TITLE: Steroids and Antiobiotics in Tonsillectomy
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Introduction

The tonsillectomy is one of the oldest and most commonly performed surgical procedures today. It is estimated that 200,000 tonsillectomies are performed annually in the United States and that tonsillectomy constitutes a third of operations performed under general anesthesia in this country. This discussion will examine the benefit, or lack thereof, of perioperative steroids and antibiotics for tonsillectomy. In the context of this topic, it will be important to briefly discuss the history of tonsillectomy, microbiology and mechanisms of action of dexamethasone and amoxicillin involved in tonsillectomy.

History

Tonsillectomy is defined as the complete removal of the tonsil from its capsule and is derived from the Latin word *tonsilla*, which means a stake to which boats are tied, and the Greek word ektome which means excision. Aulus Cornelius Celsus, a first century A.D. Roman writer and physician gives the earliest account of the removal of the tonsil using a finger and suggested the use of a knife in situation where the finger proved ineffective. He wrote: "…[tonsils] should be loosened by scraping around them and then torn out. When this is not possible, they should be picked up with a little hook and excised with a scalpel…." Following this description the methods for tonsillectomy eventually evolved from the use of specialized knives, wires, strings, tonsillotomes and guillotines of the past to the present day techniques.

Tonsillectomy Morbidity

Despite the evolution of anesthetic and surgical techniques available, post-tonsillectomy morbidity remains a significant clinical problem not only for the patient, but the family and physician as well. Pain is an important morbidity of this procedure, and the current methods to relieve pain are limited by side effects and outpatient care. Close to 40% of patients needed to visit their primary care physician or a general physician following surgery due to insufficient analgesia. A study from the Royal College of Surgeons of England demonstrated that pain was

poorly controlled in 46% of patients following tonsillectomy. A study in 1997 found that postoperative pain was more troublesome for the non-pediatric age group. An NHS Acute Inpatient Survey submitted by the Picker Institute in May 2003 unveiled that postoperative pain control is often inadequate with almost two-thirds of patients reporting moderate to severe pain which was not, in the opinions of 27% of patients, adequately managed. In addition to pain, nausea, vomiting and inadequate oral intake and fever are common morbidities encountered after tonsillectomy. The incidence of vomiting after tonsillectomy with or without adenoidectomy has a reported range between 40-70%. The delay in postoperative oral fluid and solid intake as a result of nausea, vomiting, or pain prolongs the time until discharge and also increases dehydration risks in early and late postoperative periods.

Corticosteroids as a Method to Reduce Post-tonsillectomy Morbidity

Methods for reducing pain, nausea, and vomiting after tonsillectomy are important to improve the standard of care our patients receive. During the past 35 yrs, investigators have studied the effects of systemic corticosteroids in reducing post-tonsillectomy morbidity. Unfortunately, there is no agreement regarding the routine use of corticosteroids in tonsillectomy. Results of randomized, double-blind, placebo-controlled studies of single dose intravenous steroids in tonsillectomy have been conflicting; some showing benefit and others showing no benefit.

Dexamethasone as an antiemetic

The mechanism of action of dexamethasone as an antiemetic remains unknown. Some postulate that dexamethasone exerts effects either outside the blood-brain barrier (area postrema of the brainstem) or inside the blood-brain barrier (vomiting center). In spite of the fact that the mechanism is not understood, an antiemetic benefit of corticosteroids is supported by the literature and widely accepted. In other trials, dexamethasone has been shown to be an effective antiemetic in randomized trials with emetogenic chemotherapy. In fact, significant reduction of emesis after pediatric tonsillectomy was demonstrated in the dexamethasone-treated group in randomized trials of a serotonin antagonist (i.e. odansetron) plus either dexamethasone or placebo.

Dexamethasone as an anti-inflammatory

In conjunction with antiemetic effects, dexamethasone may reduce inflammation at the operative site, subsequently reducing the release of inflammatory mediators into the circulation. This could also lead to less stimulation of the vomiting center mentioned previously. Dexamethasone causes inhibition of the inflammatory response by blocking factors like bradykinin, prostaglandin, and leukotrienes which results in a decreased level of inflammation and reduction of the accompanying signs and symptoms including pain. Also, dexamethasone can modulate inducible COX-2 .

The following is a synopsis of studies that were highlighted in this presentation that attempt to illustrate the benefit or lack thereof, of steroids in tonsillectomy:

Study #1
Author: McKean *et al*
Journal*: Clinical Otolaryngology* **31**, 36-40
Title: "Use of intravenous steroids at induction of anesthesia for adult tonsillectomy to reduce post-operative nausea and vomiting and pain: a double-blind randomized controlled trial"

Objective: To assess the effectiveness of intravenous steroids at induction of anesthetic to reduce post-operative nausea and vomiting and pain after adult tonsillectomy.

Design: Prospective, double-blind, randomized, placebo controlled trial, with ethical approval, following Consolidated Standards of Reporting Trials guidelines.

Participants: Seventy-two adults between 16 and 70 years, American Association of Anesthetists (ASA) 1, listed for elective tonsillectomy. Intervention: Single dose of either 10 mg of dexamethasone or 2 mL of saline after induction with a consistent anesthetic technique.

Main outcome measures: Patients filled in a visual analogue scale relating to pain and post-operative nausea and vomiting for the day of operation and 7 days after operation.
The time to first ingestion of food and drink after operation was also noted.

Results: Data completion rate of 64% (46 of 72 patients enrolled). Statistically significant relative decrease (62% $P = 0.001$) in the incidence of post-operative nausea and vomiting was seen in those treated with dexamethasone. Statistically significant relative decrease (23% $P = 0.016$) in post-operative pain scores for the day of operation was seen in those treated with dexamethasone. Significant decrease (17.5%, $P < 0.001$) in mean pain score for seven post-operative days was seen in those treated with dexamethasone. No adverse effects were seen.

Conclusions: Dexamethasone given as a single dose of 10 mg at induction of anesthesia for adult tonsillectomy is an effective, safe and inexpensive method for reducing morbidity in adult tonsillectomy.

Study #2
Author: Kaan *et al*
Journal: *International Journal of Pediatric Otorhinolaryngology* (2006) **70**: 73-79
Title: "The effect of preoperative dexamethasone on early oral intake, vomiting and pain after tonsillectomy"

Objective: Postoperative morbidity in patients undergoing tonsillectomy with or without adenoidectomy includes inadequate oral intake, pain, nausea, vomiting and bleeding. The purpose of this study is to evaluate the effect of preoperative 0.5 mg/kg intravenous dexamethasone on postoperative early oral intake, pain, vomiting in patients undergoing adenotonsillectomy while performing standard anesthesia technique and sharp dissection tonsillectomy.

Methods: In this prospective, double-blinded, placebo-controlled study 62 children, aged 4—12 years, who underwent tonsillectomy with or without adenoidectomy were

randomly assigned to receive single dose of 0.5 mg/kg intravenous dexamethasone preoperatively. Patients started to receive 100 ml of clear fluids 2 h postoperatively, then were offered every hour. When pain score was 3 or above, paracetamol was given for pain control. Tolerating 400 ml of clear fluids, no bleeding and no vomiting were accepted as discharge criteria. The discharge time was also recorded. The incidence of early vomiting, pain scores, amount of oral intake were recorded until the discharge time.

Results: Compared with placebo, the patients who received preoperative dexamethasone had significantly less pain score during the first 6 h postoperatively ($p < 0.05$), adequate amount of oral intake time was shorter ($p < 0.05$) and the discharge time was earlier ($p < 0.05$). No difference was found in vomiting incidence in both groups.

Conclusion: Preoperative dexamethasone use significantly reduces early post-tonsillectomy pain, improves oral intake and facilitates meeting the discharge criteria while using standard anesthesia technique and sharp dissection tonsillectomy without any significant side effects.

Study #3
Author: Steward *et al*,
Journal: *Laryngoscope* 111: October 2001
Title: "Do Steroids Reduce Morbidity of Tonsillectomy? Meta-Analysis of Randomized Trials"

Objectives/Hypothesis*:* The study aims to reconcile conflicting published reports regarding the clinical efficacy of a single intraoperative dose of dexamethasone in reducing post-tonsillectomy morbidity.

Study Design*:* Systematic overview (meta-analysis).

Methods: To critically evaluate the existing evidence, the authors performed a formal meta-analysis of eight double-blinded, randomized, placebo-controlled studies of dexamethasone in pediatric patients undergoing tonsillectomy or adenotonsillectomy. Reduction in postoperative emesis and pain, as well as early return to soft or solid diet, were studied as distinct end points.

Results*:* Children being given a single intraoperative dose of dexamethasone (dosing, 0.15–1.0 mg/kg; maximum dose, 8–25 mg) were two times less likely to vomit in the first 24 hours than children being given placebo (relative risk [RR] = 0.55; 95% confidence interval [CI], 0.41–0.74; $P < .0001$). Routine use in four children would be expected to result in one less patient having post-tonsillectomy emesis (risk difference [RD] = -0.24; 95% CI, -0.38 to -0.10; $P = .0006$). In addition, children being given dexamethasone were more likely to advance to a soft or solid diet on post-tonsillectomy day 1 (RR= 1.69; 95% CI, 1.02–2.79; $P = .04$) than those being given placebo. Because of missing data and varied outcome measures, pain could not be meaningfully analyzed as a distinct end point.

Conclusion: Given the frequency of tonsillectomy, relative safety and low cost of

dexamethasone, and the reduction in postoperative morbidity, the authors recommend routine use of a single intravenous dose during pediatric tonsillectomy.

Study #4
Author: Lachance et al
Journal: *Laryngoscope* **118**: February 2008
Title: "The Use of Dexamethasone to Reduce Pain After Tonsillectomy in Adults: A Double-Blind Prospective Randomized Trial"

Objectives/Hypothesis: To determine the effectiveness of dexamethasone to reduce pain after tonsillectomy in adults by at least 13 mm on the visual analogue scale. The secondary objective was to reduce the use of narcotics by at least 20%.

Study Design: This multicentric study is a prospective double-blind randomized controlled trial.

Methods: A total of 102 patients were enrolled and received a 4-day trial either of dexamethasone in decreasing doses or placebo. The patients were asked to note the level of pain on the visual analogue scale daily for 7 days. They also had to record their consumption of analgesic and any eventual side effects.

Results: There were no statistically or clinically significant differences between the two groups for the level of pain noted on the visual analogue scale for the first 4 and 7 days. There were no statistical differences for the consumption of hydromorphone between the two groups.

Conclusion: The authors do not recommend the use of dexamethasone on a routine basis following tonsillectomy in adults for the reduction of pain or narcotics consumption.

Dexamethasone is the most powerful anti-inflammatory steroid with the advantage of a long half-life. Use of this drug for less than 2 weeks is considered safe even in supraphysiologic doses. Complications from corticosteroid therapy such as increased infection rates, peptic ulcers, and adrenal suppression are usually related to prolonged use. The risk of steroid therapy for a single dose or for less than 24 hrs is negligible. There are no reports in the literature of complications from use of intravenous dexamethasone during pediatric tonsillectomy. The use of dexamethasone, if proven useful like the above mentioned studies, would allow pain relief, decreased use of narcotics, decreased frequency of unscheduled consultation and decrease the social costs of this surgery by a faster return to work.

Role of Infection and Antiobiotics in Post-tonsillectomy Morbidity

According to O'Reilly et al, the most significant post-tonsillectomy morbidity is due to bleeding and pain. Secondary hemorrhage is now more common than primary hemorrhage, particularly in the adult population. The reason for secondary hemorrhage is not understood completely, but is often attributed to infection. Gaffney and Cafferkey illustrated the presence of organisms within the tonsils of patients with recurrent tonsillitis and that amoxicillin could reduce their concentration. Below is the table of results of tonsil core swabs of children who had recurrent acute tonsillitis from this study:

	No. (β-lactamase producers)
Haemophilus influenzae	94 (17)
Haemophilus parainfluenzae	2
Staphlococcus aureus	39 (37)
β-haemolytic streptococci	24
Streptococcus pneumoniae	9
Moraxella catarrhalis	0
Number with mixtures	47

49/119 (41.2%) of tonsils contained one or more β-lactamase producer.

The same article also had a chart showing the bacteriology of the tonsil core of 5 adults who also had recurrent acute tonsillitis:

Haemophilus influenzae	4
Staphlococcus aureus	3
β-haemolytic streptococci	1

Amoxicillin Mechanism of Action:

Beta-lactam antibiotics such as amoxicillin are mainly bactericidal. Like other penicillins, amoxicillin inhibits the third and final stage of bacterial cell wall synthesis by preferentially binding to specific penicillin-binding proteins (PBPs) that are located inside the bacterial cell wall. Penicillin-binding proteins are responsible for several steps in the synthesis of the cell wall and are found in quantities of several hundred to several thousand molecules per bacterial cell. Penicillin-binding proteins vary among different bacterial species. Thus, the intrinisic activity of amoxicillin, as well as the other penicillins, against a particular organism depends on their ability to gain access to and bind with the necessary PBP. The aminopenicillins are able to penetrate gram-negative bacteria more readily than are the natural penicillins or penicillinase-resistant penicillins due to the presence of a free amino group within the structure. Like all beta-lactam antibiotics, amoxicillin's ability to interfere with PBP-mediated cell wall synthesis ultimately leads to cell lysis. Lysis is mediated by bacterial cell wall autolytic enzymes (i.e., autolysins). The relationship between PBPs and autolysins is unclear, but it is possible that the beta-lactam antibiotic interferes with an autolysin inhibitor.

Amoxicillin spectrum of activity

Amoxicillin's gram-positive spectrum is similar to the natural penicillins, although amoxicillin is slightly less active than penicillin G against *S. pyogenes, S. pneumoniae, S. and agalactiae* and slightly more active against enterococci. Gram-negative bacteria that are frequently susceptible include *N. meningitidis, H. influenzae, Gardnerella vaginalis, Bordetella pertussis,* and some enteric bacilli including *E. coli, Proteus mirabilis,* and *Salmonella*.

Amoxicillin-Clavulanate (aka Augmentin)

The mechanism of action of Augmentin is the same as amoxicillin mentioned above. The clavulanic acid is a beta-lactam drug that acts as a competitive "suicide" inhibitor of many plasmid-mediated and chromosomally mediated bacterial beta-lactamases. Like sulbactam, clavulanic acid inhibits the activity of beta-lactamase Richmond types II, III, IV, V, and VI. It will not inhibit chromosomal type I, however, found in some Enterbacteriaceae. Clavulanic acid binds to the enzyme's active site, inactivating the beta-lactamase. Clavulanic acid can penetrate the cell wall and inactivate bound, as well as extracellular, beta-lactamases. It does not, however, overcome methicillin-resistance in staphylococci since this is mediated via a different mechanism. Clavulanic acid does not alter the actions of the beta-lactam antibiotics. It exhibits weak antibacterial effects.

Augmentin spectrum of activity

Organisms that are susceptible to ampicillin and plain amoxicillin are also susceptible to Augmentin. Augmentin has an expanded gram-positive spectrum that includes the beta-lactamase- producing staphylococci and most streptococci including enterococcus. Methicillin-resistant staphylococci (MRSA) are not susceptible. Penicillin-resistant strains of *S. pneumoniae* are increasing in number. The mechanism of resistance is mediated via the development of altered PBPs and the penicillin-resistant strains will generally be resistant to amoxicillin. The addition of clavulanic acid does not overcome this type of resistance. Increased dosages of amoxicillin may be necessary to overcome penicillin-resistant *S. pneumoniae*. The gram-negative spectrum of Augmentin includes *N. gonorrhoeae, N. meningitidis, Moraxella (Branhamella) catarrhalis, H. influenzae, H. ducreyi, Gardnerella vaginalis, Bordetella pertussis,* and some enteric bacilli including *E. coli, Klebsiella pneumoniae, Proteus mirabilis,* and *Salmonella*. Augmentin is extremely active against many anaerobic bacteria since many of these organisms liberate beta-lactamases.

Current Debate over Antibiotics in Tonsillectomy

For the past 18 yrs, investigators have analyzed the use of antibiotics to reduce post-tonsillectomy morbidity, showing no clear consensus. Data from randomized studies have demonstrated conflicting results with some showing a clinical benefit whereas others fail to show any benefit. The following is a brief synopsis of articles that investigate antibiotics effects on post-tonsillectomy morbidity:

Study #1
Author: Burkhart and Steward
Journal: *Laryngoscope* 115: June 2005
Title: "Antibiotics for Reduction of Post-tonsillectomy Morbidity: A Meta-Analysis"

Objective*:* To reconcile conflicting published reports regarding the clinical efficacy of postoperative antibiotics for reduction of post-tonsillectomy morbidity.

Study Design*:* Systematic review (meta-analysis).

Methods*:* Meta-analysis of seven randomized controlled trials of postoperative oral antibiotics in patients undergoing tonsillectomy or adenotonsillectomy. Postoperative pain and time to return to normal activity and diet were studied as distinct end points using a random effects model with weighted mean difference (Rev-Man 4.2). Search strategy included electronic searches of PubMed and Cochrane library databases;
cross-referencing textbooks, reviews, and original trials; and contacting experts in the field.

Results*:* Subjects treated with antibiotics experienced an earlier return to a normal diet (-1.22 days; 95% confidence interval [CI]= -1.97, -0.48; *P*= .001) and an earlier return to normal activity (-0.99 days; 95% CI= -1.80, -0.17; *P*= .02). Evaluation of mean pain visual analogue scores (VAS 0–10) over the first 5 and 7 postoperative days failed to demonstrate any significant effect of antibiotic therapy (VAS difference over 5 days =
0.41; -1.18, 2.00; *P* = .61) (VAS difference over 7 days = -0.64; -3.46, 2.18; *P*= .66). Cost analysis suggests routine therapy may be cost-effective but did not include analysis of side effects or resistance resulting from antibiotic usage.

Conclusion*:* The results of this systematic meta-analysis suggest that postoperative oral antibiotics do not significantly reduce post-tonsillectomy pain but result in an earlier return to normal activity and diet by approximately 1 day. Given the frequency
that tonsillectomy is performed, this possible benefit should be weighed against the cost and potential side effects of routine antibiotic therapy.

Study#2
Author: O'Reilly *et al*
Journal: *The Journal of Laryngology & Otology* May 2003, Vol. 117, pp. 382–385
Title: "Is the routine use of antibiotics justified in adult tonsillectomy?"

Objective: Assess the effect of perioperative amoxicillin on the complications of pain and secondary hemorrhage.

Design: This is a randomized, double-blind, placebo-controlled, prospective trial

Outcome measures: The incidence and severity of post-operative hemorrhage was measured as well as postoperative pain.

Methods: For the first 10 post-operative days patients provided a linear pain score, a record of GP visits, and their use of additional antibiotics and analgesics.

Results: Of 95 patients considered: 23 suffered a secondary hemorrhage; 54 consulted their general practitioner (GP) because of pain; additional antibiotics were used by at least 31 and additional analgesics by at least 41.

Conclusions: No significant differences were demonstrated between the active and placebo groups for any of these measures. This study demonstrates that secondary hemorrhage is common after adult tonsillectomy. Postoperative pain remains a major problem requiring frequent GP consultations. There appears to be no justification for the routine use of

perioperative antibiotics

Although there may be some benefits with post-tonsillectomy use of antibiotics, these need to be weighed against the potential side effects of the medications. Although the antibiotics are being used to possibly decrease morbidity resulting from tonsillectomy, a fairly significant percentage of patients will likely be subject to adverse effects of the medication with the most prevalent being diarrhea. This is especially common with Augmentin. However, more life-threatening effects are rare.

Summary

Children who receive dexamethasone perioperatively during tonsillectomy usually have less morbidity than those who do not receive dexamethasone, especially a reduction in nausea/vomiting. As for adults, there have been studies using a single dose of intraoperative dexamethasone (although few) that demonstrate a reduction in postoperative morbidity. Important to note, however; is the fact that this benefit is not evident when the steroids are given as a postoperative course. When it comes to antibiotics in both populations, it seems that pain is not significantly reduced although earlier returns to normal diet and activity are achieved.

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