2018

Are Cox-2 Inhibitors Such as Celecoxib and Parecoxib Effective in Reducing Post-tonsillectomy Pain?

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Are Cox-2 Inhibitors Such as Celecoxib and Parecoxib Effective in Reducing Post-tonsillectomy Pain?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 15, 2017

Abstract

Objective: The objective of this selective EBM review is to determine where or not "Are Cox-2 inhibitors such as celecoxib and parecoxib effective in reducing post-tonsillectomy pain?"

Study Design: Review of three double blind randomized controlled trials (RTC).

Data Sources: All studies were published in peer-reviewed journals found via the use of PubMed.

Outcomes Measured: Patients were divided into two groups: those who received the Cox-2 inhibitor and those who received the placebo, in order to measure postoperative pain using patient or parent reported journals or diaries, questionnaires, and various pain scales (CHEOPS, and WP24HR with VAS).

Results: Two out of three studies show a modest, but clinically significant decrease in pain post tonsillectomy with or without adenoidectomy. However, one study did not show a change in pain scores between the Cox-2 group and the placebo. Using parecoxib as the drug, Li X showed Group P had significantly lower CHEOPS scores than Group S (7 [5-8] vs. 9 [8-11] respectively. P=0.001). Murto et al showed the celecoxib group resulted in an 11% reduction in WP24HR score averaged over POD 0-2 (95% CI: 0.3-14. P=0.04) and additionally a 14% increase in WP24HR pain scores on POD 3 after the cessation of the intervention. Van Daele et al did not show a statistically significant decrease in pain between the two groups even though the scores for the intervention group were generally lower than the placebo.

Conclusions: Two out of the three randomized controlled trials studied reported statistically significant decrease in pain post tonsillectomy with or without adenoidectomy in the intervention group versus the placebo. Van Daele et al concluded that there was no statistical significant decease in pain between the two groups, however, this study used patients eighteen and older, which varied from the other studies. With this information it can be concluded that in children aged two to eighteen, Cox-2 inhibitors do show a statistically significant decrease in pain post tonsillectomy. Further studies are warranted in order to determine significance in an older patient population.

Key Words: Cox-2 inhibitors, pain, and tonsillectomy

Introduction

Tonsils are two clusters of soft tissue located on both sides of the posterior throat. Tonsillectomies are a surgical procedure used to remove the tonsils for various reasons including recurrent tonsillitis, recurrent pharyngitis, and obstructive sleep apnea[1]. Over the years much has changed in terms of procedure, guidelines, and recovery. In 2011, American Academy of Otolaryngology released a clinical practice guideline to help physicians and parents better understand the indications of surgery and to better optimize the before and after care of patients undergoing a tonsillectomy[2]. Every patient undergoing a tonsillectomy experiences post-operative pain that is monitored and treated appropriately. Cyclooxygenase-2 (Cox-2) inhibitors are a type of NSAID that selectively blocks only the Cox-2 enzyme, which is usually responsible for the pain and swelling associated with inflammation[3]. These drugs are different than other NSAIDs, which block both Cox-1 and Cox-2 enzymes. In previous studies, 15 out of 20 have shown that when used preoperatively, COX-2 inhibitors, specifically celecoxib, are better with postoperative pain as compared to a placebo[4]. This paper evaluates three double blind randomized controlled trials that compare the efficacy of celecoxib and parecoxib (Cox-2 inhibitors) as medication to reduce post-operative pain after a tonsillectomy.

This topic is relevant to the PA scope of practice because it is important for a PA to determine the indications for surgery, and how to care for patents pre- and post -operatively. In the United States, tonsillectomies are the 3rd most common procedure performed on children or about 530,000 a year, 186,000 being performed on patients 15 years or older[4]. Patients aged 15 or younger make up 20% of all otolaryngology visits a year, patients aged 15-24 makes up 7% and patients aged 25-44 makes up 21%[5].

In the United States the cost of a tonsillectomy varies based on your location and type of insurance. There are a variety of different elements that contribute to the overall cost that

patients often do not factor in, including but not limited to, the pre-operative appointment, the post-operative appointment, if necessary antibiotics and additional any visits to deal with complications. Overall, the cost for uncomplicated tonsillectomy was around $3,832, while the cost for tonsillectomies with complications was $6,388 for hemorrhage, $5,753 for dehydration, and $4,708 for pain[6].

There are a multitude of complications associated with tonsillectomies each with their own treatment and risks. An important obstacle facing healthcare professionals is finding the best post-operative medical management to control pain with minimal side effects. Independent of the technique used, substantial pain, decreased diet and reduced activity are seen. Regardless of the age of the patient, adequate pain control is needed in order to ensure the patient stays hydrated and makes a full recovery as soon as possible[5]. Cox-2 inhibitors are not commonly used as a post-operative medication to treat pain. Instead, patients use a combination of acetaminophen and ibuprofen and on rare occasions morphine to reduce pain[6]. As stated previously, Cox-2 inhibitors work solely on the Cox-2 enzyme, which is usually responsible for the inflamed tissue. Cox-2 inhibitors have been indicated to treat acute pain as well as pain secondary to arthritis. Consequently, they could be beneficial after a surgery where there is a significant amount of inflammation causing prolonged pain for the patient.

Objective

The objective of this selective EBM review is to determine whether or not "Are Cox-2 inhibitors such as celecoxib and parecoxib effective in reducing post-tonsillectomy pain?"

Methods

The studies used in this systematic review included three double blind, randomized controlled studies. The population included males and females aged 2-32 undergoing an elective tonsillectomy with or without an adenoidectomy. Two of the studies used varying doses of

celecoxib, while one study used parecoxib as their Cox-2 inhibitors. Li X[8] used intravenous parecoxib sodium 1 mg/kg. Murto et al.[9] used celecoxib 6 mg/kg preoperatively, followed by 3 mg/kg twice a day for five doses. Van Daele et al.[4] used 200 mg celecoxib with a loading dose the night before the surgery then twice daily for ten days. Subjects in this study were also instructed to supplement the study drug with hydrocodone/acetaminophen liquid as needed. The population was compared to a blind placebo group in all three trials. The outcome measured in the studies was the average post-operative pain using various methods.

All three articles were published in English. Murto[9] was co-published in French. They were all found in peer-reviewed journals using PubMed as the database. All studies were found using keywords "tonsillectomy", "Cox-2 inhibitor" and "pain" and were chosen based on relevance to the clinical question and importance of outcome to patient (POEM). Inclusion criteria consisted of any randomized, controlled, and double or single blind trial published after 2006 that used a Cox-2 inhibitor for post-tonsillectomy pain**.** Studies were excluded from the analysis if they did not use a Cox-2 inhibitor for pain control post operatively. All of the studies used P-value as the statistic to evaluate the outcomes, where the P-value is statistically significant if it is less than or equal to 0.05. See Table 1 below for the specific demographics and characteristics of the studies included.

Table 1: Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/ D	Interventions
Li X [8]	Double blind placebo-controlled randomized clinical trial	60	3-7	Children aged 3-7 years, and scheduled for elective tonsillectomy , with or without adenoidectomy under general anesthesia.	Allergy to the Medications, serious CV disease, liver or kidney dysfunction, coagulation disorders, asthma, or an upper respiratory infection.	0	Received IV Parecoxib sodium 1 mg_ kg-1 or the same volume of saline just after induction of general anesthesia.
Murto[9]	Double Blind randomized Controlled study	282	2-18	Children (age 2-18 yr.) scheduled for elective surgery were enrolled over a three-year period (2009-2012).	-Extremes BMI, abnormal blood work, moderate to severe OSA, any CI to NSAIDs, allergy to sulfa, risk of pregnancy, recently received CYP2C9 inhibitors or inducers, language barrier, and parent/ participant cognitive impairment.	87	Study participants received either placebo or an adult dose equivalent of celecoxib (6 mg_ kg-1) preoperatively, followed by 3 mg_ kg-1 twice daily for five doses postoperatively
Van Daele [4]	Randomized Double Blind Placebo Controlled Trial	17	18+	Minimum age of 18 years and medical indication for tonsillectomy	Hx of bleeding disorder, liver /kidney, CV disease, allergy/reaction to sulfa, NSAIDs, Cox-2, pregnant, abnormal lab values, anyone currently taking celecoxib, anyone on warfarin therapy, uncontrolled HTN.	0	Were randomized to 200 mg celecoxib versus placebo with a loading dose the night before surgery then twice daily for 10 days

Outcomes measured

The outcome measured in all three studies was post-operative pain. In Li X[8] the outcome was measured using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS). The CHEOPS is a behavior scale used to monitor pain and discomfort in children after surgery. In

Murto[9] the mean "worst 24-hr pain" (WP24HR) scores were recorded on post-operative day (POD) 0-2 on a visual analogue scale (VAS) that was modified to reflect pain in the last 24 hours instead of seven days. Zero was associated with a figure and wording and indicated no pain, while 100 was similarly displayed and indicated severe pain. Children over five years old self reported their scores, while participants younger than five were evaluated with a postoperative parental pain measure modified to reflect the WP24HR by assessed twelve different behaviors to a checklist. Scores were deemed clinically significant if it was greater than or equal to 10 mm on a VAS or a 10-20% reduction in pain. Lastly, in Van Daele et al[4] the outcome was evaluated using participant recoded diaries with average daily pain, maximal daily pain, and pain after eating.

Results

In the Li X [8] randomized control trial, 60 children aged 3-7 receiving elective tonsillectomies were studied. As shown in table 1, patients were excluded if they have asthma, an upper respiratory infection, and coagulation disorder, among others. This was to ensure patient safety with anesthesia throughout the procedure and recovery period. They were randomly split into two equal groups (group P and group S), each similar with respect to age, weight, gender, surgical indication, and duration of surgery. Patients received either intravenous parecoxib sodium 1mg/kg (Group P) or the same volume of saline (Group S) just after induction of general anesthesia. After surgery the patients were taken to the PACU where they were assessed every five minutes for the first fifteen minutes and every fifteen minutes thereafter. Upon arrival to the surgical ward the patients were evaluated, they were also evaluated at 4, 8, 12, 16, 20, 24 hours, with pain being estimated with the CHEOPS. The highest pain scores were recorded and used in the final analysis. If the patients CHEOPS score was less than or equal to 8, they received morphine 25 ug/kg as a rescue medication. As shown in table 2, the CHEOPS

scores in the PACU of the patients in Group P were significantly lower than Group S (7 [5-8] vs. 9 [8-11] respectively. P=0.001). However, in the ward, the CHEOPS scores were similar between the two groups. Also, patients in Group P received a statistically significantly lower number of doses and amount of the rescue morphine for their pain (P=0.024). Overall, 57% of participants in the parecoxib group, vs. 83% of participants in the saline group used rescue morphine. Therefore, the NNT is 4 (table 3), indicating that for every 4 patients treated with parecoxib instead of saline, one fewer patient will experience a reduction in pain compared to those treated with saline.

Table 2: The number of children receiving rescue morphine, and CHEOPS scores in patients who received parecoxib sodium (group P) or saline (group S)

	Group P (n=30)	Group S (n=30)	Relative risk 95% CI	P-Value
PACU CHEOPS	7 (5-8.3)	9 (7.8-11)		0.001
Ward CHEOPS	4 (4-7)	5 (5-7.3)		0.29
# of children who received rescue morphine	17/30 (57%)	25/30 (83%)	1.5 (1-2.1)	0.024

Table 3: NNT of 4, indicating for every 4 patients who received parecoxib instead of saline, one fewer patient will experience a reduction of pain

CER	EER	Absolute risk reduction (ARR)	Numbers needed to treat (NNT) 1/ARR
83%	57%	.26	4

In Murto et al.[9] there was initially 282 children enrolled, of that 195 were included in the outcome analysis (celecoxib=101 and placebo=94). Of the 141 participants initially allocated to the celecoxib group, 31 were lost to follow up or discontinued the intervention and of the 141 in the placebo group, 38 participants were lost. The patients were randomized and the celecoxib group received 6 mg/kg preoperatively, followed by 3 mg/kg twice a day for five doses. The control group received OraBlend and a calcium carbonate excipient, which was identical in

appearance and taste of the drug being studied. WP24HR scores were reported on POD 0-2. There was a 95% drug compliance rate with those participants who returned their diaries. The study used parent reports of pain instead of child using an intra-class correlation coefficient (ICC with 95% CI: 0.75-0.82). The ICC is to measure the reliability of the measurement used. The data showed the celecoxib group resulted in an 11% reduction in WP24HR score averaged over POD 0-2 (95% CI: 0.3-14. P=0.04). The breakdown of POD 0-2 individually is shown in table 3. Furthermore, once the celecoxib was discontinued on POD 3, there was a 14% increase in WP24HR compared to the placebo group. Additional, acetaminophen and morphine consumption on POD 0-2 was lower in the celecoxib group (P=0.03 and P=0.06 respectively). Since the p-value is greater than 0.05 the data is not statistically significant. Overall, the incidence of adverse events between both groups was not significant, as was patient fatigue and parent satisfaction.

Table 3: Parent report of post-adenotonsillectomy pain score on 100-mm VAS on POD 0-2. WP24HR (95%CI))

	Celecoxib	Placebo	P-value
POD 0	50 (44-57)	62 (56-69)	0.01
POD 1	64 (59-70)	75 (69-80)	<0.01
POD 2	63 (58-68)	64 (59-70)	0.70

Van Daele et al.[4] was the only study of the three that used adults 18 or older. There were 17 patients selected for the study and 15 analyzed for the data (celecoxib=9 and Placebo=6). Two patients were lost due to discontinued intervention from the placebo group. Patients were excluded from this study if they had uncontrolled hypertension, were pregnant or could be pregnant, on warfarin therapy, among others. These exclusion criteria differed from the other studies due to the average age of the population being studied. This study also used two different

methods for the tonsillectomy, the bipolar cautery (9 subjects) and the monopolar cautery (8 subjects). Both methods were evenly spilt between the two groups. Each subject in the study provided had a self-reported journal with average daily pain, maximal daily pain, and pain after eating on a scale of 0-10. As well as any addition medication (acetaminophen or morphine) used for pain. The pain score were generally lower, but not statistically significant in the celecoxib group as compared to the placebo. There was a significantly lower amount of morphine and acetaminophen used in the celecoxib group (P=0.032). The average pain on day 0 was also slightly lower in the celecoxib group with a P value of 0.442.

Table 4: Maximum pain and total addition morphine use of celecoxib vs. placebo on POD 0-7. (Modified from the study, which showed data for POD 1-10)

		Celecoxib n=9	Placebo n=6	95% CI		
	Day	Mean	Mean	Lower Limit	Upper Limit	P Value
Max Pain	Day 1	5.0	6.0	-3.5	1.5	.918
	Day 2-4	5.1	6.0	-3.2	1.4	.918
	Day 5-7	4.4	5.9	-2.7	1.9	.435
	Treatment x day interaction P=0.67					
		Celecoxib n=9	Placebo n=6	95% CI		
	Day	Mean	Mean	Lower Limit	Upper Limit	P Value
Total Morphine equivalent	Day 1	28.9	55.0	-72.9	20.7	.209
	Day 2-4	30.4	72.4	-81.4	-2.6	.032
	Day 5-7	27.8	69.7	-81.4	-2.5	.032
	Treatment x day interaction P=0.036					

Discussion

The studies presented conflicting evidence, as two out of the three showed that a Cox-2 inhibitor could significantly help with pain post tonsillectomy with or without adenoidectomy. Van Daele et al[4] showed that celecoxib did not significantly decrease pain post tonsillectomy,

however it did show a statistically significant increase in acetaminophen and morphine use in the placebo group compared to the celecoxib group. Although overall pain scores were not significant, the data suggests patients in the placebo group may have used more pain relieving drugs in order to reach a common pain level with the celecoxib group. As shown in table 1, and stated previous, Van Daele et al[4] used a study population of 18+ that included adults, which could have also contributed to the varying results. Both Li X[8] and Murto[9] showed that, although minimal, there was a clinically significant decrease in pain scores from the Cox-2 group versus the placebo.

Cox-2 inhibitors have been used to decrease pain and inflammation for many conditions, such as rheumatoid arthritis, osteoarthritis, juvenile idiopathic arthritis ankylosing spondylitis and primary dysmenorrhea[3]. There were two different Cox-2 inhibitors used in the studies. The most common adverse effects of celecoxib are headache, nausea, diarrhea, abdominal pain and insomnia[10]. NSAIDs have a black box warning for increasing the risk for myocardial infraction, stroke, and serious stomach and intestine bleeding, ulceration or perforation. This drug should only be used in pregnant women when the benefits outweigh the risks[10]. Parecoxib, used in Li X[8], is indicated for short-term treatment of postoperative pain in adults. The most common side effect is nausea and should not be used in people who are allergic to any of the components, have had a myocardial infarction, or stroke or liver disease[11].

There were many limitations found in this review. In both Li X[8] and Van Daele et al[4] the population size studied was very small with 60 people in Li X and just 17 in Van Daele. Li X[8] also discussed a few limitations of their study. Using the CHEOPS for the assessment of pain in children aged three to seven is controversial and does not correlate with the self-reported pain measures in children[8]. They also talk about the use of remifentanil for the tonsillectomy, instead

of fentanyl, which is associated with higher postoperative pain scores, as well as the use of morphine at the end of surgery to reduce the need for postoperative rescue analgesics. Lastly, this study talks about the limitations with the safety of the drug parecoxib and the need for further study to discover the optimal dose to reduce postoperative pain. In Murto[9] they discussed limitations such as the refusal and dropout rate due to the length of the study and the use of an unapproved drug to manage pain in children. It also discussed the use of WP24HR to report pain as a subjective measurement that relied on the recall of the patients or the parents. However, the single assessment for pain was clinically significant and was less likely to miss severe pain associated with recent analgesic use or by using predetermined intervals as a measurement[9]. In all three studies another limitation was that pain could not accurately be determined due to the morphine and/or acetaminophen used in conjunction. Also, the amount of the drug used and at what times varied from study to study.

Conclusion

The evidence put forth in the three studies shows conflicting results, which warrants further research regarding the use of Cox-2 inhibitors for post-tonsillectomy pain. Li X[8] and Murto et al[9] both concluded that the use of a Cox-2 inhibitors does reduce pain post-tonsillectomy. Van Daele et al[4] concluded there was no statistically significant decrease in pain, but there was a statistically significant increase in postoperative narcotic and acetaminophen use in the placebo group for pain. Due to the difference in population and size of Van Daele et al[4], it can be said that Cox-2 inhibitors does decrease pain post-tonsillectomy with or without adenoidectomy in children aged two to eighteen, but further testing is necessary for the adult population. These studies looked at pain and co-analgesic consumption in the early stages of recovery, therefore, more research should be done to observe sustained pain relief and optimal

medication dose. These studies should consider using the intervention for a longer period of time with a standard dose throughout to ensure validity of the study. The average patient undergoing a tonsillectomy is in the pediatric population, consequently it is difficult to further study the adult population due to low number of tonsillectomies in the population.

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