the inhibition of the cyclooxygenase (COX) enzyme.[7] There are 2 specific enzymes known to act in the pain pathways, COX-1, which is always expressed in the body (expressed constitutively) and COX-2, which is expressed only in the setting of inflammation. The COX enzymes convert arachidonic acid to prostaglandin H_2, which in turn enters into different pathways to produce bioactive lipids such as thromboxane A_2, prostaglandins D_2, E_2, F_2 and prostacyclin. NSAIDs can be categorized by their affinity for inhibiting the COX-1 and/or COX-2 enzymes.[8] For example, aspirin, ibuprophen, indomenthacin and naproxen are non-selective inhibitors of the COX enzyme, whereas NSAIDs such as celecoxib and rofecoxib are known as selective COX-2 inhibitors.[1] The latter class of NSAIDs have the advantage of minimizing gastric symptoms (see below) and maximizing pain relief, as COX-2 has been found to have more concentrated expression in inflamed tissue.

Prostacyclins, which are a product of the COX-pathways, cause local smooth muscle relaxation and vasodilation, as well as inhibition of the prostaglandin receptor on platelets, which physiologically acts to decrease platelet aggregation.[9] Platelets also contain COX-1, which has a downstream byproduct called Thromboxane A_2 (TXA_2). TXA_2 has the contrary effect of vasoconstriction and increased platelet aggregation, and it is believed that the known cardiovascular side-effects of selective COX-2 inhibitors is due to the unopposed

action of TXA_2 in the absence of counteraction of COX enzyme byproducts causing local vasodilation and decreasing platelet aggregation. Moreover, NSAIDs are known to increase blood pressure and can precipitate congestive heart failure in susceptible patients, and this effect has been observed especially with the use of COX-2 inhibitors.[8]

Most NSAIDs are active upon administration of the drug, meaning that they do not need to be metabolized by the body to serve their function. The clearance of NSAIDs is performed by the liver through the action of the enzyme CYP2C9, a cytochrome P450 enzyme. This enzyme puts the NSAID through the several cycles of glucoronidation. Once this process is completed, the NSAID is excreted by the kidney in its inactive form.[10]

Cardiovascular risk with NSAIDs

The mechanisms of cardiovascular risk with NSAIDs are mentioned above. To summarize, the products of the COX-enzyme pathways in the cardiovascular system act at the level of the platelets and the vessel walls. Prostacyclin is primarily produced by the endothelial vessel wall via COX-2 activity and acts in an anti-thrombotic fashion to cause vasodilation through smooth muscle relaxation, as well as inhibit platelet aggregation through interaction with the IP receptor on platelets. Platelets mainly contain COX-1 and produce TXA_2, which causes platelet aggregation and vasoconstriction.[8] In the setting of selective COX-2 inhibition, a pro-thrombotic state exists in the cardiovascular system, which explains the side effects observed in this category of medications.

Amongst the greater class of non-steroidal anti-inflammatory drugs that act on the COX pathways, there exist different levels of selectivity for either COX-1 or COX-2. As such, the risk of developing adverse coronary vascular events varies with the relative degree of

COX-2 selectivity. For example, a population based case control study conducted in Boston revealed that the COX-2 selective NSAID rofecoxib was the only NSAID identified with a statistically significantly higher rate of cardiovascular events and diclofenac was found to have an increased risk of myocardial infarction, whereas naproxen, a preferentially COX-1 inhibitor, was found to have a decreased risk of cardiovascular events.[11] A similar phenomenon was found by Solomon et al[11] who published their findings of increased cardiovascular events with rofecoxib (adjusted hazard ratio [AHR] 1.22, 95%CI 1.14-1.30) and a decreased risk with naproxen use (AHR 0.79, 95%CI 0.67-0.93). Figure 1, which is published in a review by Antman et al[1] on the subject of cardiovascular risk factors, shows the various NSAIDs within their chemical classes, as well as a chart indicating their level of COX-1 versus COX-2 selectivity.

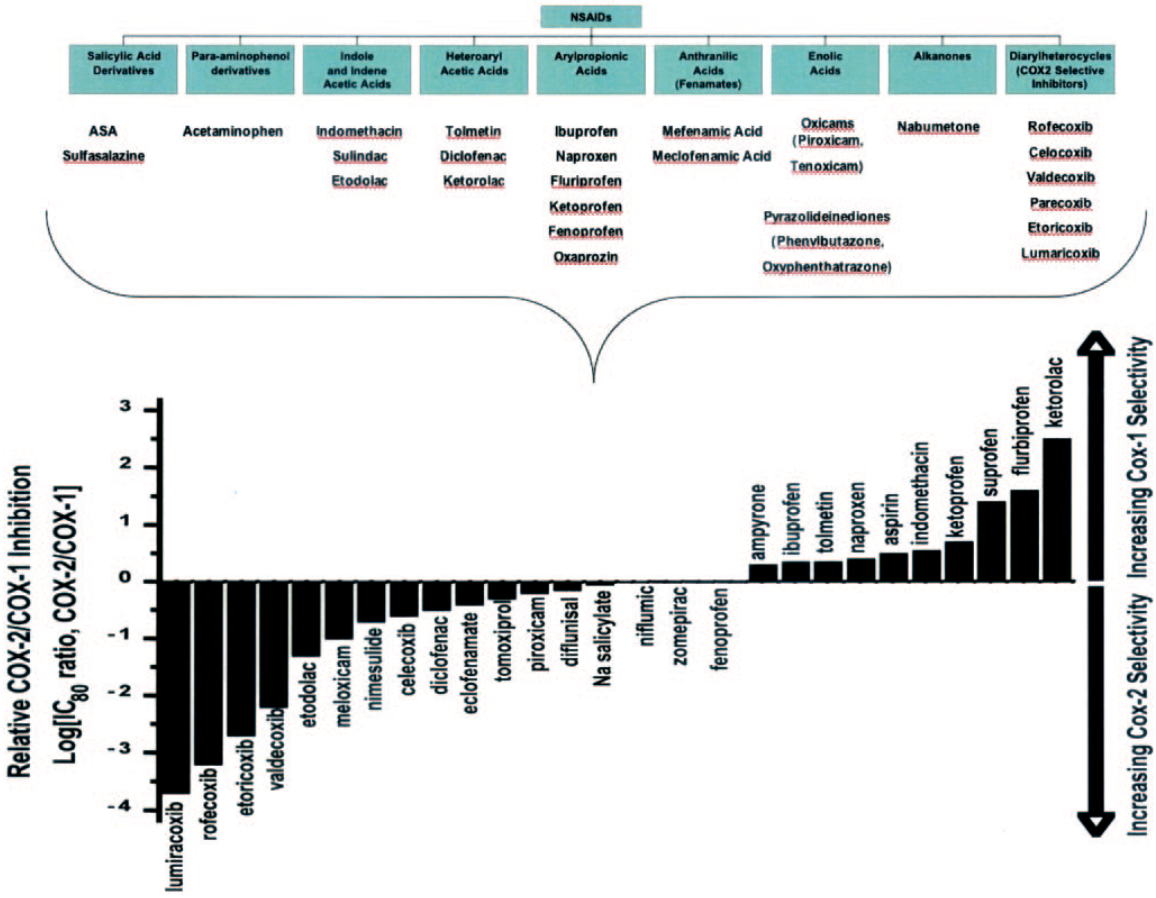

Figure 1: NSAID relative COX-1 and -2 reactivity (from Antman et Al[1])

The magnitude of the cardiovascular risk associated with NSAID is well documented in the literature. A systematic review and meta analysis of observational studies (case control and cohort studies) by Patricia McGettigan and David Henry[12] reports a hazard ratio of cardiovascular events for various NSAIDs. Namely, rofecoxib was found to have the largest relative risk (RR) for cardiovascular events (1.45, 95%CI 1.33-1.59), followed by diclofenac (1.40, 95%CI 1.27-1.55). The lowest RR was found in ibuprofen (1.18, 95%CI 1.11-1.25) and naproxen (1.09, 95%CI 1.02-1.16). As well, a systematic review of RCT's addressing the effectiveness and side effects of various COX-2 inhibitors[13] found that the RR of

myocardial infarction (MI) was 2.92 (95%CI 1.36-6.28) times higher in rofecoxib than in non-selective NSAIDs, whereas celecoxib had a non-significant increase in RR for MI (1.77 95%CI 1.00-3.11).

Gastrointestinal side effects and management

As previously discussed in this chapter, NSAIDs have several known side effects including gastric side effects ranging from gastroesophageal reflux to gastrointestinal bleeding as a result of gastric acid production. These side effects stream from the inhibition of the COX-1 enzyme, through the depletion of prostaglandin in the gastric mucosa.[14] Prostaglandins are thought to be gastroprotective. PGE_2 (prostaglandin) and PGI_2 (prostacyclin) stimulate synthesis and secretion of mucous and bicarbonate, promoting epithelial proliferation and increase mucosal blood flow. These are considered primary (factors secreted into the lumen such as mucous, bicarbonate, and immunoglobulins), secondary (epithelium) and tertiary (microcirculation) levels of gastric protection mechanisms.[15] Notably, microcirculation acts to neutralize acid, preventing its accumulation to cytotoxic levels. In the absence of these protective factors, NSAID use can result in the formation of petichiae, erosions, and much less commonly, ulcerations, bleeding, perforations and gastric outlet obstruction.

The goal of preventative therapy is to avoid complications of mucosal damage, namely ulceration and bleeding,[16] but also dyspepsia, as it is often a limiting factor in its therapeutic use.[17] Risk factors for developing gastrointestinal complications include ongoing aspirin use for cardioprotection, previous history of ulcers, age >60, corticosteroid use, anti-platelet or anti-coagulant drug use, and significant cardiovascular disability. Modifiable risk factors such

as aspirin, corticosteroid and anti-coagulant use should be addressed prior to placing patients on long-term NSAID therapy. As well, treatment of active H. Pylori infection can also reduce ulcer formation.

For patients being given non-selective NSAIDs with gastrointestinal risk factors for complications, such as previous history of peptic ulcer disease. Pharmacological gastroprotective measures have been shown to decrease adverse gastrointestinal outcomes when compared to placebo.[18] There are three main classes of medications that can be used for gastroprotection, namely synthetic prostaglandins, H2-receptor blockers and proton pump inhibitors (PPI). Misoprostol is the main synthetic prostaglandin used clinically, and has been shown to provide benefit in the setting of gastroprotection for prolonged NSAID use.[19,20] However, its use for ulcer prophylaxis has been limited due to its side effects that include nausea, vomiting, diarrhea, pyrexia[21] anaphylaxis and inability to use it in women of childbearing age because of risk of abortion.[22] H2-receptor blockers inhibit release of acid into the stomach by blocking the histamine receptor at the level of the gastric parietal cells. Although they are effective at decreasing the overall incidence of gastrointestinal ulcers, they have not been found to effectively decrease the incidence of gastric ulcers.[23] Proton pump inhibitors, or PPIs, block gastric acid secretion by inhibiting the H/K ATPase and have been found to be more effective at preventing acid-related mucosal injury and disease. PPIs have been shown to decrease the symptomatology and endoscopic evidence of peptic ulcer disease in several meta-analyses,[18,23] and are now commonly used for gastroprotection in the setting of NSAID use.[24] It is important to note that the large majority of evidence available in this field is obtained from studies performed on adults.

Renal side effects

Nephrotoxicity is another side effect of NSAIDs that is well recognized. Although rare, such events do occur in a small proportion of people, ranging from less than 1 to 5% of NSAID users.[25] The pathophysiological process is related to the inhibition of prostaglandin production through the COX enzyme blockade conferred by NSAIDs.[26] Prostaglandins regulate blood flow within the kidney by modulating vascular tone, sodium balance, and renin release.[26] COX-1 is constitutively expressed in the kidney, as it is in many other tissues, and COX-2 has also been found to a lesser extent to be expressed in certain parts of the kidney.[27] A variety of prostaglandin receptors exist in the kidney and impact the hemodynamics and overall function of the kidney. Inhibition of prostaglandin production as a result of NSAID use causes decrease in blood flow and subsequent injury. Although NSAID-induced nephropathy is rare, and increase in blood pressure of roughly 5mmHg is common in chronic NSAID users.[28] Patients with predisposing factors such as advanced age, diabetes, diuretic use, congestive heart failure, cirrhosis, and nephrosis are more likely to suffer renal injury,[26] although patients without predisposing factors are also at risk for renal complications.[29] The nephrotoxic effect of NSAIDs is dose-dependent, with lower doses having a lower likelihood of causing renal injury.[30,31] In most cases, the nephrotoxic effects are reversible and the risk of developing these disappear with discontinuation of treatment, but nonetheless, the risk exists with short and long term NSAID use.

NSAID-induced asthma

NSAID-induced asthma, more commonly known at aspirin-induced asthma [32], is a phenomenon that was well documented by Samter and Beers in the 1960's.[33] AIA is

observed in a constellation of clinical findings known as Samter's triad, and consists of presence of aspirin hypersensitivity, nasal polyps and asthma. The mechanism for AIA is related to COX-1 inhibition results from the local accumulation of arachidonic acid. As mentioned above, arachidonic acid is converted to prostaglandins by COX-1. In the setting of NSAID-induced inhibition of this enzyme, arachidonic acid enters an alternate pathway leading to the production of a leukotriene LTA_4. LTA_4 is metabolized into the byproduct cysteine leukotriene, which causes bronchoconstriction.[34] Ultimately, patients who suffer from AIA or who have a clinical presentation suspicious for Samter's triad are managed primarily by avoidance of NSAID use.[35]

How this relates to children

Adverse events after use of NSAIDs in children have also been studied, though to a lesser extent. In this population, NSAIDs are often used in the context of acute pain[36] or for treatment of pyrexia.[37,38] Although gastrointestinal complications tend to be less common than in adults,[36] they still do occur in the pediatric population. A study published by Autret-Leca et Al[39] reviewed all reported adverse drug events associated with pediatric NSAID use that occurred from inception (up to 9 years from the date of case identification) of the respective medication prior to 2000 in France. They found 61 cases of endoscopically proven NSAID induced gastritis, ulceration and upper gastrointestinal bleed. The majority of these cases were as a result of an ENT related indication (42%) and the mean time of onset of therapy to time of presentation was 5 days, with a median of 3 days. Another study, by Levy et Al,[36] reported the results of a survey of physicians who mainly treated children. Interestingly, amongst other pediatric specialists, pediatric rheumatologists were the ones

who identified the incidence of adverse drug reactions with the use of NSAIDs. Overall, these medications were thought to be safe for use in children. Although this study was limited by a low (28%) response rate, it demonstrated the fact that NSAIDs are commonly used by pediatric specialists and that they are deemed safe for use in children.

With regards to renal side effects, there have been reports of nephrotoxicity, flank pain and metabolic acidosis in children in the literature.[26,40,41] Predisposing factors such as dehydration, hypovolemia, hypotension and use of other nephrotoxic medications have been associated with the incidence of renal failure following NSAID use,[35] though this complication does occur in the absence of predisposing factors as well. In a study of children with juvenile arthritis, only one patient of the 226 studied had urinary tract abnormalities attributable to NSAID use, yielding a rate of nephrotoxicity of 0.4% in this population.[42] There is also evidence that ibuprofen is safe in the neonatal period for use in patent ductus arteriosus closure.[43] However, our knowledge of side-effects of NSAIDs in the general pediatric population is based on two studies, the Children's Analgesic Medicine Project (CAMP)[44] and the Boston Fever Study[45,46] Combined, these two studies included 114,539 patients with 76,000 patients given Ibuprofen and the rest receiving acetaminophen. These studies were randomized controlled trials that looked at the safety of short-term use of NSAIDs for treatment of fever when compared with acetaminophen. Neither study systematically performed renal function testing but reported complications as they occurred. The CAMP study reported no events of renal failure, but did find that there was significantly more abdominal pain but not digestive problems in the ibuprofen group than the acetaminophen group. The Boston Fever Study reviewed the charts of all admitted

patients for their blood work and renal function tests. Seven hundred ninety five patients were admitted into hospital during the trial and renal function tests were available for 288 of these. There were no patients who took NSAIDs admitted for renal failure and there was no significant difference in renal function tests between the two treatment groups.

Finally, there is little literature regarding cardiovascular risk in children is scarce.[35] Given the specific pro-thrombotic risk factors present in adults such as hypertension and atherosclerosis, we will consider the cardiovascular risk for children to be negligible. As well, aspirin-induced asthma is rare in childhood, with only 5% of asthmatic children having AIA as opposed to adults where AIA is the underlying cause in 20% of asthmatics. [47]

Conclusion

Although NSAIDs do have several known and potentially morbid side effects associated with their use, overall they confer a low risk of severe complications in the pediatric population. As well, short-term use with regular doses presents the lowest risk for use in all populations. In the context of post-operative pain, use of NSAIDs has a finite duration and requires a lower dose than that required in the setting of arthritis, namely juvenile arthritidies, which are the source of many of the side effects reported in the pediatric population. Proper patient selection, patient education and early recognition of side effects is important in mitigating the possible side effects of the medication.

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Chapter 3

The effect of Non-Steroidal Anti-Inflammatory Drugs for management of post-tonsillectomy pain: A systematic review and meta-analysis of randomized controlled trials

Abstract

Introduction: Controversy surrounding the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for post-tonsillectomy analgesia exists due to concerns about bleeding and pain control. However, with increasing use in other post-operative settings, and recent severe complications associated with the use of a widely accepted opioid (codeine), and subsequent black box warning from the FDA and Health Canada, experts have let the medical community to change their practice surrounding post-operative pain management.

Objectives: To determine the effect of NSAIDs compared to placebo and other analgesics in the post-tonsillectomy setting.

Data sources: Medline, EMBASE, the Cochrane trial registry, and Web of Science including the grey literature.

Study eligibility criteria: Randomized-controlled trials (RCTs) of post-tonsillectomy patients, comparing an NSAID to either placebo or a non-NSAID anadlgesic and reporting pain-related outcomes.

Participants: We included trials of patients treated with NSAIDS after undergoing tonsillectomy alone, adenotonsillectomy, tonsillectomy with bilateral myringotomy and tubes, or adenotonsillectomy with bilateral myringotomy and tubes.

Outcomes: Primary outcomes included pain score, total mean doses of rescue medication doses, time to first rescue dose and number of patients requiring rescue pain medication. Secondary outcomes were vomiting, severe bleeding, and severe post-operative complications.

Analysis and data synthesis: We used a random-effects model to pool data across studies, where possible. RevMan 5.0 was used to synthesize and analyze the data extracted from studies reviewed.

Results: Fifty-eight studies with a total of 4765 patients were eligible for analysis. NSAIDS provided better pain control compared to placebo when measured with pain scores (standardized mean difference (SMD) -0.45, 95%CI -0.84, -0.07) and mean total dose of rescue opioid (mean difference (MD) -1.87, 95%CI -3.27, -0.47). There were no statistically significant benefit to using NSAID for pain control compared to opioids or other analgesics when measured with pain score (SMD 0.01, 95%CI -0.34, 0.36), time to first rescue dose (MD 2.5 minutes, 95%CI -9.90, 14.96) and number of patients requiring rescue (Odds Ratio [OR] 0.96, 95%CI 0.62–1.47). Mean total dose of rescue morphine (MD -0.17, 95%CI -0.20, -0.14, I^2 85%) was found to be less in the NSAID group but could not be meta-analyzed due to differing study methodologies. The risk of vomiting was lower in patients treated with NSAIDS compared to patients treated with another analgesic or placebo (OR 0.55, 95%CI 0.43, 0.70 and 0.54, 95%CI 0.33, 0.88, respectively).

Limitations: Challenges included small sample sizes, limited follow up and methodological variability between included studies, which limited our capacity to pool patient-important outcomes.

Conclusion: NSAIDs are not significantly more effective than opioids and other classes of analgesics for controlling pain post-tonsillectomy. However, the quality of

the evidence is poor. We recommend a large-scale RCT to further explore the effect of NSAIDs in the management of post-tonsillectomy pain.

Background

Tonsillectomy is the most commonly performed surgery in North America.[1] Considered a relatively safe procedure, the most significant risks associated with tonsillectomy are post-operative pain,[1] dehydration, and bleeding, which can range in severity from self-limiting sputum tingeing to lethal hemorrhage.[2]

Pain control can be achieved using different combinations of analgesics. Although codeine has previously been a commonly prescribed drug, the last decade has seen several deaths in children as a result of its use in the post-operative period. Subsequent investigations have identified a mutation of the cytochrome P450 2D6 or CYP2D6 enzyme predisposing children to such adverse events[3,4]. Codeine is converted to morphine in the liver by CYP2D6, but in a subset of the population, known as ultra-rapid metabolizers, codeine is converted to morphine at a dangerously rapid rate, resulting in opioid overdose, respiratory depression and failure, and in several cases, death. As a result, surgeons are now searching for safe yet effective options for pain control.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen, naproxen, ketorolac, and others have been used for non-surgical pain relief[5,6], but surgeons have been reticent to include them in their post-operative care regimens because of a theoretical increased bleeding risk. Moreover, the impetus to replace codeine and avoid the many side effects of opioids, including nausea, vomiting, constipation, delirium, hallucinations, somnolence, respiratory depression and

pruritus have fuelled research initiatives for exploring NSAIDs as alternative analgesics. In fact, there now exists a substantial body of literature demonstrating that NSAIDs have a role to play in post-operative pain management in a variety of surgical fields, including orthopedics[7], neurosurgery[8], ophthalmology[9], oral surgery[10] and otolaryngology[11]. Several reviews, including 3 Cochrane reviews[12-14] and a systematic review from our center[15], addressing the risk of bleeding post-tonsillectomy with NSAIDs have demonstrated that the bleeding risk does not increase in patients who were treated with NSAIDs post-tonsillectomy[14]. However, the only systematic review of analgesics and their efficacy post-tonsillectomy was conducted in 2005.[16] This review was limited to studies in the pediatric population and did not focus on the analgesic efficacy of NSAIDs. In fact, no systematic reviews focusing on NSAIDs for tonsillectomy pain control were identified following a thorough literature search of the Cochrane, the Database of Abstracts of Reviews of Effects [17], Medline and EMBASE databases or the Prospero registry.

Objectives

The primary objective of this review was to assess the effect of NSAIDs compared to other classes of analgesics for management of patients with post-tonsillectomy pain. The secondary objective was to assess the effect of NSAIDs on other adverse events including vomiting, bleeding, dehydration, infection, re-operation and death. Our main research question is: based on the available evidence, are NSAIDs significantly better at controlling post-operative pain compared with placebo and/or other analgesic options in patients of all ages after

tonsillectomy?

Methods

The study was conducted according to a detailed protocol, which was finalized prior to beginning the study. We only included randomized controlled trials published in English or French. We did not discriminate for participants' age. We followed PRISMA reporting guidelines in redacting this manuscript.

Search Strategy

We searched Medline, EMBASE and the Cochrane Trial Registry for potentially eligible publications (see Appendix A for Medline and EMBASE search strategy). We searched published abstracts from relevant conference proceedings and abstracts available through the Web of Science (grey literature) were screened for relevance. Published and unpublished studies were included if data reported was sufficient for extraction of a pain-related outcome. Two independent reviewers (NC, STL) conducted the literature search and performed a title search, as well as abstracts screening and full-text review for inclusion of articles. The search was conducted on September 17th, 2013. Data was extracted from the published articles, and although trial registries were screened, no ongoing studies met inclusion criteria for this review. No primary authors were contacted.

Inclusion criteria

Randomized controlled trials published in English or French were eligible for inclusion. Patients in the studies had to have undergone one of the following procedures: tonsillectomy alone, adenotonsillectomy, tonsillectomy with bilateral

myringotomy and tubes, or adenotonsillectomy with bilateral myringotomy and tubes. There were no restrictions on patient age. Patients had to be randomized to treatment with an NSAID, and compared with placebo or with any combination of analgesics excluding use of NSAIDs. Studies had to state pain as an outcome in their methods, or report a pain-related outcome in their results section to be considered for inclusion. We included studies reporting pain using pain scores (eg: Wong-Baker FACES, CHEOPS [Childrens Hospital of Eastern Ontario Pain Score], Visual Analog Scales, etc), as well as total mean doses of rescue medication doses, time to first rescue dose and number of patients requiring rescue medication.

Exclusion Criteria

We excluded studies that compared NSAIDs to any of the following: non-pharmacologic interventions or non-systemic comparators including topical or injected local anesthetic (eg: lidocaine, bupivacaine, Marcaine), the other group was given an NSAID without a placebo arm.

Outcome measures

Primary outcomes

Our primary outcome was pain measured by any methods, including total mean doses of rescue medication doses, number of patients requiring rescue, pain scores (eg: Wong-Baker FACES, Children's Hospital of Eastern Ontario Pain Scale, Visual Analog Scales, etc), as well as time to first rescue dose.

Secondary outcomes

We recorded all reported adverse outcomes such as episodes of vomiting,

bleeding (any range of bleeding was noted, including those requiring return to operating room), infection, death, and complications that can be attributed to NSAID's (other than bleeding) such as renal failure or thromboembolic events.

Data Extraction

Data extraction was performed using a data extraction sheet (using Excel; Microsoft ® Excel ® for Mac 2011, version 14.3.8), and was internally validated with the first 10 studies extracted. Once extracted, data was then transferred to Cochrane Review Manager (RevMan, Version 5.2.3) data analysis software. Data extraction was performed independently by two reviewers (NC, SL). We collected patient demographics, number of patients included and randomized to each arm, type of surgery and surgical techniques, type of anesthetic, type and dose of NSAID, type and dose of comparator analgesics, and rescue medications and doses. We did not extrapolate numerical information from graphical interpretations of pain scores to avoid interpretational inaccuracies.

Measurement of bias

All studies included were assessed for risk of bias using the Cochrane tool for Bias in duplicate. Judgments of the risk of bias were made according to the criteria listed in the Cochrane Handbook for Systematic Reviews[18]. Judgement of the risk of bias due to blinding were made according to the algorithm presented by Akl et al.[19]

Analysis

Planned data and statistical analysis

Study characteristics, namely number of patients in included studies were

analyzed using basic means and standard deviations, median, and range, which were calculated using Microsoft ® Excel ® for Mac 2011 (version 14.3.9). All meta-analyses were performed using Cochrane Review Manager (RevMan, Version 5.2.3) data analysis software. Meta-analysis was conducted on data from concordant comparator groups, i.e. NSAID vs placebo or NSAID vs active analgesic comparator group. We used standardized mean differences to analyze differences between pain scores in order to compare studies that used different pain scoring systems. We converted the reported mean total doses of opioids used in the studies into equivalent intravenous (i.v.) morphine doses and calculated the mean differences. The proportion of patients requiring rescue analgesia were compared between arms using odds ratios or relative risk. We also calculated the odds ratios and relative risk for incidence of vomiting between arms.

All meta-analyses were performed using random effects models. Heterogeneity of studies was assessed using the I^2 statistic. We attempted to explain heterogeneity when the I^2 statistic was greater than 50% by performing sensitivity analyses based on pre-identified subgroups. These included allocated drug class of the comparator (eg: acetaminophen, opioid), dose and route, timing of administration of medications (preoperative, intraoperative or postoperative administration), timing of outcome measurement, type of surgery included, and high risk of bias, which can all theoretically affect the reported outcomes. When relevant, subgroup analyses were conducted, for example by age category (adult or pediatric), concomitant pain medications administered in either allocation group, and subgroup analyses were

considered when heterogeneity remained unexplained or if clinically relevant.

Results

Description of studies

A total of 58 studies met all inclusion criteria (See flow-diagram on Appendix B). The Kappa coefficient for level of agreement between the two reviewers was 0.96 (95% CI 0.88–1.00). The exclusion criteria within the individual studies were similar between studies. Most excluded patients with known allergy to study drug, or a personal or family history of bleeding disorder. A total of 4765 patients were included, ranging from 1 to 68 years of age. The average number of patients in each study was 82.2 (standard deviation [SD] 52.1) subjects, with a median of 73 subjects (range: 60 to 340). There were 35 studies that reported data on trials comparing NSAIDs to a non-NSAID active comparator, and 32 studies included a placebo group. There was variability between studies in the pain measures reported and therefore meta-analysis could only be performed on pain measures that were comparable, including mean total dose of rescue at 24h, mean number of rescue doses for time period, pain scores and time to first rescue. We focused our analysis on the latest time point that was most frequently reported in studies, and due to clinical relevance, the 24 hour mark was chosen as the time point for the outcomes analyzed. Outcomes at later time points were inconsistently described by very few studies, and could not be considered for meta-analysis.

Risk of Bias

Risk of bias is summarized in Figures 1 and 2. Allocation was graded as unclear in fifty-one studies due to insufficient reporting. There were 36 studies that were double blind, nine that were single blind, two that were unblinded and 14 that did not describe blinding. With regards to reporting bias, there are many studies that could not be included in the pain score analyses since 21 studies reported their pain scores in graphs alone and therefore could not be included into the analysis. Three studies, Courtney[20], Nishiike[21] and St-Charles[22] have severe risk of bias for performance, detection and attrition bias, making them the studies with the highest risk of bias amongst all the studies included. As well, eleven studies were found to have high risk of bias for selective reporting.

Primary outcomes

NSAID vs active comparator

Forty-seven studies compared NSAID to an active comparator (eg: acetaminophen, opioids). In 27, the NSAID was administered in the perioperative period and 19 that looked at postoperative analgesia.

Mean total dose of rescue opioid at 24h

Four studies reported the mean total dose of rescue opioid at 24h (Figure 3). However, due to heterogeneity of methods, outcome reporting and study population studies could not be meta-analyzed. All studies compared preoperative or intraoperative doses of NSAIDS with active comparators. Antila et al[23] studied children given ketoprofen (2mg/kg i.v.) to tramadol (1mg/kg i.v.) intraoperatively and

at 6h post-operatively. The rescue opioid used for breakthrough pain was fentanyl. The study showed no statistically significant difference in the mean total dose of equivalent i.v. morphine rescue (mean difference -0.33mg/kg, 95% CI -0.95, 0.29). Hiller et al[24] studied adults administered intraoperative diclofenac (75mg i.v.) to intraoperative propacetamol (2g i.v.) as well as a combination of propacetamol and diclofenac (2g and 75mg i.v. intraoperatively). There was no statistically significant difference in the total mean opioid dose between the paracetamol and diclofenac groups (mean difference -5.80mg, 95%CI -16.17, 4.57). There was also no statistically significant difference between the combined paracetamol/diclofenac group when compared with the paracetamol alone (mean difference -9.50mg, 95%CI -20.59, 1.59) and when compared with diclofenac alone (mean difference -3.70 95%CI -13.71, 6.31). Yegane et al[25] compared rectal diclofenac 1mg/kg to gabapentin 20mg/kg given preoperatively in individuals aged 10 to 25 years of age. Intramuscular meperidine was the rescue opioid, which was reported as an absolute dose, rather than in a per kilogram format. The absolute difference in morphine-equivalent dose of meperidine administered was 0.33mg (85%CI -0.21, 0.87) favoring gabapentin, though the difference was not statistically significant. Finally, the study by Sutherland et al[26] reported findings from a trial comparing intraoperative intramuscular tenoxicam (0.75mg/kg) to intraoperative intramuscular morphine (0.2mg/kg). Morphine was given for rescue (20-50mcg/kg i.v.), as well as acetaminophen. This study found a statistically significant decrease in opioid use in the tenoxicam group (mean difference -0.17mg/kg, 95%CI -0.20, -0.14).

Number of patients requiring rescue doses at 24h

Eleven studies reported the number of patients requiring doses of rescue analgesia (Figure 4). Overall, the odds of requiring rescue analgesia was not significantly different between patients treated with an NSAID and patients treated with another analgesic (OR 0.96, 95%CI 0.62 – 1.47, I^2 35%). Subgroup analysis was performed for the categories of analgesic comparators. Patients treated with and NSAID were 81% less likely to require rescue pain control compares with acetaminophen (OR 0.19 95% CI 0.04, 0.99; I^2 51%). The risk of requiring rescue analgesia was not different between patients treated with an NSAID and patients treated with an opioid (OR 1.21, 95%CI 0.85, 1.72, I^2 0%).

Pain scores at 24h

Ten studies reported sufficient data for inclusion in the analysis of pain scores at 24h. However, four studies could not be included because of the method with which the data was reported: three studies reported as median or mean and ranges[27-29], rather than interquartile ranges or standard deviations, and one study only reported the average of pain scores over 14 days. Therefore six studies were eligible for meta-analysis for pain scores (Figure 5). All studies investigated intraoperative or preoperative administration of study medications. There was no statistically significant in pain scores reported by patients treated with NSAIDs and patients treated with another analgesic at 24 hours (SMD 0.01, 95%CI -0.34, 0.36; I^2 72%). None of the subgroup analyses outlined in the methods explained heterogeneity (Figure 6 and 7)

Time to first rescue dose

Four studies that reported time to first rescue dose (Figure 8). Data could not be meta-analyzed as there was significant statistical and methodological heterogeneity in the time to first rescue outcome. In the study by Sutherland et al[26], an intraoperative intramuscular dose of morphine 0.2mg/kg (n=25) was compared to an intramuscular tenoxicam 0.75mg/kg dose (n=24). There was a benefit for tenoxicam use, with patients in this group receiving rescue medications 171.40 minutes later than in the morphine group (95% CI -356.34, 13.54), though this was not a statistically significant difference. Two studies compared acetaminophen to NSAIDs. A study by Lindgren et al[30] compared aminophenazone (n=40) in the postoperative period during POD 1, to acetaminophen (n=42), whereas Schmidt et al[31] compared preoperative diclofenac (n=40) to acetaminophen (n=40). Both studies showed no difference in time to first rescue dose in either group (mean difference respectively -0.71 95%CI -3.16, 1.76; 9.00 95%CI -1.78, 19.78).

NSAIDs vs placebo

Twenty-seven studies compared an NSAID to a placebo arm. There was sufficient data to analyze outcomes for the mean total dose at 24 hours, number of patients requiring rescue and pain scores. Included studies compared preoperative or intraoperative but not postoperative administration of NSAIDs to placebo.

Mean total dose of opioid rescue

Five studies reported the mean total dose of opioid rescue when comparing NSAID to placebo (Figure 9). Two studies additional could not be included in the

analysis as they did not report the meant total dose outcome for the full 24h they follow patients for other outcomes.[32,33] Antila et al[23] compared intraoperative and 6h postoperative administration of i.v. ketoprophen 2mg/kg/dose in children aged 5 to 15 years old. There was no statistically significant benefit to the administration of ketoprophen over placebo in diminishing the administration of the rescue opioid (intravenous fentanyl; mean difference in mg of morphine equivalent -0.20mg/kg, 95%CI -0.80, 0.40). Joshi et al[34] compared preoperative rofecoxib 1mg/kg orally to placebo in children (3-11 years old). This study administered fentanyl in the recovery unit (not reported), and acetaminophen and codeine elixir on the inpatient units. Codeine doses were only reported in absolute difference rather than in a per kilogram format. This study also did not find any statistically significant difference in opioid intake (mean difference -0.25mg of morphine, 95%CI -0.69, 0.19). Naesh et al[35] also compared rofecoxib 50mg orally with acetaminophen 1.5g po compared with placebo in an adult population. There was no statistically significant difference in rescue opioid (i.v. morphine) between the two groups (mean difference -12.30mg, 95%CI -59.88, 35.28). Oztekin et al[36] evaluated diclofenac given rectally (1mg/kg) and placebo in children 5 to 14 years of age given intra-operatively. The study did find a statistically significant decrease in i.v. morphine given in the diclofenac group (mean difference -0.08, 95%CI -0.12, -0.03). Yegane et al[25] similarly looked at 1mg/kg of rectal diclofenac 1mg/kg compare with placebo in children 8 to 15 years of age given in the preoperative period. Findings showed benefit for diclofenac, but the mean difference was reported as an absolute difference rather than a mg per

kilogram format (mean difference -2.13, 95%CI -2.92, -1.34). Therefore, all studies show a benefit for NSAIDs over placebo, although only the studies by Oztekin and Yegane showed a statistically significant advantage for NSAIDs.

Number of patients requiring at least one dose of rescue drugs

Twelve studies reported the number of patients requiring at least one dose of rescue analgesia. One study was excluded as it reported this outcome as number of patients requiring rescue every 15 minutes for the first 67 minutes, but it was unclear how many patients needed more than one doses, and therefore the total of number of patients requiring rescue could not be determined[37]. The odds of requiring at least one rescue dose in the first 24 hours was 84% less in the group given NSAIDs compared with those given placebo (OR 0.16, 95%CI 0.10, 0.25; I^2 33%); (Figure 10).

Pain scores at 24h

Six studies reported pain scores at 24 hours post-operatively. There was no statistically significant difference in pain scores between patients treated with an NSAID and patients treated with placebo (SMD-0.81, 95%CI -1.75, 0.14; I^2 94%). Exclusion of the study by Roy et al[38] reduced the heterogeneity by half. This study was excluded because they used a three-point scale rating the participants' response to the analgesic given (excellent, good and poor). Furthermore, they only reported the number of patients in each category at different time-points. For the purpose of this analysis, we converted the scale into a numerical scale, where 1=excellent, 2=good, 3=poor, and calculated a mean and standard deviation for

each treatment arm. After exclusion of this study, there was a statistically significant decrease in pain scores in favor of NSAID use (standardized mean difference -0.45, 95%CI -0.84, -0.07); (Figure 11).

Secondary outcomes

There were no reports of severe adverse outcomes such as death or life-threatening conditions such as bleeding requiring major transfusion or severe infections. Re-admission to the hospital for any reason was reported in six studies with variable methodology, and was not analyzed for the purposes of this systematic review

Vomiting at 24h

The risk of vomiting was analyzed for all studies that reported outcomes at 24h post-op. Studies that reported vomiting on post op day 1 were also included. Data was divided by comparator class, namely opioids, non-opioid and placebo. The risk of vomiting was lower in patients treated with an NSAID compared to all the groups listed (OR of vomiting for NSAID vs opioid 0.55 95%CI 0. 42, 0. 74, vs non-opioid 0.54 95%CI 0.35, 0.84, vs placebo 0.54 95%CI 0.33, 0.88). Forest plots for these comparisons are found in Figure 12 (active comparator) and Figure 13 (placebo comparator).

Bleeding

Twenty-six studies with 2149 participants were included in the comparison of bleeding between NSAIDs and an active comparators, and 18 studies with 1266 participants were included in the NSAIDs and placebo comparison. There was no

statistically significant difference in the risk of bleeding when NSAIDs were compared to either an active comparator or placebo (NSAID vs active comparator OR 1.19, 95%CI 0.93, 2.12; NSAID vs placebo 1.07, 95%CI 0.41, 2.77, I^2 0% for both comparisons, see Figures 14 and 15). This result did not change when limited to studies comparing NSAIDs to an active comparator administered during the post-operative only (OR 1.06, 95%CI 0.47, 2.40).

GRADE Summary of Findings Tables

GRADE summary tables are presented in Tables 1 to 4. Since mean total morphine dose is a clinically relevant outcome, based on the assessments made with the GRADE summary of findings methods, more evidence will improve our understanding of the use of NSAIDs post-tonsillectomy with regards to that outcome. The same can be said about pain scores, which is important to note, since pain scores are a direct measurement of pain and in the absence of high levels of evidence for this outcome, further studies are recommended to investigate the question at hand. With regards to the placebo comparator in the pain outcome comparison, there was definitive evidence available, as the quality of studies was found to be high in the mean total dose and number of patients requiring rescue drugs outcomes, and moderate in the pain score outcomes. As well, as noted in previous studies, NSAIDs have been shown to have a protective effect with regards to postoperative nausea and vomiting, and our study confirms that with high quality of evidence to support this statement. With regards to the non-opioid and placebo comparisons, the studies were downgraded to moderate level of evidence due to

indirectness since the optimal information size calculated was significantly over the number of patients available in these comparisons. The bleeding comparisons were on the other hand found to have poor evidence, due to multiple reasons, including sample sizes that was largely underpowered based on the optimal information size, which would need to be at least 3 times as large for the active comparison and nearly 65 times as large in the placebo comparison to increase our confidence in the estimates. Moreover, the bleeding comparisons had certain methodological issues, including inadequate reporting of type of or severity of bleeding in the studies, reporting bleeding at different time points or lack of reporting at which time point the bleeding occurred, and inadequate reporting of how the data was collected. As such, it is difficult to have confidence in the results presented for the bleeding comparison, although there does not seem to be a statistically significant difference in bleeding rates based on included studies.

Discussion

Importance of this research

This is the first systematic review addressing the effect of NSAIDs on pain post-tonsillectomy. It is also the first systematic review that addresses pain in the post-tonsillectomy period in both children and adults. We were able to conclude that there was no significant difference in pain outcomes when comparing NSAIDs and other analgesics, including opioids. However, we were able to confirm that NSAIDs conferred a statistically significant benefit to placebos in treating post-tonsillectomy pain for the first 24 hours after surgery.

To our knowledge, based on an in depth literature search, only one other systematic review exists regarding the topic of post-tonsillectomy pain.[16] This study was published in 2005 by Hamunen and Kontinen, and included 36 studies that compared two different analgesic regimens and focused solely on the pediatric population. The search was updated as of April 2003, and included only studies that used any of the following classes of systemic medications: opioids, NSAIDs, or acetaminophen. No meta-analysis was performed due to heterogeneity of the data collected for the outcomes they reported. All the studies included in this review were retrieved in our systematic search of the literature. The authors in this study stated that they could conclude that NSAIDs were considered at least as effective as opioids based on the evidence they reviewed, but this was not confirmed by specific statistical analysis. Our analyses showed that NSAIDs were no different than opioids in the treatment of tonsillectomy pain, providing the first meta-analysis to support the efficacy of NSAIDs in this setting. However, based on the GRADE recommendations for systematic reviews, we determined that further research will likely improve our understanding of this issue, and by extension, the care we provide our patients.

Nature of post-tonsillectomy pain

Pain post-tonsillectomy is often described as ranging from moderate to intense, and can manifest in a variety of ways such as behavioral changes, to poor oral intake and need for medical attention for analgesia and rehydration.[39] This systematic review revealed a previously unrecognized gap in the literature regarding

the pain characterization over the duration of recovery from tonsillectomy. Since most studies only reported outcomes up to 24h post-operatively, we are unable to draw conclusions as to the benefit of administering NSAIDs post-tonsillectomy. Moreover, different studies measured pain using various measurement tools, which led to a decrease in power for each statistical comparison. As well, in the pain score comparisons, many studies could not be included due to the exclusive reporting of scores in graphical representation.

Concerns with the use of opioids post-tonsillectomy are increasing due to the recognition that opioids cause respiratory depression. Following tonsillectomy, respiratory depression may become more severe due to post-operative pharyngeal swelling. As such, the outcome of mean total dose of rescue opioid used is particularly clinically relevant to physicians. Yet, as our study showed, we were unable to pool data due to high level of statistical and methodological heterogeneity, making meta-analysis impossible for this outcome. Thus, it is important for future studies to address this outcome more consistently and reliably in order to optimize patient care and minimize patient risk of adverse respiratory outcomes.

Adverse outcomes

We demonstrated that the most commonly reported adverse outcomes were vomiting and bleeding. There was a significant benefit for NSAIDs in reducing vomiting as compared with all opioids, placebo and other comparators, including acetaminophen, gabapentin and lidocaine injection. The number needed to treat to

prevent one episode of vomiting is 11 (95%CI 7 – 18.3), meaning that 11 patients would have to be given NSAIDs to prevent 1 episode of vomiting in the first 24h.

Bleeding was not statistically significantly more frequent in the NSAID group compared with opioids and other comparators, as well as placebo. These findings are consistent with previous research, including a recently updated Cochrane review,[12,13] as well as an independent systematic review.[15] Of note, given the rare incidence of bleeding as an adverse event, there is insufficient literature to make a precise enough estimate to rule out the possibility of NSAIDs causing a slight increase in the risk of post-operative bleeding. However, the clinical relevance of this fact should be questioned, since removing NSAIDs from the analgesic regiment post-tonsillectomy would require use of opioids. This can, in turn, increases the likelihood of an adverse respiratory event, the severity of which can be comparable to that of a major bleeding event. This further reinforces the importance of further research to be done to determine the reduction in opioid consumption in patients given NSAIDs for pain control, in order to better understand and quantify this benefit, and make evidence-based recommendations with regards to post-tonsillectomy pain control.

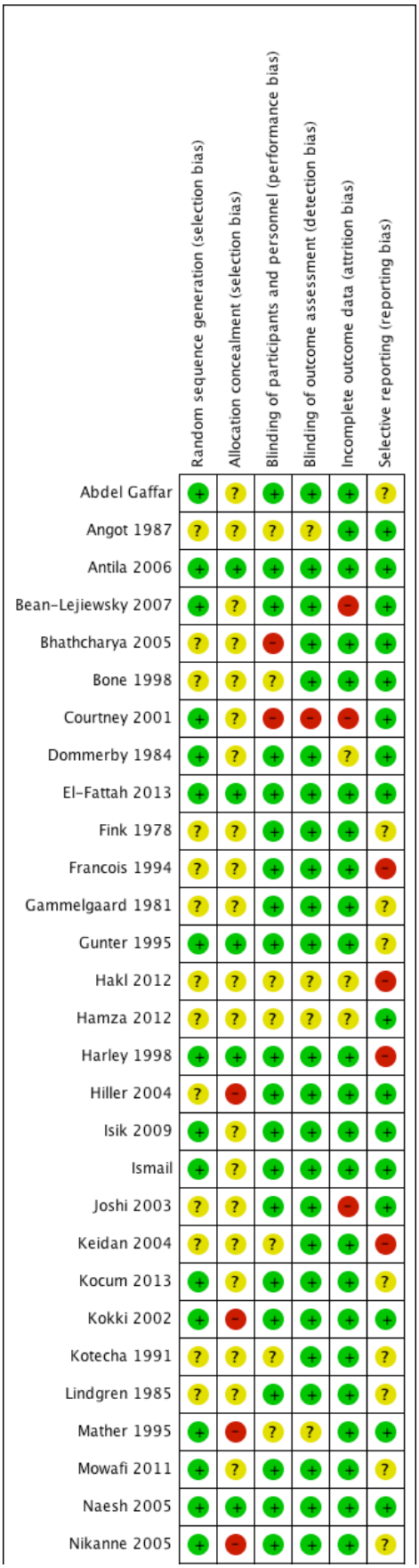
Limitations

This study identified 58 studies that potentially answer the question at hand. However, because of heterogeneity in length of follow up, method of pain assessment and medications given, we were unable to meta-analyze large numbers of studies to be able to increase the confidence in our findings. Moreover, many

studies in the pain score outcome could not be included in analyses because only graphical representation of results was provided.

Conclusion

This study addresses an important and controversial question, and shows that NSAIDs are not statistically significantly better or worse than other medications at controlling pain in the first 24h hours after tonsillectomy, while significantly decreasing the odds of vomiting. Bleeding does not appear to be increased in patients given NSAIDs, though further investigation is necessary to make evidence-based conclusions regarding this issue. Future studies are necessary to determine post-tonsillectomy efficacy with longer follow up periods.



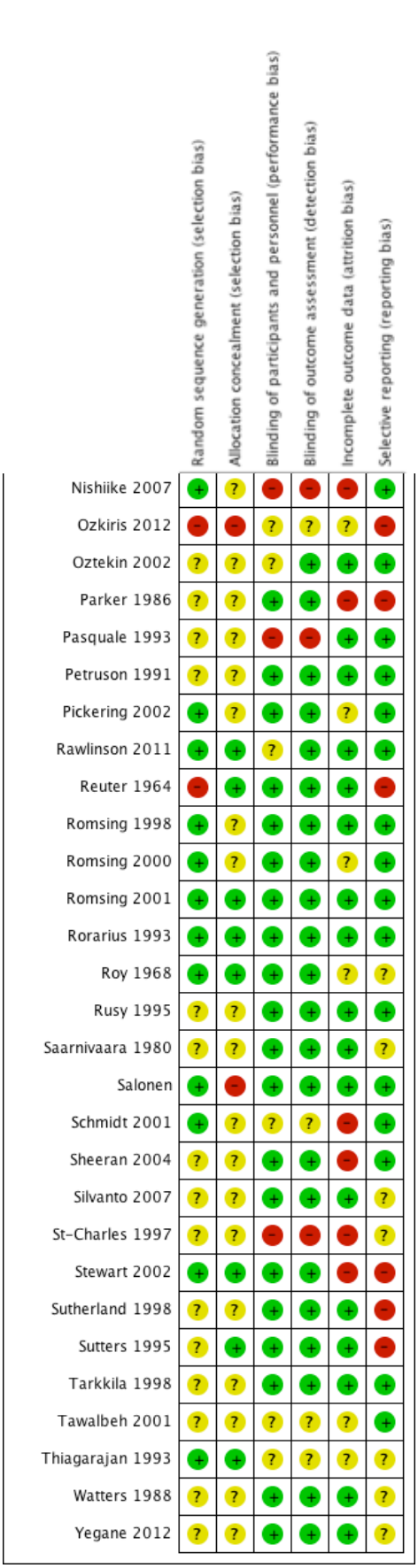


Figure 1: Risk of bias summary table

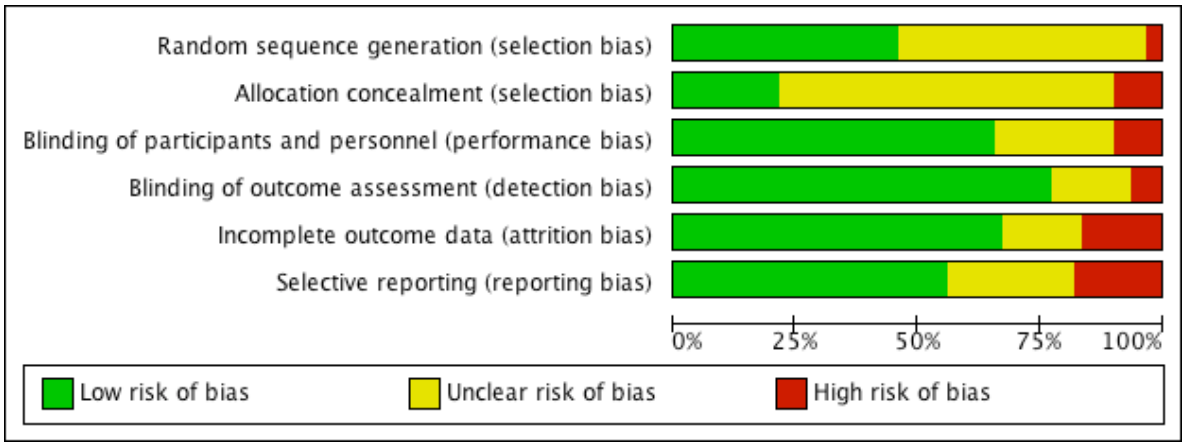


Figure 2: Risk of bias graph

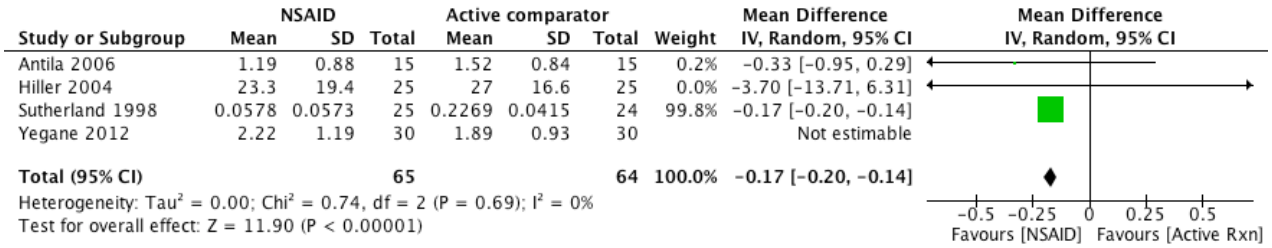


Figure 3: Mean total dose rescue opioid in mg/kg at 24h (Active)

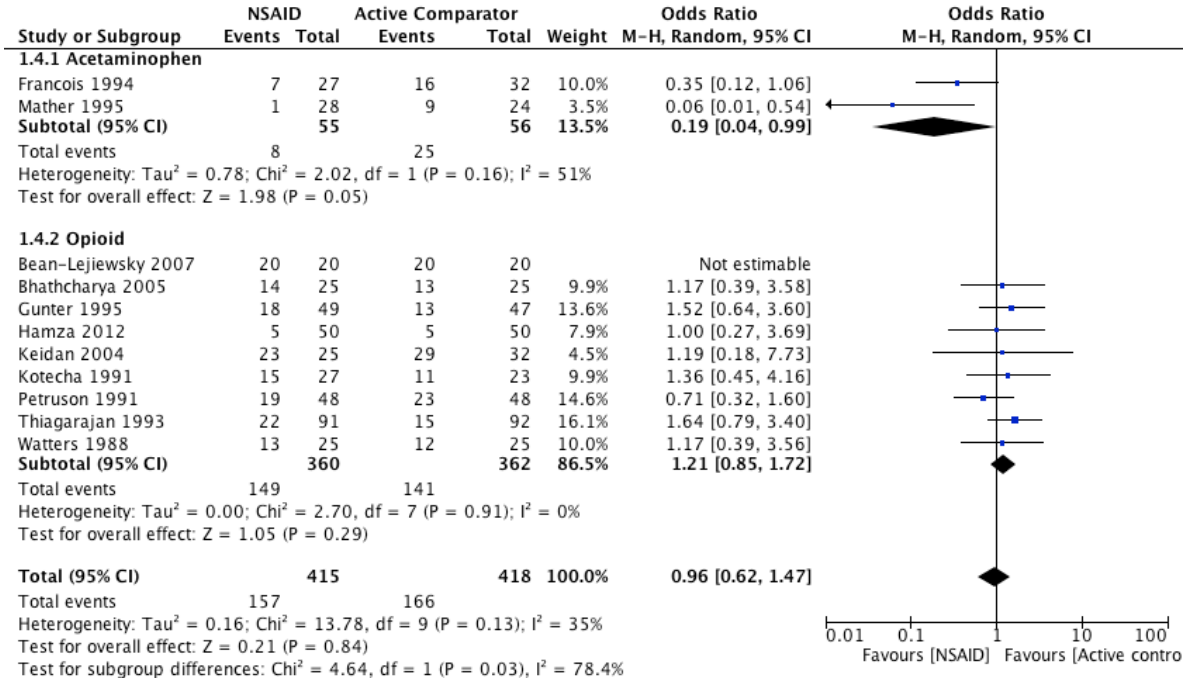


Figure 4: Number of patients requiring at least one rescue opioid dose (Active comparator)

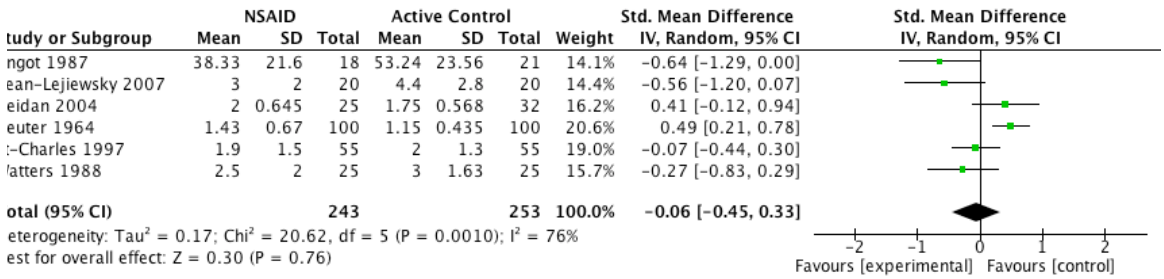


Figure 5: Pain scores at 24h (Active)

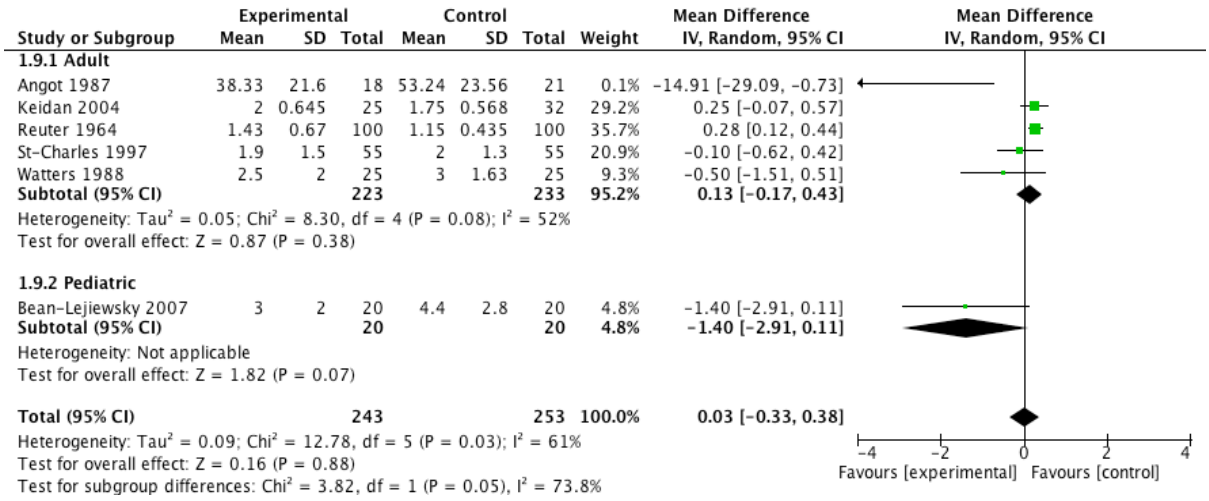


Figure 6: Pain score subgroup analysis by age

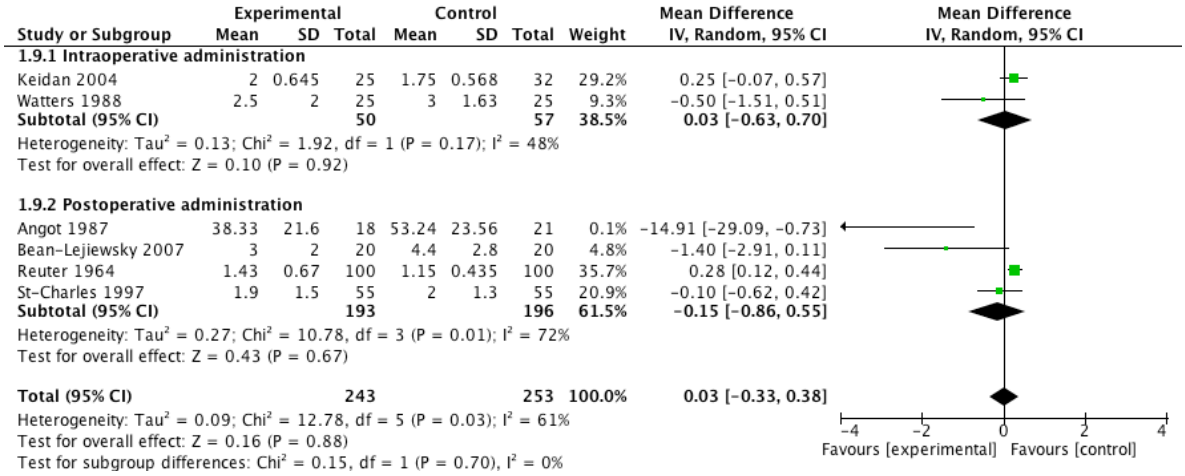


Figure 7: Pain score subgroup analysis by time of administration of analgesic

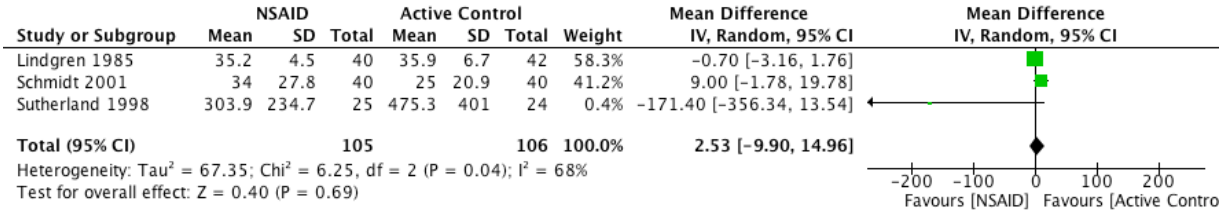


Figure 8: Time to first rescue (Active)

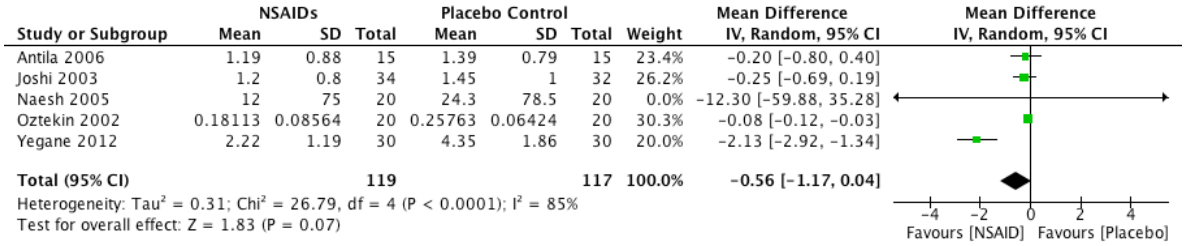


Figure 9: Mean total dose at 24h (Placebo)

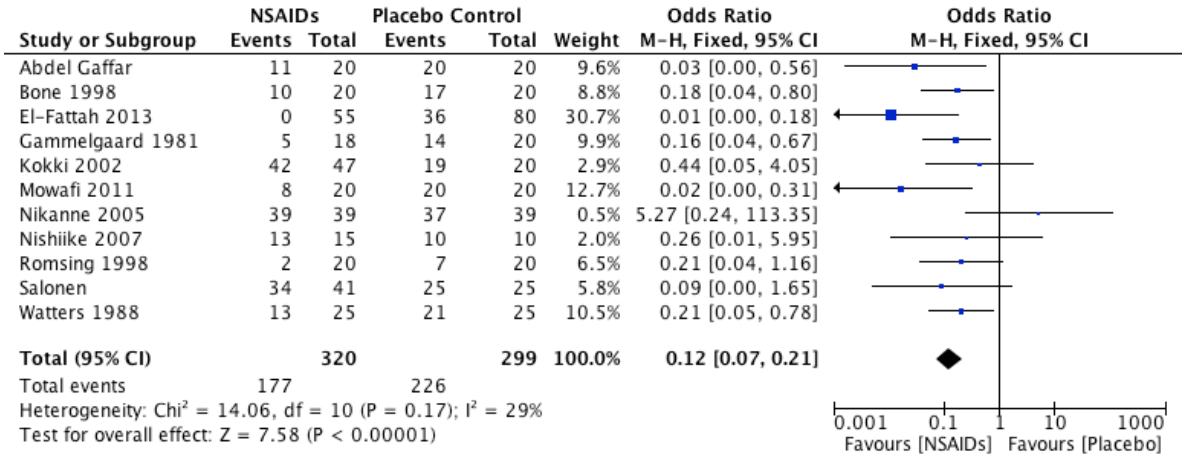


Figure 10: Number of patients requiring at least one rescue dose (Placebo)

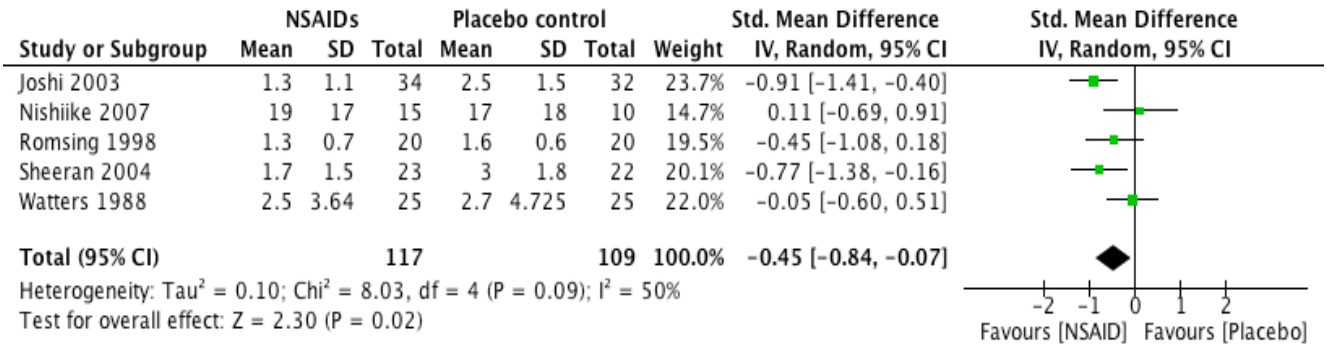


Figure 11: Pain scores at 24h (Placebo)

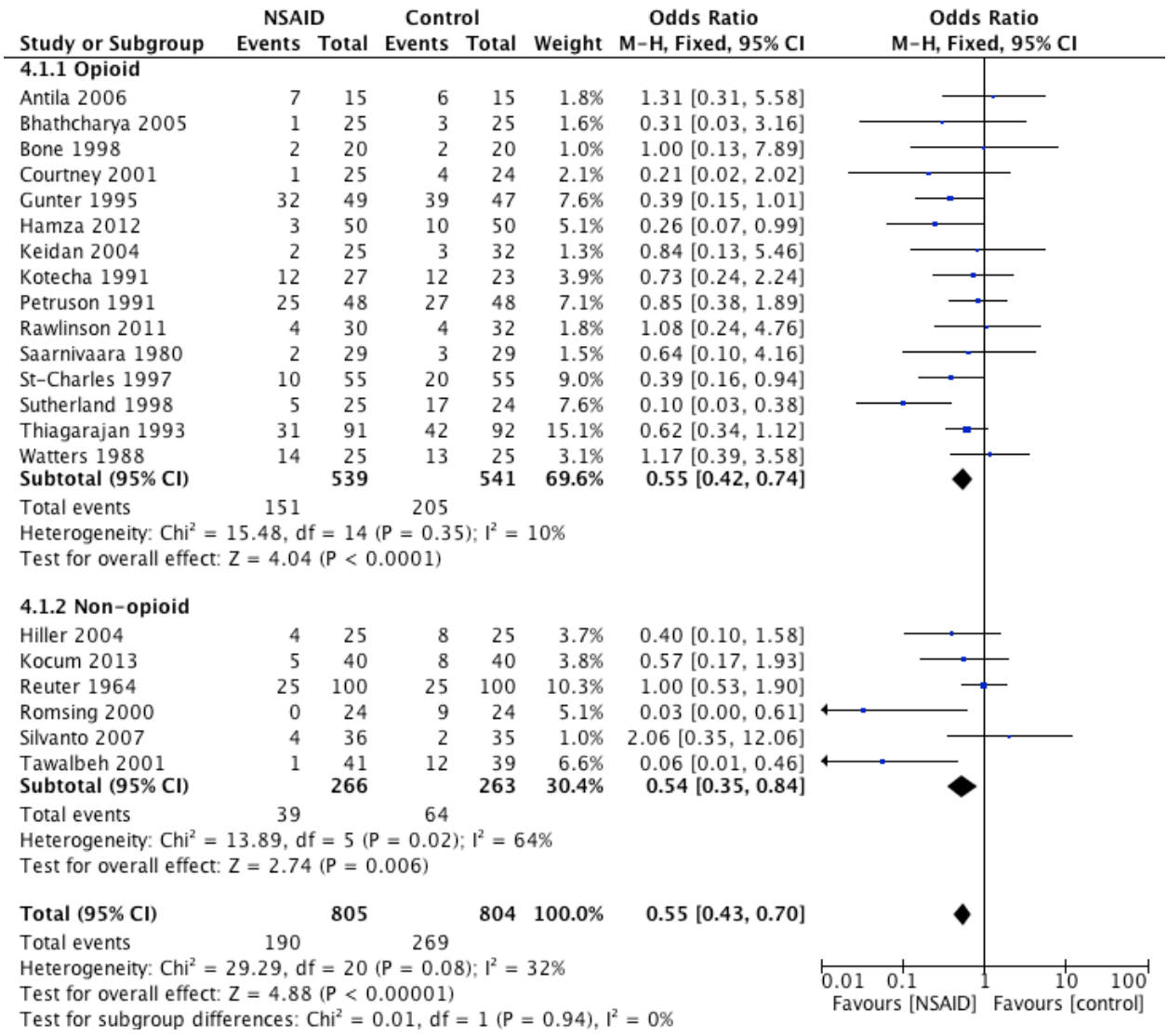


Figure 12: Vomiting (NSAID vs Active comparator)

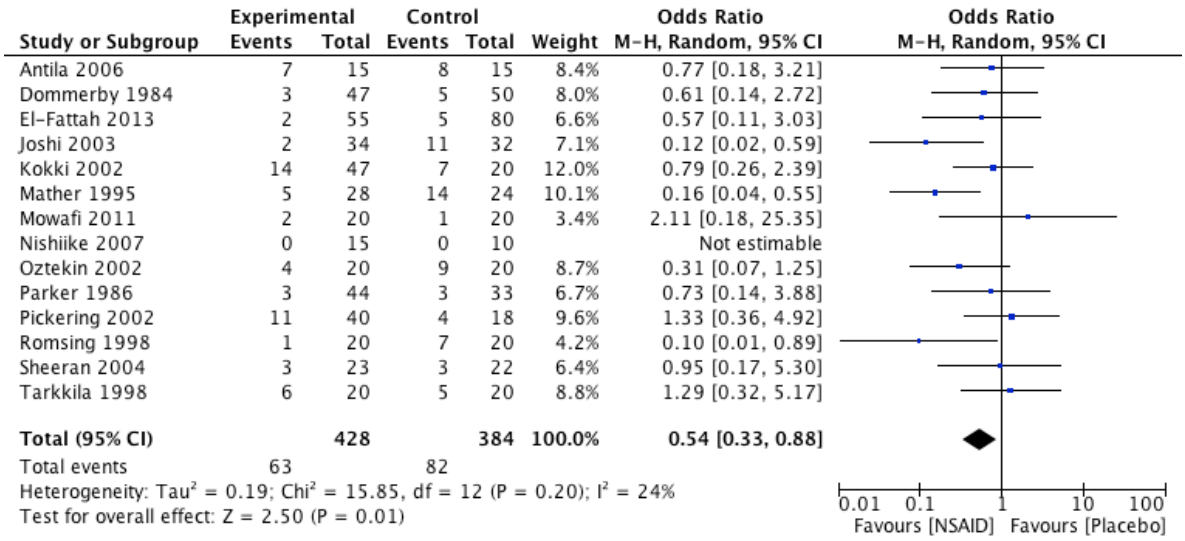


Figure 13: Vomiting (NSAID vs Placebo)

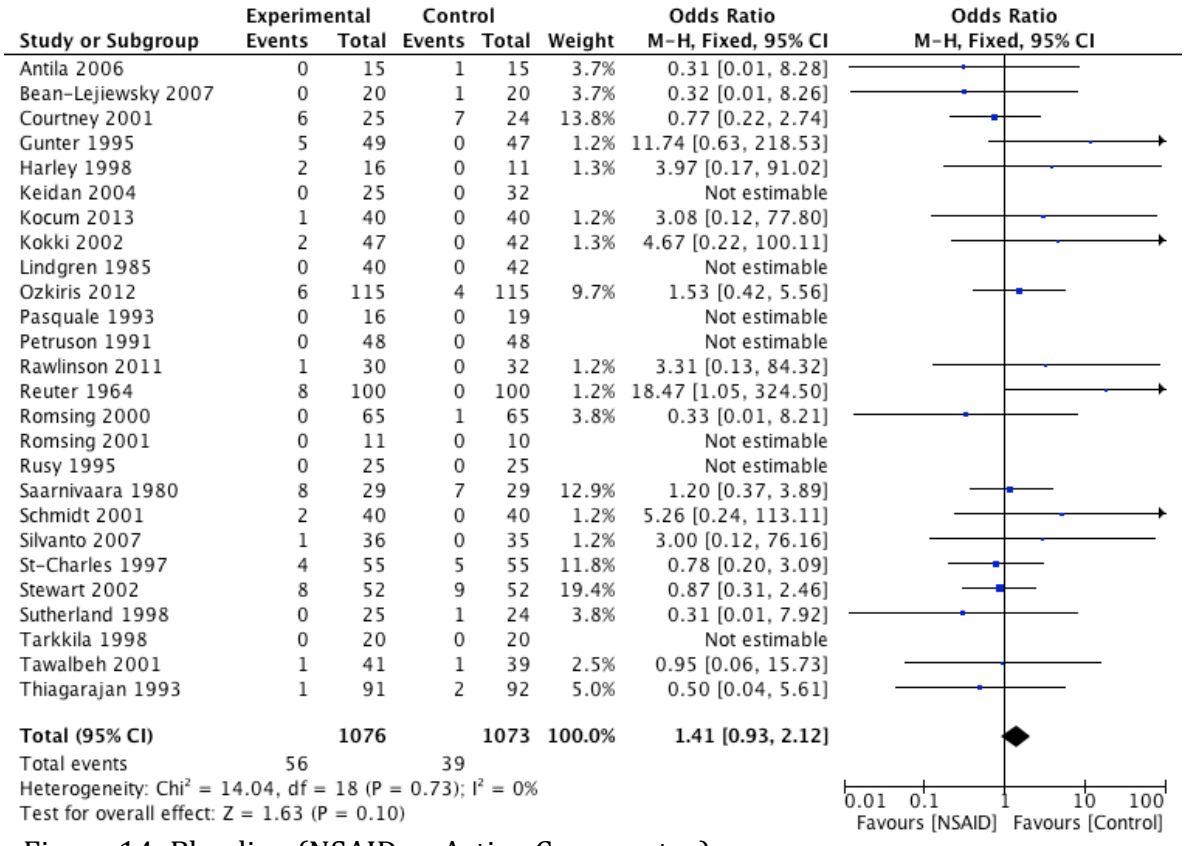


Figure 14: Bleeding (NSAID vs Active Comparator)

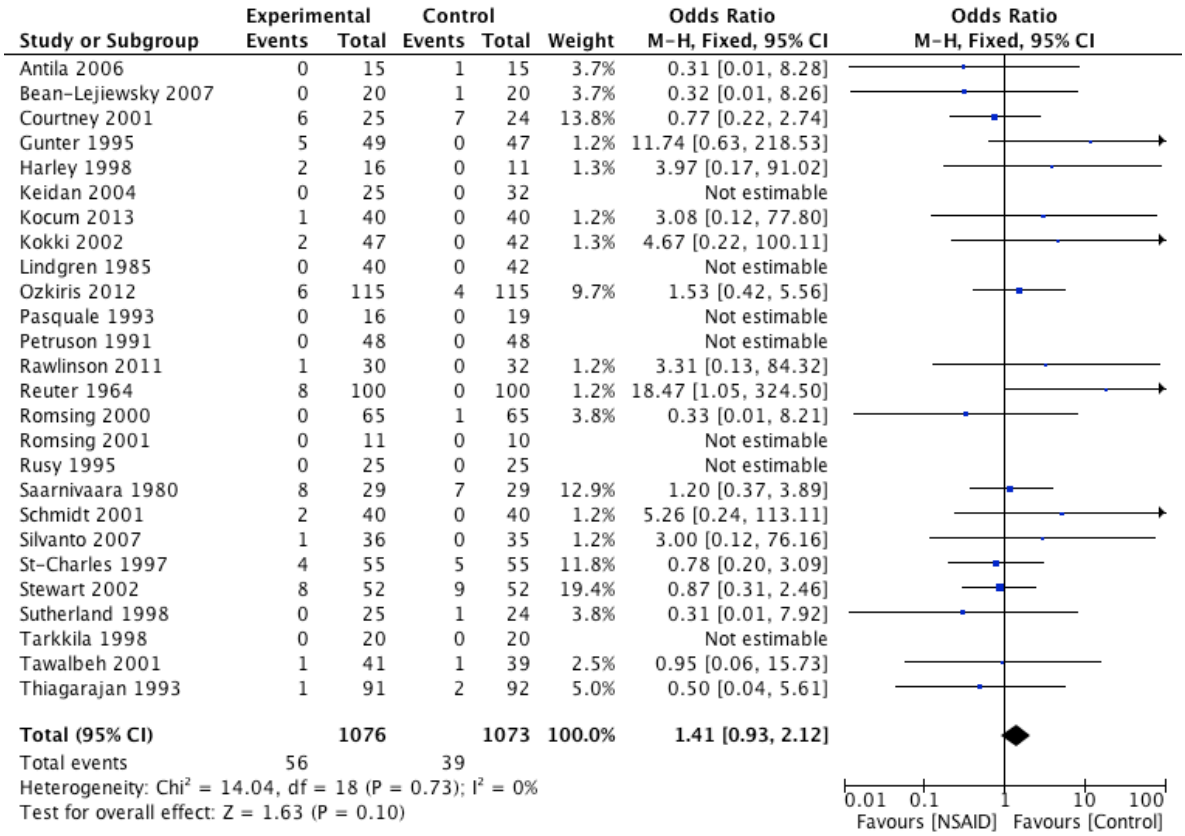


Figure 15: Bleeding (NSAID vs placebo)

Table 1: Summary of Findings table for pain outcomes (NSAID vs Active comparator)

NSAIDs compared to Active comparator for post-tonsillectomy pain						
Patient or population: post-tonsillectomy pain **Settings:** **Intervention:** NSAIDs **Comparison:** Active comparator						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Active comparator	**NSAIDs**				
Mean total dose 24h	64	The mean undefined in the intervention group was MD 0.08 lower (0.22 lower to 0.07 higher)	-	129 (4 Studies)	⊕⊕⊕⊖ MODERATE	
# pts req rescue 24h	Study population		OR 1.00 (0.67 to 1.47)	893 (11 Studies)	⊕⊕⊕⊕ HIGH	
	157/418 (37.8)%	397 per 1000 (306 to 492)				
# pts req rescue 24h - Acetaminophen	Study population		OR 0.19 (0.04 to 0.99)	111 (2 Studies)	⊕⊕⊕⊕ HIGH	
	25/56 (44.6)%	133 per 1000 (31 to 444)				
# pts req rescue 24h - Opioid	Study population		OR 1.21 (0.85 to 1.72)	722 (9 Studies)	⊕⊕⊕⊕ HIGH	
	141/362 (39.0)%	436 per 1000 (352 to 523)				
Pain score	273	The mean	-	536	⊕⊕⊕⊖	

24h		undefined in the intervention group was SMD 0.01 higher (0.34 lower to 0.36 higher)		(7 Studies)	MODERATE	
Time to first rescue	126	The mean undefined in the intervention group was MD 5.84 higher (9.51 lower to 21.18 higher)	-	251 (4 Studies)	⊕⊖⊖⊖ VERY LOW	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1]No explanation was provided

[2]all NSAIDs were either different medications, or in the case of diclofenac, the route was different across studies

[3]all comparators were different across studies, including different classes of medications

[4]Hiller et Al studied adults, but all other were pediatric

[5]small sample size - only 219 for all pooled studies (less than 400)

[6]Sample size is below OIS for all studies given SD's

[7]CI do not overlap for several studies

[8]certain studies show clear benefit and others clear inferiority of NSAIDs

[9]indirectness due to mixed NSAIDs and active comparators in the comparison

[10]Kedek: high risk of reporting bias, unclear for other categories

[11]Lindgren: unclear for selection and reporting bias

[12]Schmidt: high risk for attrition bias, unclear for selection, detection and performance bias

[13]Sutherland: high risk of selective reporting, unclear for selection bias

[14]outcome may be subjective based on the assessors of the pain

[15]different NSAIDs used in each study

[16]age of population not reported for Lindgren

[17]fewer than 200 patients in each arm across studies

Table 2: Summary of Findings table for pain outcomes (NSAID vs Placebo)

NSAIDs compared to placebo for post-tonsillectomy pain						
Patient or population: post-tonsillectomy pain **Settings:** **Intervention:** NSAIDs **Comparison:** placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	placebo	**NSAIDs**				
Mean total dose rescue at 24h	117	The mean undefined in the intervention group was MD 0.56 lower (1.17 lower to 0.04 higher)	-	236 (5 Studies)	⊕⊕⊕⊕ HIGH	
Number of patients requiring at least one rescue dose	Study population		OR 0.16 (0.10 to 0.25)	699 (12 Studies)	⊕⊕⊕⊕ HIGH	
	253/339 (74.6)%	320 per 1000 (227 to 424)				
Pain scores at 24h	109	The mean undefined in the intervention group was SMD 0.45 lower (0.84 lower to 0.07 lower)	-	226 (5 Studies)	⊕⊕⊕⊖ MODERATE	
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and						

the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval;
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.

Footnotes

[1]No explanation was provided

[2]sample size less than 400 across all pooled studies

[3]sample size smaller than most rigorous OIS based on mean difference morphine 0.2mg/kg IV

[4]sample size greater than OIS (=83 per arm)

[5]sample size smaller than most rigorous OIS based on SMD 0.4 and SD 4.217 [40] = 1380 per arm

Table 3: Summary of Findings table for Vomiting

NSAIDS compared to comparators for post-tonsillectomy vomiting						
Patient or population: post-tonsillectomy vomiting **Settings:** **Intervention:** NSAIDS **Comparison:** comparators						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	comparators	**NSAIDS**				
Vomitting 24h -	Study population		OR 0.56	1689 (23	⊕⊕⊕⊕ HIGH	
	269/844	208 per 1000				

Active comparator	(31.9)%	(171 to 252)	(0.44 to 0.72)	Studies)		
Vomitting 24h - Opioid	Study population		OR 0.55 (0.42 to 0.74)	1080 (15 Studies)	⊕⊕⊕⊕ HIGH	
	205/541 (37.9)%	251 per 1000 (204 to 311)				
Vomitting 24h - Non-opioid	Study population		OR 0.59 (0.38 to 0.90)	609 (8 Studies)	⊕⊕⊕⊖ MODERATE	
	64/303 (21.1)%	136 per 1000 (92 to 194)				
Vomitting 24 placebo	Study population		OR 0.54 (0.33 to 0.88)	812 (14 Studies)	⊕⊕⊕⊖ MODERATE	
	82/384 (21.4)%	128 per 1000 (82 to 193)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1]No explanation was provided

[2]sample size does not meet OIS of 527 per group

[3]sample size does not meet OIS of 374 per group

Table 4: Summary of Findings table for bleeding

NSAIDs compared to comparators for post-tonsillectomy pain re: bleeding						
Patient or population: post-tonsillectomy pain re: bleeding **Settings:** **Intervention:** NSAIDs **Comparison:** comparators						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk comparators	**Corresponding risk NSAIDs**				
Bleeding - Comparator	Study population 39/1093 (3.6)%	50 per 1000 (33 to 73)	OR 1.41 (0.93 to 2.12)	2189 (25 Studies)	⊕⊖⊖⊖ VERY LOW	
Bleeding - Placebo	Study population 6/590 (1.0)%	9 per 1000 (3 to 31)	OR 0.88 (0.25 to 3.07)	1266 (18 Studies)	⊕⊖⊖⊖ VERY LOW	
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval;						
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.						

Footnotes

[1]No explanation was provided

[2]studies did not all report the severity of bleeding

[3]mixed adult and pediatric studies

[4]Did not meet the OIS of 2743 subjects per arm

[5]inconsistent reporting of this outcome across studies

[6]no study assessed bleeding using scoring system

[7]Did not meet the OIS of 64189 subjects per arm

Appendix A

EMBASE:

11	**limit 10 to (english or french)**	**644**
10	7 and 8 and 9	807
9	2 or 3 or 4 or 5	432019
8	1 or 6	37346
7	exp analgesic agent/	652373
6	tonsil*.mp.	36445
5	diclofenac.mp.	29532
4	ketorolac.mp.	7726
3	ibuprofen.mp.	37041
2	NSAID.mp. or exp nonsteroid antiinflammatory agent/	430604
1	exp palatine tonsillectomy/ or exp adenotonsillectomy/ or exp tonsillectomy/	

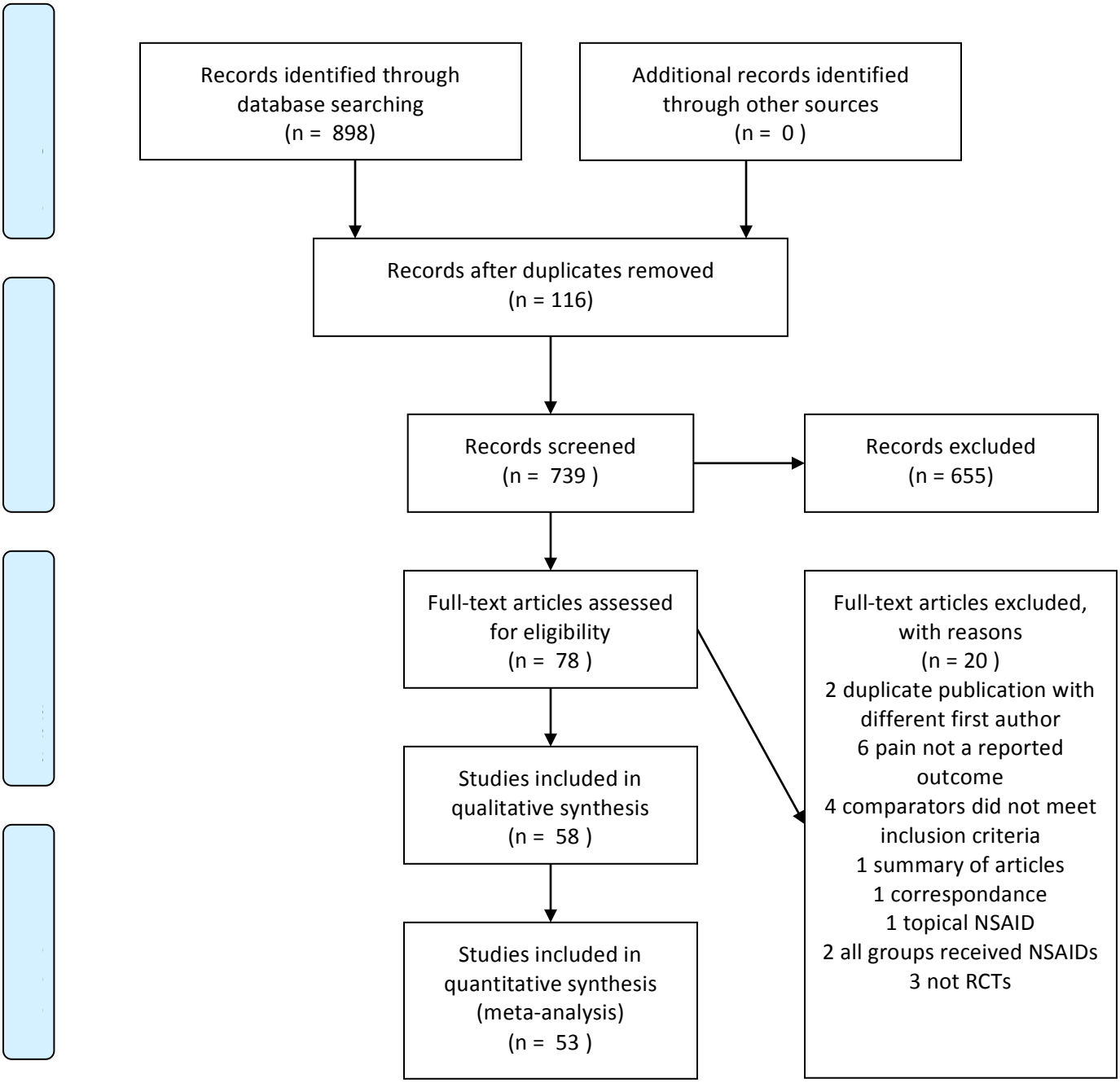
Medline

16	**limit 15 to (english or french)**	**211**
15	2 and 13 and 14	284
14	6 or 7	29435
13	1 or 5 or 8 or 9 or 10 or 11 or 12	170513
12	ketorolac.mp.	2285

11	diclofenac.mp.	9032
10	ibuprofen.mp.	10472
9	exp phenylpropionates/ or ibuprofen/	11441
8	exp Anti-Inflammatory Agents, Non-Steroidal/	159966
7	exp Tonsillectomy/	7490
6	tonsil*.mp.	29435
5	nsaid*.mp.	18391
4	1 and 2 and 3	173
3	Tonsillectomy/	7490
2	exp Analgesics/	441282
1	exp Anti-Inflammatory Agents, Non-Steroidal/	159966

Appendix B

PRISMA 2009 Flow Diagram



Appendix C - PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional	6

		studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	30
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	31-4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	35-40
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	31-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	17-8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-15
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-25
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	25
Conclusions	26	Provide a general interpretation of the results in the context of other	26

		evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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Chapter 4

TreatIng Pain post-TOnsillectomy (TIPTO): a single center, parallel-group, fully blinded randomized controlled trial of ibuprofen and acetaminophen vs acetaminophen alone in children aged 1-15 years of age

Abstract

Background: Tonsillectomy is a surgical procedure that has been performed for thousands of years, and it is one of the most commonly performed surgeries in North America, with 530 000 tonsillectomies being performed yearly in the US alone. Recently, there has been an increased interest in discerning the intricacies of pain control in the perioperative period for tonsillectomies. Though there is no single standard of care for post-operative analgesia, most children receive a regimen of an over-the-counter analgesic in combination with an opioid (eg: acetaminophen, ibuprofen, codeine, morphine, etc). With recent concern with the safety profiles of opioids post-tonsillectomy, it becomes relevant to investigate the effectiveness of treating pain with other alternatives.

Objectives:

Phase 1: The objective of the first phase is to assess the feasibility of conducting a large scaled trial. The primary objectives are to address procedural factors such as recruitment rate and attrition, whereas secondary objectives include the assessment of the mean and variance of the primary outcome of phase 2, as well as addressing other feasibility issues such as missing data, financial considerations and qualitative stakeholder feedback on study procedure.

Phase 2: The primary objective of this study is to assess the efficacy of adding NSAIDs to a post-tonsillectomy analgesia regimen in reducing the need for opioids. The secondary objective is to assess whether pain is better controlled by the addition of NSAIDs, while minimizing side effects of opioids. We are also addressing possible adverse events following tonsillectomy, including admission to hospital and other forms of medical attention including physician and emergency room visits, as well as bleeding and vomiting rates.

Methods and design: We are proposing a two-phase single-center parallel fully blinded placebo-controlled superiority randomized trial of ibuprofen and acetaminophen versus acetaminophen alone. Phase one will consist of an internal pilot aiming to assess feasibility outcomes, and phase two compare the efficacy between the two treatment regimens. All patients will receive morphine for breakthrough pain. We will be recruiting children aged 1 to 15 years of age.

Outcomes: The primary outcome will be the difference in total in opioid (morphine) requirement for the ibuprofen and acetaminophen group compared with the acetaminophen only group for 2 weeks postoperatively. Secondary outcomes will be pain scores, time to first oral intake, and safety/adverse event outcomes such as bleeding, vomiting, return to the ER or re-admission to the hospital post-operatively. *Analysis*: For the first phase, simple proportions will be calculated to gauge feasibility and compared to predetermined goals. Qualitative data will be coded and analyzed for themes and used to optimize study procedure. For the second phase, primary analysis will be by done using an intention-to-treat approach. The primary outcome will be analyzed using a one-sided t-test. Sensitivity analyses will be undertaken to assess per-protocol effect. Analysis of covariates will be undertaken to determine factors that affect the success of pain management.

Discussion: This protocol tests the important and controversial question of whether NSAIDs such as ibuprofen are beneficial in treating post-tonsillectomy pain and reduce opioid requirements in the pediatric population.

Trial registration: We plan to register the trial in clinicaltrials.gov.

Background

Tonsillectomy is one of the most commonly performed surgeries in North America, particularly in children, with over 530 000 surgeries taking place in the US alone.[1] According to the AAO HNS, *tonsillectomy* is defined as a procedure that:

"completely removes the tonsil, by dissecting the capsule off the muscular wall. This procedure is commonly performed in association with adenoidectomy."

This procedure is performed using a variety of techniques, including electrocautery, coblation, cold dissection (eg: snare), laser, harmonic scalpel and thermal welding. The ultimate goal of tonsillectomy is the removal of the tonsillar tissue, which is also known as the palatine tonsil. With careful patient selection, it is a safe and effective procedure. Though many techniques for performing tonsillectomy exist, the ultimate goal is excising the lymphoid tissue residing in the oropharynx, alleviating symptoms of airway obstruction, as well as minimizing the frequency of strep throat infections.

Pain control can be achieved using different combinations of analgesics, and codeine has previously been a commonly prescribed drug. However, the last decade has seen several deaths in children as a result of codeine being used in the post-operative period.[2] Subsequent investigations have identified a mutation of the cytochrome P450 2D6 also known as the CYP2D6 enzyme predisposing children to such adverse events. Codeine is converted to morphine in the liver by CYP2D6, but in this subset of the population, known as ultra-rapid metabolizers, codeine is converted to morphine at a dangerously rapid rate, resulting in opioid overdose, respiratory depression and failure, and, in several cases, death.[3] As a result, surgeons are now searching for safe yet effective options for pain control.

Tonsillectomy can result in severe pain, which often results in repeated returns to the emergency room, or family practitioner's and surgeon's offices, as well as re-admissions to the hospital for management of pain and or dehydration, all of which are potentially preventable costs to the healthcare system. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as Ibuprofen, Naproxen, Ketorolac, Ketoprofen and others have long been used for non-surgical pain relief,[4-6] but surgeons have been reticent to include them in their post-operative care regimens because of a theoretical increased bleeding risk. There now exists a substantial body of literature demonstrating that NSAIDs have a role to play in post-operative pain management in a variety of surgical fields, including orthopedics,[7,8] neurosurgery,[9] ophthalmology,[10] oral surgery,[11,12] urology[13,14] and otolaryngology.[15] As well, several reviews, including several systematic reviews[15-17] addressing the risk of bleeding post-tonsillectomy with NSAIDs have demonstrated that there is no increase in bleeding risk in patients having been given NSAIDs post-tonsillectomy, but that larger studies are still needed to improve the confidence in these results. The question remains whether NSAIDs can be efficiently added to pain control regimens to minimize adverse events and health care costs associated with opioid use, premature follow up visits for pain management and admissions for dehydration, without increasing life-threatening events such as post-tonsillectomy bleeding.

Based on the systematic review presented in Chapter 3, there are currently no studies that compare ibuprofen and acetaminophen (treatment, T) to acetaminophen alone (control, C) for the treatment of post-tonsillectomy pain. This protocol outlines our proposed methods to test a pragmatic regimen of over-the-counter medications for the treatment of post-tonsillectomy pain in order to decrease the amount of opioids given to children for that purpose.

2.0 Methods and design

We plan to register the trial to clinicaltrials.gov.

Funding

We plan to seek funding to allow the conduct of this trial as described in this protocol. We plan to apply for funding through local and national awards including the McMaster Surgical Associates, the Hamilton Health Sciences New Investigator Fund, CIHR, and others.

Phase 1: Internal pilot study

Rationale

This study is the first of its kind to compare a pragmatic pain treatment algorithm including over the counter pain medications for the treatment of post-tonsillectomy pain. The protocol includes following patient outcomes two weeks post-tonsillectomy, which covers the complete duration of significant post-operative pain in the vast majority of patients, as widely believed by otolaryngologists. However, pain patterns post tonsillectomy have not been well studied and documented in the literature. This leaves many factors that need to be addressed to ensure that our study is appropriately powered and that the procedure of this trial is sound to obtain valid results. We will begin this study with an internal pilot phase using the same standardized procedure as the full-fledged randomized controlled trial described below. The rationale for performing a pilot study is to assess feasibility of the study and assess any methodological issues and optimize these prior to beginning the larger study. As described by Thabane et Al,[18] there are four reasons to conduct a pilot study, namely to evaluate aspects of the process, resources, management, and scientific factors. We are interested in investigating factors

relating to each of these areas such that we can optimize them prior to the onset of the study.

Primary outcomes

Specific outcomes for the pilot are found in Table 1. Notably, our primary outcome for phase 1 is the recruitment rate, which we are aiming at 70% as our target for success. We are also looking to assess the completeness of follow up to ensure reliability of results pertaining to the primary outcome in our large scale trial (i.e. total morphine intake over 2 weeks). As such, we will consider loss to follow up, and recruitment rate as the primary outcomes for the pilot study.

Secondary outcomes

The secondary outcomes we are interested in assessing include determining the financial feasibility of conducting this study, as well as obtaining an estimate of the treatment effect and variance, which are currently unknown for our primary outcome. Therefore an estimate for the mean difference and the variance is necessary to better estimate a sample size necessary to obtain reliable results for our study. Completeness of data collection will also be assessed in the pilot study to optimize internal validity and consistency for secondary outcomes for the larger scale study. Finally, we will obtain feedback from participants on the usability of the case report forms.

Analysis

All analysis will be performed using Stata/SE version 12.1 (StataCorp, TX, 2013). Analysis for the pilot outcomes will be performed at the completion of recruitment of 100 patients. The primary outcomes, recruitment and attrition, will be analyzed using simple proportions. Measures of success for feasibility are listed in Table 2, and are 70% for recruitment and 10% for attrition. As part of secondary analyses, missing data for the

primary outcome will be analyzed as a percentage of all values missing, with the aim of having less than 5% of outcomes being missing. The reason for this is due to online methods of data entry and phone calls possible for confirming doses, which we believe will minimize missing data. As well, we will calculate an exact per-patient cost estimate based on participants in the pilot study to allow an accurate financial calculation for the complete study. Finally, we will conduct qualitative analysis on interviews held to receive feedback regarding study procedure from participants. Interviews will be coded and analyzed for themes.

Phase 2: Randomized controlled trial

Study design and recruitment

The study will be a single site randomized controlled trial.

Randomization and stratification

A randomization list will be generated by a project statistician, and provided to the pharmacy at the McMaster University Medical Center. The randomization list will be stratified by age (age 1 to 3, and 3 to 15) in 5:1 ratio. Physicians practicing at McMaster University Medical Center will be approached to allow enrollment of their patients into the trial. Once approved by the local ethics board (Hamilton Integrated Research Ethics Board), patients will be approached to enroll into the study during their preoperative clinic visit, which is typically a few days prior to the day of surgery. Informed consent will be provided by parents of eligible patients, with assent given by all children participants capable of doing so. Patients will be assigned to a treatment arm on the day of surgery, upon their arrival for the procedure by a project pharmacist who will use the randomization table to allocate the participant. An allocation code will be provided to the participant's caregiver, as well as two packages containing an intraoperative study drug

to be given to the anesthesiologist and a postoperative package containing the medications provided. An anesthesiologist who will remain blinded to patient allocation will administer the intraoperative medication.

Objectives

Primary objective

The primary objective of this study is to determine whether post-tonsillectomy pain is better managed with the addition of NSAIDs to a multimodal analgesic regimen. As such, we will measure the difference in total rescue opioid intake between the treatment and control groups. This information will be recorded at the time of every dose given. Participants will be given a 0.1mg/kg dose of oral morphine to administer in case of breakthrough pain, and will be required to administer a pre-specified quantity of a 1mg/ml concentration of liquid morphine. We hypothesize that the addition of NSAIDs (intraoperative ketorolac and postoperative ibuprofen) in the treatment group will decrease the amount of morphine required compared to standard therapy (control) as their pain will be less than that of children not receiving NSAIDs. This is considered the primary outcome because of the importance of minimizing opiate related adverse events post-tonsillectomy including sedation, itchiness, constipation, headache and confusion.

Secondary objectives

Tonsillectomy can cause several complications including intractable pain and subsequent dehydration. It can also cause bleeding, ranging from subclinical, which is self-limited and not requiring medical attention, to significant and potentially life-threatening hemorrhage requiring operative management. Intermediate bleeding can be self-limited but requiring medical attention, or may persist and require bedside

interventions and even surgery. As such, our secondary outcomes focus on measuring the difference in the occurrence of adverse events post-tonsillectomy.

We will require participants to measure pain using age-appropriate pain scales. As well, surrogate measures of pain such as paucity of oral intake, especially fluids, will be considered treatable pain. If oral intake is severely decreased with decrease of urine output (eg: less than two episodes of voiding in 24h), or if pain is too severe to be controlled with the available medications, participants will be instructed to go an emergency room, preferentially to the McMaster Children's Hospital (location of the surgery), for medical attention. We hypothesize that pain and dehydration will be decreased in the treatment arm compared with the control arm.

If patients have onset of any bleeding they are instructed to call an ambulance and go to their nearest emergency room for assessment and management. Patients will record any amount of bleeding and the course of action taken. We will also ask participants to record episodes of vomiting. We hypothesize that these outcomes will be equal between groups.

We also will be looking to better describe the typical course of pain and analgesic requirements post-tonsillectomy and therefore will address the total amount of analgesics given to participants daily, including acetaminophen and ibuprofen, as well as breakthrough morphine. We expect that patients will have similar requirements non-opioid analgesics, but that the daily morphine requirement will be reduced in patients in the treatment group. We anticipate that patients in the treatment arm will also require morphine for fewer total days because they have an additional analgesic option prior to resorting to using morphine, which will allow them to have mild to moderate pain treated effectively without resorting to opioids.

We plan to evaluate economic impact of the intervention on various stakeholders. As such, we will be incorporating data recording measures regarding economic outcomes into our study plan. Namely, we will be looking at the costs of medications from the standpoint of patients, since acetaminophen and ibuprofen are over the counter medications, as well as for productivity lost for parents who need to take days off work to care for their children. We will also be monitoring the effects on health care system, as there may be a proportion of patients who will require medical attention in one form or another and this will be factored into our analysis. We will investigate the differences in those costs between the two groups, to see if there is an economical benefit to our treatment intervention. We anticipate there will be a decrease in the overall healthcare cost in the treatment arm.

Setting and participants

Subjects will be patients having been assessed and requiring a tonsillectomy for any cause by a participating otolaryngologist at the McMaster University Medical Center in Hamilton, Ontario. Eligible patients are children aged 1 to 15 years of age scheduled to undergo tonsillectomy alone or in combination with adenoidectomy, bilateral myringotomy and tubes, bronchoscopy and/or inferior turbinate cautery. Any patients undergoing procedures other than those listed above alongside their tonsillectomy will be excluded. Other exclusion criteria include any of the following: NSAID-triggered asthma, ongoing renal or hepatic dysfunction, allergy and adverse reaction to any of the study drugs, patients with developmental delay, known or family history of bleeding diathesis or a history of nasal polyposis. As well, participants whose parents are illiterate will be excluded. Participants without access to a computer will be given a paper form collecting the same information.

Participants will be compensated for their parking expenses for the day of surgery and the follow up visit two weeks after surgery.

Intervention

Our centre recently stopped using acetaminophen and codeine because of the discovery of aberrant metabolism of codeine in certain children that can lead to respiratory depression and death. The intervention being evaluated is the addition of an NSAID regimen to the current standard therapy. Specifically, ketorolac 0.5mg/kg intravenously after induction, and ibuprofen 10mg/kg orally given every 6 hours as required for treatment of post-operative pain. In addition to that, children will also receive a suppository of acetaminophen (30-40mg/kg) intraoperatively, and oral acetaminophen 15mg/kg every 4 hours as required to treat post-operative pain. The control group will only receive the acetaminophen regimen, and all patients will receive an additional opioid medication (morphine) to control breakthrough pain at a dose of 0.1-0.2mg/kg orally every four hours if the pain is not controlled on the base regimen of pain medications allocated.

All study medications will be unlabeled in order to maintain blinding, except the intraoperative rectal acetaminophen dose and the postoperative rescue morphine, since both groups will be receiving these medications. As well, we felt it would be potentially dangerous to blind participants to morphine because of the possible side effects of morphine including sedation, relaxation of pharyngeal musculature which can worsen snoring and in the case of an accidental overdose, can cause severe respiratory depression and even death. A flow diagram of the study procedure is found in Figure 1.

Participants will be given their allocated medications after arrival and registration at the hospital. Shortly after their arrival to the preoperative area usually 30 minutes before

their surgery, they will be assessed by the anesthesiologist assigned to their operation, and at this time, will give them the intraoperative medication (i.e. either ketorolac or NS). Subjects will receive a standardized anesthetic regimen, which will include the insertion of an intravenous line before either an IV induction with Propofol 2-4 mg/kg or inhalational anesthesia with Sevoflurane mixed with air and oxygen. After induction patients will receive fentanyl 1-2 mcg/kg IV, dexamethasone 0.1 mg/kg (max 10mg) and ondansetron 0.05 mg/kg (max 4 mg). Subsequently, intravenous ketorolac or NS will be administered, as well as the acetaminophen suppository. Patients will then undergo their surgery and will be transferred to the recovery room as routinely done after completion of the surgery and arousal from anesthetic. The recovery room nurses will be instructed to assess pain every 15 minutes using the pain scales provided (Wong Baker FACES and CHEOPS) and provide patients with intravenous or oral morphine (0.05 mg/kg IV or 0.1-0.2 mg/kg po) until pain is well controlled.

Once awake and ready for transfer, children below the age of 3 years old will be transferred to the pediatric inpatient ward for post-operative observation. This group of patients will be given post-operative analgesia as dictated by this protocol with the help of inpatient nurses. Pain measurements will be conducted per protocol as well. Patients will be examined by the otolaryngology team at least daily, and will be discharged if meeting the usual standard of adequate oral intake, absence of desaturations during sleep, and lack of bleeding. Children above the age of 3 will be transferred to the same day surgery (SDS) unit for further monitoring to ensure onset of oral intake. They will also be treated with the post-operative pain management protocol in concordance with the study. Patients will be discharged once deemed ready for discharge (i.e. able to drink

water and not actively bleeding) after a minimum of 4 hours of post-operative monitoring.

Upon discharge, participants will continue to monitor pain every 4 hours for the administration of pain medication, and will complete pain scales prior to every dose of analgesic and 30 minutes after each dose. Participants who do not have adequate pain control will receive breakthrough morphine doses. All information pertaining to pain scales and administration of pain medication and breakthrough will be entered on the online data collection sheets

Participants will be contacted twice weekly by the research coordinator to monitor for any adverse events such as inadequate pain management, dehydration, bleeding, excessive vomiting, and to address participant concerns. At this time, the participants will also be encouraged to be thorough with the data collection and recording. At the conclusion of 2 weeks following surgery, participants will be seen by their surgeon in follow up and will also be asked to meet with the research coordinator for half an hour to review any issues with data collection. At this time, participants will have completed the study. Upon completion of the trial, participants will be sent the results of the study, unless having indicated lack of interest in such a follow up.

Control

Patients in the control arm will be receiving the standard of care treatment, with acetaminophen administered rectally in the OR at a dose of 30-40mg/kg, and acetaminophen 15mg/kg given post-operatively for pain control, with oral morphine given for treatment of breakthrough pain. Patients will also be given placebo ibupfophen and ketorolac to minimize bias.

Outcome measures

Sampling and enrollment

Patients will be enrolled in a continuous fashion. Operative bookings will be screened for eligibility based on type of procedure. Eligible patients will be approached at their routine preoperative visit (typically within 2 weeks of the date of surgery) with the anesthesiologists and will further be screened for eligibility. If eligible, consent will be taken at this time. Patients will not be screened if undergoing procedures that do not include tonsillectomy, or if they are undergoing additional procedures not acceptable within the eligibility criteria.

Primary outcome

A complete list of outcomes can be found in Table 3. The primary outcome of this study is the total amount of rescue morphine required to maintain adequate pain control during the postoperative period, considered to be two weeks following tonsillectomy. As such, we will sum the daily intake of morphine for each participant throughout the follow up period and divide it by the patient's weight such that we obtain a total mg/kg dose of morphine for the duration of the course. This is a continuous variable and will be analyzed as the difference between a continuous variable between two arms. We consider a decrease in total morphine intake of 10% clinically significant.

Secondary outcomes

For children 1-3 years of age, the CHEOPS scale will be used, as it is validated for children above the age of one. Those at least 3 years of age will use a combination of the CHEOPS and the Wong-Baker FACES scale to quantify pain that requires treatment. Pain scores above 3 for the Wong-Baker and seven [19] for CHEOPS will be considered elevated and requiring treatment. Pain scores will be measured prior to medication doses, and repeated if pain persists or recurs between these times to determine need for

breakthrough morphine. The quantity of morphine given over 24h will be compared for each day, as well as the difference in the duration of use of morphine between the two groups. We will assess duration of analgesic use and the frequency of analgesic requirements on a daily basis (including treatment drugs and morphine). We will also seek to measure the difference in incidence of vomiting and bleeding of any amount.

We will also integrate economic assessment outcomes to measure the impact of our intervention from the point of view of the patient/caregivers, as well as from the health care system. We used the GRADE guidelines: 10[20] to guide the choice of economic analysis outcomes based on the relevance to this study. A complete list of specific outcomes that will be examined is found in Table 4. Outcomes: we are going to be looking at include return back to school for the children, impact on caregiver work status (total days off of work), cost of transportation to see the physician (including gas and parking) and we will add the cost of standard over-the-counter analgesics which would have been utilized for the patient's care, though this will be provided free of cost through the trial. From health care systems' point of view, we will track the hours in hospital and medications given in the post-operative period, the number of visits to health care providers for any reason, as well as the instances of return to the emergency room and admission to hospital and all associated costs related to these, including procedural/operative costs associated with management of bleeding. As well, we will include the cost of EMS in the case of bleeding, or transfer between hospitals if done by EMS.

Sample size

The primary objective of this trial is to maximize pain control post-tonsillectomy while minimizing use of morphine. The sample size calculation is based on the expected

difference in total morphine requirement during the two-week recovery period between the treatment and control group. The criterion of significance (alpha) was set at 0.05. The sample size table was created using Stata/SE 12.1 (Texas USA). We varied the presumed effect size and standard deviation and obtained a variety of sample sizes. Ultimately, the pilot study will be used to approximate the appropriate sample size based on a true estimate of the effect size and standard deviation. The results of these calculations are listed in Table 4. The target sample size for phase 1 is 100 participants, or 50 per treatment arm. Assuming a reduction in total morphine intake of 20% and estimating a standard deviation of 10, a total sample size of 1052 will likely be necessary for the final study.

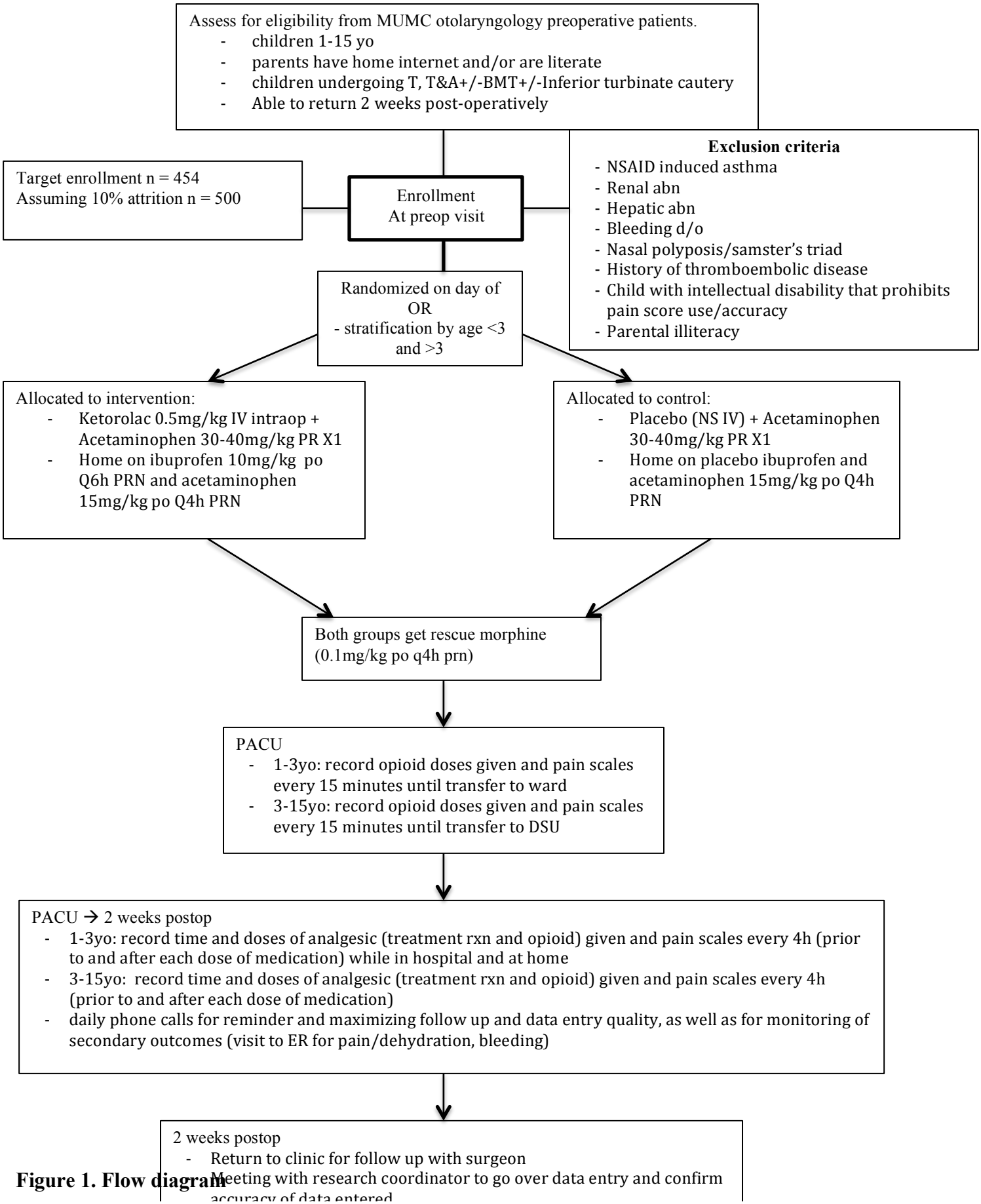

Figure 1. Flow diagram

This study will have a power of 90% to detect such a difference. The calculated sample size is 647, and assumes 1:1 recruitment. A Bonferroni correction will be applied to the analysis of the secondary outcomes. To control for attrition, we will over-enroll by 5% to control for this amount of possible loss to follow up.

Data collection

Data collection tools include an online data entry methodology for at home entries, provided by REDCap Software, Version 5.1.0, (2014 Vanderbilt University). Data to be entered includes the quantity of analgesics administered to the participating children every time they are given, as well as the pain scores prior to each dose. The pain scores used are the Childrens Hospital of Eastern Ontario Pain Score, which is validated for children ages 1 to 15, and the Wong Baker FACES scale, which is validated in children ages 3-15.[21,22] The Wong Baker FACES scale consists of black and white circular faces that visually represent the level of pain experienced by the child. The CHEOPS pain scale observes six behavioral components (cry, facial, child verbal, torso, touch, legs) yielding a score ranging from 4-13.[23] Twice weekly phone calls will be made to enrolled participants to assess for the presence of dehydration, intractable pain, bleeding, and vomiting, and these variables will also be recorded in the online data collection records. These phone calls will also be used to ask patients if they have sought medical attention for these conditions, including GP or ER visit or admission to hospital. It will also be required that patients record the medication doses given in hospital unless they have been admitted to MUMC. In fact, we will encourage participants to return to MUMC for any issues relating to pain or dehydration, vomiting, but not bleeding, as the latter requires immediate medical attention at the nearest hospital to the patient. If admitted at remote sites, attempts will be made to obtain

medication records for the purposes of this study, through the appropriate releases required by provincial policies.

Analysis plan

Analysis of primary and secondary outcomes

We will use Stata/SE version 12.1 (StataCorp, TX, 2013) to conduct the analysis of this trial. We will report all outcomes according to the CONSORT standards for reporting randomized controlled trials. We will use intention-to-treat principles for data analysis, meaning that patients will be analyzed in the groups they were randomized to. We will use multiple imputation to manage missing data.[24] Participants who do not attend the follow up visit and have a formal review with the research coordinator will be considered to have dropped out. In these situations, the total morphine dose will be considered inaccurate and these participants will be excluded from the final analysis. Data from such participants will only be used to contribute to total daily dose of analgesics, and attempts will be made to contact them to inform secondary outcomes regarding adverse events (eg: visit to MD/ER, admission, bleeding, death).

Sensitivity analyses

Sensitivity analyses are used to control for factors that may affect the results of the final analyses, and therefore are done to verify the robustness of results based on pre-determined hypotheses for factors that may affect these results. Our sensitivity analysis will include a per-protocol analysis, which includes only patients who did not have any significant deviations in the treatment protocol or significant missing data. Because these is an intensive monitoring process requiring data entry online multiple times daily, participants deemed to have more that 10% missing data will be excluded in

the per protocol analysis, as well as those having received analgesics other than those included in the protocol. An exception to the latter condition is in the case of admission to hospital, patients who receive an opioid other than morphine will have their opioid included and converted to equivalent morphine dose using standard conversions for both the intention-to-treat and per protocol analyses.

We will also perform sensitivity analyses based on statistical methods used to analyze the data based on stratification by age as previously described. We will perform a meta-analysis of the groups, as well as a regression analysis and pooled t-test as sensitivity analyses. As well, we will analyze our results based on demographic variables recorded using univariate and multivariate regression.

Statistical methods

The primary outcome will be compared between the intervention arm (NSAID) and the comparator arm using an unpaired two-sided t-test. Analysis of stratification groups will be performed using multivariate linear regression analysis. For secondary analysis, we will use unpaired t-test for continuous variables and chi-squared analysis for categorical variables. Univariate and multivariable linear regression analysis will also be used to address covariates and demographic factors in addressing regarding the primary outcome.

Secondary outcomes will be analyzed as stated in Table 3. We will perform a multilevel longitudinal analysis for repeated pain score and daily morphine intake to measure trends in pain scores as they change over time, and address whether treatment group affected this trend. All results will be reported as an estimate of the effect (corresponding and 95% confidence interval) and associated p-value.

Discussion

The intervention being tested stands to improve not only the post-operative care we provide to thousands of children undergoing tonsillectomy yearly, but also to better understand the trends in post-tonsillectomy pain and factors that influence it. Although the use of NSAIDs post-tonsillectomy has been previously studied, it remains under-utilized due to bleeding concerns. However, with evolving controversies surrounding the use of codeine, and reticence to prescribe opioids altogether due to the possibility of airway compromise following pediatric tonsillectomy invite the question of developing an evidence-based approach to this incompletely studied issue. In fact, even though there are many studies available that study the first 24-48h post-tonsillectomy, there are no studies that have reliably described the complete post-operative course for tonsillectomy with regards to pain and how best to manage it. In fact, we have identified only 4 randomized controlled trials that compared NSAIDs to other analgesics with pain as an outcome for more than one week post-operatively.

Courtney et Al[25] addressed pain control two weeks post-tonsillectomy, and compared the use of tramadol to ketorolac in patients older than 11 years of age. The study found no statistically significant difference in VAS pain scores throughout the 2 weeks, but suffered from a 24% dropout rate and an unexplainable high secondary hemorrhage rate of 27% (usual secondary hemorrhage rates are 5% on average[26]), with a higher incident in the tramadol group. The study also reported the duration of analgesia needed, and reported that study medications were taken for under 12 days on average in each group, although the data for this outcome was 88% complete, and the quantity of medications is also not reported. A study by El-Fattah and Ramsey[27] looked at children aged 5 to 12 receiving either a triple analgesic regimen administered intra-operatively

consisting of rectal diclofenac, and intravenous paracetamol and tramadol, or control, with all children receiving local anesthetic infiltration of the tonsillectomy bed. Parents were required to assess pain daily, but only data from days 1 to 3, and those on days 7, 9, 10 and 14 were recorded as part of the study. Participants with scores greater than their pain score cutoff were given oral or rectal diclofenac, regardless of allocation group. The study recruited 135 children, and found that children having received the triple analgesic regimen intra-operatively required significantly less analgesic than the control group for 3 days post-operatively. Moreover, they noted that all patients stopped meeting their pain score cutoffs for diclofenac on day 7 and that all patients had pain scores of 0 on day 9, 10 and 14.

Harley and Dattolo[28] studied an analgesic regimen where children aged 6 to 16 years of age were randomized to either acetaminophen with codeine or ibuprofen. Pain was measured by parents daily and graded using a mild-moderate-severe scale, where parents were to classify the pain based on ability to tolerate a normal diet and quantity of sleep. It is important to note that there was no mention of a validation process for this scale and there were only 27 children recruited. They found that there was no statistically significant difference between the acetaminophen-codeine and ibuprofen groups with regards to pain score and time to return to normal diet. Finally, Nikanne et Al[29] compared intraoperative celecoxib and ketoprofen to placebo, with regards to immediate post-operative pain, followed by direct comparison of celecoxib and ketoprofen for post-operative pain (patients in the placebo group were re-allocated to either treatment arm). They found that celecoxib outperformed ketoprofen both immediately post-operatively and in the first week of treatment, but only asked parents to record pain measures on the second, third, fourth and seventh day post-operatively. And although a phone call was

made to the participants after 3 weeks post-operatively to collect information as to the total of study medication and rescue drug (acetaminophen and codeine) that was given to children, this data was not reported in the results section.

The above evidence proves that there is currently little description of post-tonsillectomy pain and its behavior in the setting of NSAID use in comparison with its absence. Therefore, we are focusing on answering the questions listed in this protocol, with an emphasis on reliable study methodologies for this extremely clinically relevant research question.

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Appendix

Table 1. Pilot objectives and outcomes

	Objective	Outcome/Aims
Process	Missing data	Less than 5% missing data for primary outcome
	Recruitment*	Recruitment of 70% of eligible participants
	Attrition*	Loss to follow up less than 10%
Resources	Financial/staffing	Assessment of total costs and need for multi-center trial
Scientific	Effect size/sample size	Mean and variance of total morphine dose
	Safety	Measurement of baseline outcome measures
Management	CRF appropriateness	Feedback on data collection forms with key stakeholders (parents, nursing staff for PACU/SDU and admissions) – assessment of qualitative data at midpoint for consideration

*Primary outcomes

Table 2. Pilot (phase 1) variables, measures and methods of analysis

Variable/Objective	Hypothesis/Aim	Outcome measure	Method of analysis
Primary			
Recruitment	Recruitment of 70% of eligible participants	Number of patients recruited into study	Percentage
Attrition	Loss to follow up less than 10%	Number of patients recruited who do not attend 2 week follow up	Percentage
Secondary			
Missing data	Less that 5% missing data for primary outcome	Number of missing total morphine doses	Percentage
Financial feasibility	Total cost to run pilot	Projected costs given sample size calculation	Per patient cost
Sample size	n/a	Mean and variance of primary outcome	Sample size calculation using t-test
Case report form	Feedback regarding	Qualitative data	Qualitative analysis

adequacy	study procedure		

Table 3: Variables, measures and methods of analysis

Variable/Objective	Hypothesis	Outcome measure	Method of analysis
1) Primary			
a) Difference in total rescue opioid intake	Decrease in total rescue opioid	Amount (mg/kg) of opioid consumed at the end of the follow up period (2 weeks) – recorded on CRF	Unpaired t-test
2) Secondary			
Difference in daily rescue opioid intake	Decreased in treatment arm	Recorded amount of opioid consumed daily	Unpaired t-test
Duration of morphine use	Decreased in treatment arm	CRF	Unpaired t-test
Pain scores	Lower in treatment arm	VAS (wong-baker faces for >3yo and CHEOPS for all)	Multilevel regression
Time to return to solids/normal diet	Faster in treatment arm	Difference between time of end of OR and time to first oral intake	Unpaired t-test
Daily frequency of study drug intake	Equal between arm	CRF	Unpaired t-test
Visit to ER or GP for pain &/or dehydration	Decreased in treatment arm	CRF and daily phone calls	Chi-squared
Admission to hospital for pain &/or dehydration	Decreased in treatment arm	CRF and daily phone calls	Chi-squared
Daily frequency of vomiting	Equal between arms	CRF and daily phone calls	t-test and Chi-squared
Subclinical bleeding (self-limiting not requiring hospital visit)	Equal between arms	CRF and daily phone calls	Chi-squared
Self-limiting clinically relevant bleeding requiring physician attention	Equal between arms	CRF and daily phone calls	Chi-squared
Bleeding requiring clinical intervention, but not requiring return to operating theatre	Equal between arms	CRF and daily phone calls	Chi-squared
Bleeding requiring surgical intervention	Equal between arms	CRF and daily phone calls	Chi-squared
Death due to bleeding	Equal between arms	Mortality/death records	Chi-squared
Death due to respiratory compromise/depression	Equal between arms	Mortality/death records	Chi-squared
Death not due to surgery	Equal between arms	Mortality/death records	Chi-squared
3) Sensitivity Analyses			
a) Per protocol analysis			t-test

b) Adjusting for demographic/baseline co-variates	Multiple regression
c) Stratification	c) Meta-analysis between groups, regression with stratum as covariate, and pooled analysis using t-test

Table 3: List of outcomes

Outcome	Time frame	Type
Primary		
Pain		
Total morphine intake	2 weeks	Continuous
Secondary		
Pain related		
Pain scale	daily average, trend over 2 weeks, pre-meds, overall average	Continuous
Time to first normal meal	Immediate post-operative	Continuous
Daily morphine intake	Daily for 2 weeks	Continuous
Return to the ER for pain	Incidence and frequency over 2 weeks	Dichotomous and continuous
Return to the ER for dehydration	Incidence and frequency over 2 weeks	Dichotomous and continuous
Admission to hospital for pain or dehydration	Incidence and frequency over 2 weeks	Dichotomous and continuous
Adverse events		
Vomiting	Overall incidence, daily incidence, trend over 2 weeks	Dichotomous and continuous
Bleeding (not requiring medical attention, requiring medical attention but no intervention, requiring medical attention with non-surgical intervention, and requiring surgery)	Overall incidence	Dichotomous
Mortality (bleeding, dehydration, adverse drug reaction, other)	Overall incidence	Binary
Economic analysis		
Total cost to patient	Total cost related to tonsillectomy relative to treatment group	Continuous

Total cost to health care system	Total cost related to tonsillectomy relative to treatment group	Continuous

Table 4: Health economic analysis parameters

Parameter	Classification	Outcome
Change in use of health care resources	Medications	Difference in total morphine prescribed
		Intravenous hydration
		Oral rehydration
	Health care visits	Emergency room visits
		Emergency transportation (EMS)
		Examination
		Physician visits (surgeon, GP, pediatrician)
		Home visits (nursing, or physician)
Change in non-health care resources	Special diets	Oral rehydration solution
		Special/soft foods
		Transportation to health care facilities
Change in use of patient and informal caregiver resources		Time of family and other informal caregiver
Change in productivity		Time off work for caregiving
		Time off school

Table 4. Sample size calculations for morphine consumption difference at 14d post-op

Reduction in morphine (m1:m2)	SD	10	9	8	7	6	5	4	3
25%= 10:7.5		337 (674)	273 (546)	216 (432)	165 (330)	122 (244)	85 (170)	54 (108)	31 (62)
20% = 10:8		526 (1052)	426 (852)	337 (674)	258 (516)	190 (380)	132 (264)	84 (168)	48 (96)
15% = 10:8.5		934 (1868)	757 (1514)	598 (1196)	458 (916)	337 (674)	234 (468)	150 (300)	85 (170)
10% = 10:9		2102 (4204)	1709 (3418)	1345 (2690)	1030 (2060)	757 (1514)	526 (1052)	337 (674)	190 (380)

Chapter 5 - Conclusion

Summary of findings

Non-steroidal anti-inflammatory drugs are very commonly used over-the-counter [1] analgesics.[2,3] They have been studied in a variety of clinical settings, particularly in children and adults for the treatment of pain and fever as well as for their use in management of musculoskeletal injuries and rheumatologic disorders, and there is now growing evidence supporting their use in the post-operative setting.[3] Namely NSAIDs have been show to have analgesic benefits and opioid sparing effects for many surgical procedures,[4,5] without significantly increasing the post-operative risk of complications.[6-8] Tonsillectomy has been no exception to this research topic, which enabled our research group to perform a systematic review of the literature and meta-analysis of collected outcomes. We found that NSAIDs were not statistically significantly better or worse than other medications including opioids and acetaminophen across the outcomes measured. The major limitation of this review is the paucity of long-term outcomes for analysis, which limited our analysis of pain outcomes to the first 24 hours of post-operative period. Although this was a clinically relevant outcome, the greater question pertains to the use of NSAIDs for pain throughout the post-tonsillectomy recovery period of two weeks. The lack of evidence for this outcome highlights the importance of further research in this field. However, there has previously been a lot of reticence in using NSAIDs in the post-tonsillectomy setting because of their potential to increase bleeding risk due to their anti-platelet activity.[3] Our systematic review also extracted data regarding bleeding, specifically bleeding, and we found no statistically significant difference in bleeding rates when comparing NSAIDs to either placebo or active comparator drugs. However, the optimal information size was calculated to be at least three

times larger than the population of patients available in the data available to us, therefore no definite conclusions can be made regarding bleeding risk in this setting. Moreover, because the timing and duration of NSAID administration was variable, the method of follow up for this outcome was heterogeneous and poorly described in many studies, making the quality of the data we used highly biased. We also meta-analyzed data on the incidence of vomiting and there was a clear and significant benefit for the use of NSAIDs. The conclusion of our findings is that there is insufficient evidence on the effectiveness of NSAIDs for pain control following tonsillectomy. Since we remain uncertain about the true risk of bleeding with NSAIDs post-tonsillectomy, it is important to determine the efficacy of this analgesic to make conclusions on whether the benefit of their use is worth their potential risk.

Significance and importance of the research

Tonsillectomy has remained one of the most common surgical procedures performed in North America.[9] The findings of our systematic review have established a need for a study investigating the efficacy of NSAIDs for pain post-tonsillectomy. As such, the goal of this thesis was to create a protocol for a randomized controlled trial investigating the efficacy of their use following this procedure, namely comparing acetaminophen alone to acetaminophen with ibuprofen in the post-tonsillectomy setting. We will be studying the pediatric population, since this is the population that undergoes the largest proportion of tonsillectomies as a whole. The goal and one of the greatest strengths of this protocol is its focus on a pragmatic approach and generalizable outcomes. For example, since ibuprofen and acetaminophen are very common over the counter analgesics administered to children, it follows that these are often selected by parents for treatment of various conditions,

including post-operative pain. Therefore, a protocol based on common over-the-counter medications is pragmatic and can easily be applied in the clinical setting. As well, we are focusing on a patient-relevant outcome as our primary outcome, which is the mean total dose of opiates (in our case morphine) that children receive to control their pain. In fact, common side effects associated with their use include sedation, nausea, vomiting, constipation, and respiratory depression, the latter of which can especially be problematic in the setting of tonsillectomy due to the airway swelling induced by this procedure. On the other hand, our goal is to minimize common adverse events such as intractable pain and subsequent dehydration, which cause repeat visits to health care providers and possibly admission to the hospital for pain management and hydration. The incidence of these is a planned secondary measure in our study, as well as serious adverse outcomes such as bleeding and vomiting. We are also planning to measure pain with pain scales, which have been validated in children.[10]

Future Plans

The upcoming plans for this protocol is to take steps towards enacting the study and begin recruitment. We are actively seeking funding for the initial pilot study, which is geared towards determining the feasibility of this study. We are also in process of obtaining ethics approval from Hamilton Integrated Research Ethics Board, as well as obtaining a No Objection Letter from Health Canada, which is required for randomized controlled trials of drugs for new indications for the drug being studied.

Some of the limitations of this study include the exclusion of children with intellectual disabilities, which limits generalizability to this population. This decision was made to

decrease bias with collection of the primary outcome, as our team's clinical consensus was our primary outcome was likely to be affected by such a disability. A separate study focusing on a protocol tailored to such a population should be undertaken, and we would consider this as a next project for this research stream. Another limitation is the fact that our sample size calculation for the randomized controlled trial is based on extrapolations and assumptions from studies that follow different protocols than ours, either in the duration of follow up, or in the nature of the surgery. However, this is the best estimate we were able to make due to the paucity of research available on long-term surgical pain for the duration of surgical recovery.

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