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Evaluation of Postoperative Efficacy and Safety of Celecoxib in Children Hospitalized After Adenotonsillectomy

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OBJECTIVE The choice of optimal analgesia following an adenotonsillectomy is a clinical issue because of the risk of respiratory depression and bleeding. The objective of this study was to assess the effect of celecoxib on opioid use and pain scores in children hospitalized after adenotonsillectomy and to document its adverse effects.

METHODS This retrospective study was conducted in a tertiary care pediatric hospital. We compared a group of subjects aged 1 to 17 years who were prescribed celecoxib and opioids between January 2017 and June 2020 following an adenotonsillectomy during a 3-day or less hospitalization to a group of matched controls for sex, age, and length of stay who were prescribed opioids.

RESULTS A total of 228 patients were identified (76 in the celecoxib + opioids group, 152 in the control group). Opioid use, in oral morphine equivalent daily dose, was lower in the celecoxib + opioids group at 0 to 24 hours of hospitalization (0.15 vs 0.20 mg/kg/day, p = 0.05). Initiating celecoxib within 24 hours of surgery (n = 60) significantly reduced opioid requirement for up to 48 hours compared with controls (0–24 hours: 0.12 vs 0.20 mg/kg/day, p = 0.002; 25–48 hours: 0.02 vs 0.09 mg/kg/day, p = 0.001). A shorter length of stay was observed for patients receiving celecoxib + opioids during the first 24-hour post-operative period (27 vs 32 hours, p = 0.01). With celecoxib use, no significant change in pain scores and occurrence of adverse effects including bleeding was found.

CONCLUSIONS Using celecoxib early after an adenotonsillectomy has reduced both opioid use and duration of hospital stay without increasing adverse effects or bleeding.

ABBREVIATIONS AT, adenotonsillectomy; COX-2, cyclo-oxygenase-2; MEDD, oral morphine equivalent daily dose; NSAIDs, nonsteroidal anti-inflammatory drugs

KEYWORDS adenotonsillectomy; celecoxib; morphine; nonsteroidal anti-inflammatory agents; opioid; pediatrics

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Introduction

Adenotonsillectomy (AT) is a common pediatric surgery associated with severe acute pain requiring substantial postoperative analgesia to ease food intake and prevent dehydration.[1–4] Furthermore, the risk of respiratory complications with this intervention in the pediatric population is an important factor in the choice of analgesia.[5] Sleep apnea, one of the main indications of AT, increases the risk of respiratory depression.[6–11] Opioids has been associated with an increased risk of respiratory depression and mortality after AT, particularly in children.[8,9,12–14] However, morphine is often preferred over nonsteroidal anti-inflammatory drugs (NSAIDs) because of the hemorrhagic risks associated with the latter when used after AT.[1,15–19]

The safety of NSAIDs has been demonstrated, and they are recommended by the American Academy of Otolaryngology-Head and Neck Surgery, but their role in the postoperative period remains limited because of conflicting data.[1,12,20–22] Celecoxib acts by inhibiting cyclo-oxygenase-2 (COX-2) with minimal impact on platelet function and has the potential to significantly reduce the need for postoperative opioid utilization without increasing the risk of bleeding.[23,24]

There is no formal recommendation for pediatric dosage of celecoxib after AT or any other surgery. The only published study evaluating the use of celecoxib after AT in children reported a dosage of 3 mg/kg twice daily and reported no significant difference in opioid use.[25] This study excluded children with severe sleep

apnea, for whom a short hospital stay post-AT is recommended.[1,25,26] Due to the increased risk for respiratory depression associated with opioids in this population, it is of interest to minimize their exposure and determine if an adjuvant drug (celecoxib) would be beneficial.[8,9,26] The purpose of the present study was to evaluate the impact of celecoxib administration on opioid use and pain scores post-AT and describe adverse events associated with use of celecoxib.

Materials and Methods

Study Design. This observational retrospective study was conducted at the Centre Mère-Enfant of the CHU de Québec-Université Laval, a Canadian pediatric tertiary care hospital. A group of children who received celecoxib post AT was compared with matched controls who underwent AT but did not receive celecoxib.

Participants. Subjects aged 1 to 17 years old, who were admitted for 3 days or less following an AT or a tonsillectomy between January 1, 2017, and June 19, 2020, were eligible for the study. Patients who were prescribed celecoxib on an as needed or scheduled basis by an otolaryngologist (ENT) specialist and an as needed opioid were assigned to the treatment group (celecoxib + opioids). Patients who received celecoxib were identified using the pharmacy software GesphaRx (version 8, CGSI@solutions-ti Inc., Canada) and Syphac (version 1.8.0.0.0069, Logibec, Canada). Decision to initiate and timing of initiation of celecoxib were up to the discretion of the clinical team. The celecoxib + opioids group was divided based on celecoxib timing of initiation after surgery (before and after 24 hours post-operation). Patients assigned to the celecoxib + opioids group were matched to 2 control patients based on sex, age, and length of stay. Subjects who were not prescribed an as needed opioid were not considered for matching. To identify all potential control patients for matching, the institution medical records department extracted a list from the MED-ECHO clinical-administrative database with patients aged between 1 and 17 years who underwent an AT or a tonsillectomy and were admitted for a short-term hospitalization, for example, 1 to 3 days, at the Centre Mère-Enfant between January 1, 2017, and March 31, 2020. In our institution, AT patients were hospitalized for at least 1 of the following reasons: age < 3 years old, moderate to severe sleep apnea (defined by more than 3 events of oxygen saturation less than 85%), presence of 1 or more significative comorbidity (e.g., obesity, mucopolysaccharidosis) and/or home more than an hour away from the hospital. Patients with coagulation disorders were included in analysis. Renal and hepatic function of patients were not considered for inclusion or exclusion in the study. Children hospitalized for more than 3 days were excluded due to a higher prevalence of complications (e.g., postoperative bleeding) in these patients, which may be a confounding factor.

Data Collection. The following baseline characteristics were collected for all participants from their electronic medical records: demographic data, risk factors for respiratory depression (craniofacial abnormalities, CHARGE syndrome, Prader-Willi syndrome, Stickler syndrome, mucopolysaccharidosis, increased body mass index, respiratory disorders including obstructive sleep apnea, neuromuscular disorders), bleeding risk (hematological disorders, hemoglobin at admission), heart disease, medications at home (NSAIDs, corticosteroids, acetaminophen or opioids), AT surgical technique (hot or cold), duration of anesthesia, surgical blood loss and administration of opioids, ketorolac or dexamethasone in the recovery room. Cold technique, performed by 1 ENT specialist in our institution at the time of the study, consisted of creating knots in blood vessels to stop bleeding rather than using electric cautery and might be associated with less pain. All post-operative pain scores were obtained from a standardized form used for monitoring opioids analgesia in our institution. The following pain scales are used at our institution: Face, Legs, Activity, Cry, Consolability (FLACC) scale for young children (0–6 years old), Faces Pain Scale – Revised (FPS-R), numerical rating scale (NRS) or visual analog scale (VAS) for older children (7 years old and over). Every pain score recorded for a patient is converted on a scale of 0 to 10 (0 for no pain, 10 for being the worst pain), by the nursing staff. Frequency of assessment is standardized according to pain scores (e.g., assessed more frequently if acute pain), time to peak concentration of the opioid administered and route of administration. In addition, the following information was collected: celecoxib dosage, administration of a loading dose, dose (mg/kg), frequency of administration (including scheduled and as needed doses) and duration of treatment. Co-administration of NSAIDs, corticosteroids, and acetaminophen (mg/kg/day) during hospital stay was also documented. Daily opioid administration frequency and oral morphine equivalent daily dose (MEDD) in mg/kg/day were collected. Conversions used for 1 mg of oral morphine were parenteral morphine 0.33 mg; oral hydromorphone 0.23 mg; and parenteral hydromorphone 0.06 mg.[27,28] The data were collected in 24 hours increments after return from the recovery room. Data collected on the day of patients' medical discharge were included in the corresponding 24-hour period, even if departure occurred before the end of this period. The words "nausea, vomiting, diarrhea, rash, abdominal pain, gastroesophageal reflux or dyspepsia, headache, constipation, confusion" in the medical notes were used to identify adverse effects, as were anti-nausea medication administrations (ondansetron and dimenhydrinate). The word "bleeding" in the medical notes

was associated with a bleeding occurrence if it was "active," "light red," or when a medical evaluation by the attending physician was required. Bleeding that possibly occurred during surgery was not considered. The elapsed time between bleeding and surgery and celecoxib initiation was also collected. Emergency room visits or hospitalizations at the CHU de Québec-Université Laval for bleeding within 10 days after discharge were recorded. Adverse effects on vital signs (hypotension, hypertension, and decrease in saturation requiring oxygen) were collected from nursing notes. Constipation and need for oxygen administration were considered as adverse effects of special interest associated with taking opioids.

Objectives of the Study. The primary objective was to assess whether adding celecoxib to the standard analgesic treatment reduced the need for opioid use in children hospitalized after AT. Secondary objectives were to assess the effect of celecoxib on pain scores and document its adverse effects.

Statistical Analysis. Based on a review of opioid use after AT in our hospital, we postulated that a decrease in MEDD from 0.35 to 0.25 mg/kg/day and a 33% reduction of daily opioid administration (3 to 2 doses/day) frequency within the celecoxib + opioids group would be clinically significant. A sample size of 75 cases (celecoxib + opioids group) and 150 matched controls was calculated to detect these differences with 80% power, assuming a 5% α-error.

Data were analyzed using descriptive analysis. Discrete variables, including baseline characteristics and occurrence of adverse events, were compared with the χ^2 test, while the continuous variables, including mean MEDD, mean number of opioids doses, and mean pain scores, were compared using the Student *t* test. $P < 0.05$ was considered statistically significant for all analyses. Analyses were not adjusted to account for multiplicity. The XLSTAT Microsoft Excel version 16.32 was used for analysis. Missing data were not considered in the statistical analysis.

Results

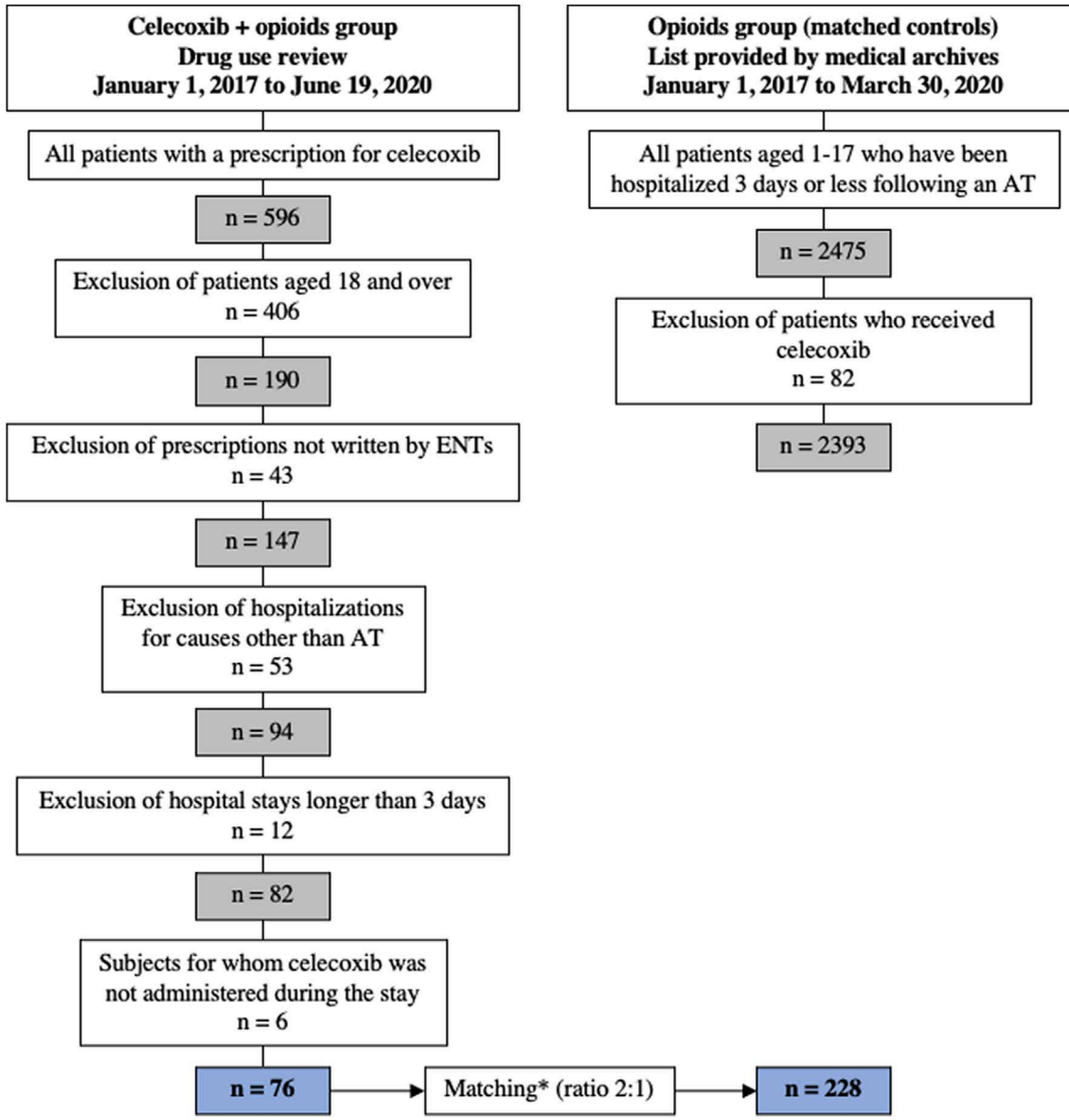
A total of 76 patients who received celecoxib + opioids and 152 matched controls who received opioids were included in the study (Figure 1). The 2 groups were similar in all of their baseline characteristics except for perioperative blood loss that was statistically significantly higher in the control group (Table 1). Most of the patients had a diagnosis of suspected or confirmed sleep apnea (92% of celecoxib group and 91% of controls). Among patients in the celecoxib + opioids group, 60 (79%) initiated celecoxib within 24 hours, 11 (14%) between 25 and 48 hours, and 5 (7%) between 49 and 72 hours after discharge from recovery room.

Primary Objective. In the celecoxib + opioids group, opioid use was lower than in the control group in the first 24 postoperative hours only (mean MEDD: 0.15 mg/kg/day vs 0.20 mg/kg/day, p = 0.05) (Figure 2). Opioid exposure in patients who started celecoxib within 24 hours of the procedure was reduced throughout the stay compared with controls, mostly at 0 to 24 hours post-operation (0.12 mg/kg/day vs 0.20 mg/kg/day, p = 0.002) and 25 to 48 hours post-operation (0.02 mg/kg/day vs 0.09 mg/kg/day, p = 0.001). Opioid exposure in patients who started celecoxib early was also lower than for the whole celecoxib + opioids group and patients who started celecoxib after 24 hours (Figure 2). Opioid use for patients who started celecoxib after the initial 24 post-operative hours was higher than for controls throughout the hospitalization: 0.27 mg/kg/day vs 0.20 mg/kg/day, p = 0.09 (0–24 hours), 0.25 mg/kg/day vs 0.09 mg/kg/day, p < 0.01 (25–48 hours) and 0.14 mg/kg/day vs 0.04 mg/kg/day, p = 0.01 (49 hours and more) (Figure 2). Mean duration of hospital stay for subjects who initiated celecoxib within the first 24 hours post-surgery was significantly reduced compared with both those who initiated after 24 hours (27 vs 62 hours, p < 0.01) and controls (27 vs 32 hours, p = 0.01). Mean duration of hospital stay for subjects who initiated celecoxib after 24 hours post-surgery was significantly longer than for controls (62 vs 32 hours, p < 0.01).

There was no statistically significant difference in the mean MEDD for the entire hospital stay according to age group. Mean opioid exposure for children aged from 1 to 7 years was 0.12 mg/kg/day for the celecoxib + opioids group and 0.15 mg/kg/day for controls (p = 0.14). Mean opioid exposure for the 8 to 17 years of age group was respectively 0.22 mg/kg/day and 0.14 mg/kg/day (p = 0.09).

Mean time before initiation of celecoxib after discharge from the recovery room was 16 hours with a range from 0 to 72 hours. Table 2 describes the characteristics of celecoxib administration. The mean weight-based celecoxib dose prescribed for children 1 to 12 years of age was significantly higher than for the 13- to 17-year-old age group (3.0 ± 0.7 mg/kg/dose vs 1.4 ± 0.5 mg/kg/dose, p = 0.001). The mean celecoxib daily dose within 0 to 24 hours following discharge from recovery room for patients started on celecoxib during this period was 5.0 ± 2.5 mg/kg/day, which was prescribed at a mean weight-based dose of 2.9 mg/kg/dose and administered at a mean of 1.7 doses/day. The coadministration of other NSAIDs and acetaminophen for co-analgesia was similar between groups. No patient in the control group received any NSAID. However, the incidence of dexamethasone administration during hospital stay trended upwards in the celecoxib + opioids group, with a significantly higher incidence of use at 49 hours and beyond (16% vs 14%, p = 0.69 at 0–24 hours; 15% *vs* 9%, p = 0.17 at 25–48 hours; 4% vs 0%, p = 0.01 at 49 hours and more). Within the celecoxib + opioids group, 7 patients (64%) who received dexamethasone at 25 to 48 hours post-operation and 3 patients (100%) who received

Figure 1. Selection and recruitment of the subjects.



AT, adenotonsillectomy; ENT, otolaryngologist.

* All included patients who were prescribed celecoxib (n = 76) were also prescribed an as needed opioid. Hence, subjects who were not prescribed an as needed opioid were not considered for matching. Patients who were prescribed celecoxib + opioids were matched with controls by gender, age, and length of stay with a 1:2 ratio. Sixty-nine (69) patients were matched according to all criteria. For 7 patients, either one or both of the matched subjects had a different length of stay or could not be matched by age.

dexamethasone at 49 hours post-operation and beyond initiated celecoxib after the first 24 hours. Overall, more patients who initiated celecoxib after 24 hours received dexamethasone during their hospital stay compared with controls (88% vs 22%, $p < 0.01$).

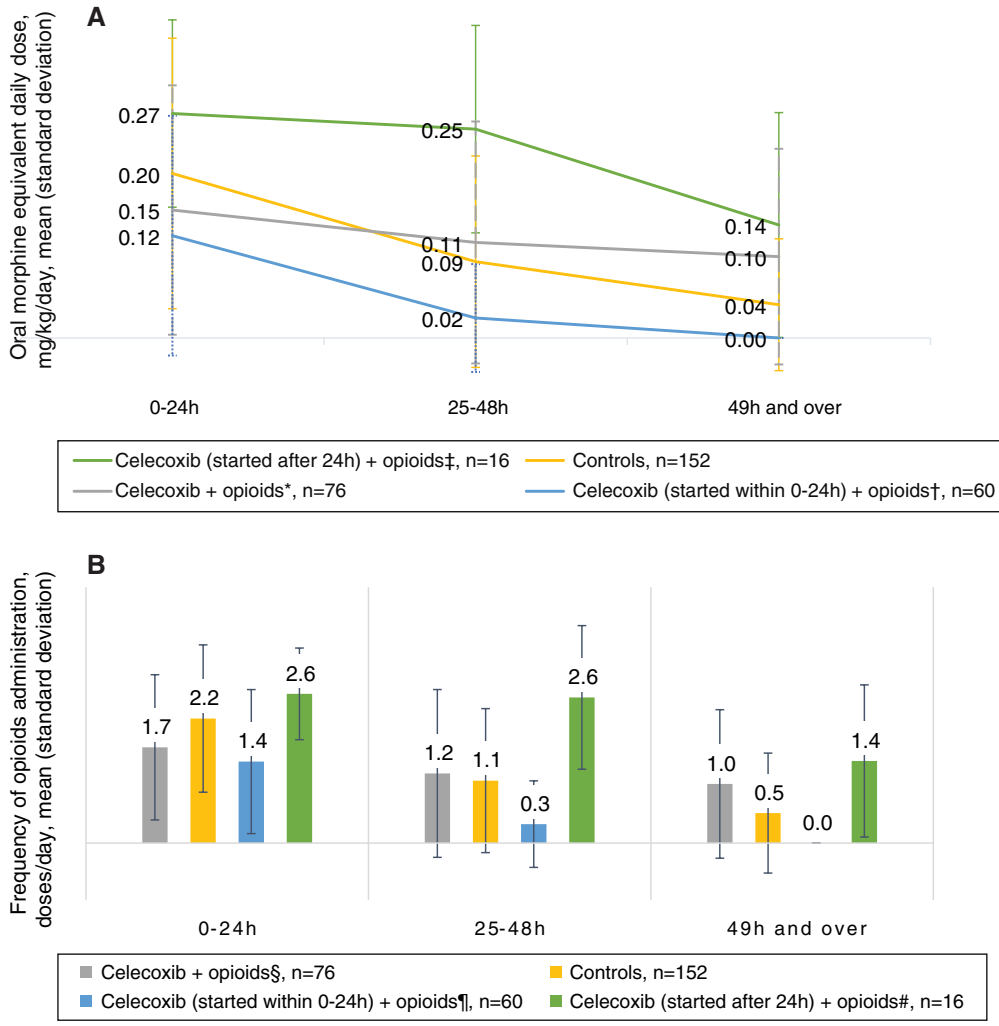
Secondary Objectives. There was no difference between the two groups for mean pain scores, all of which were less than 2 (1.0 vs 1.1 at 0–24 hours; 1.5 vs 1.5 at 25–48 hours; and 1.2 vs 1.4 at 49 hours and more). The incidence of adverse events was comparable between the 2 groups (Table 3). There was no significant difference between groups in terms of bleeding during hospitalization up to 10 days after discharge. Also, none of the bleeding that occurred during the hospital stay has been documented after the initiation of celecoxib.

Table 1. Sociodemographic and Clinical Characteristics of Children Hospitalized Postoperatively After Adenotonsillectomy

Characteristics	Groups		p value
	Celecoxib + Opioids (n = 76)	Controls (n = 152)	
Age, yr, mean (±SD)	4 (±3.0)	4 (±2.9)	
Age group, n (%)			
1–4 yr old	50 (66)	100 (66)	
5–7 yr old	17 (22)	34 (22)	
8–12 yr old	7 (9)	14 (9)	
13–17 yr old	2 (3)	4 (3)	
Age less than 3, n (%)	21 (28)	42 (28)	
Female sex, n (%)	35 (46)	70 (46)	
Body mass index percentile, mean (±SD)*	61 (±31)	57 (±32)	0.40
> 85th percentile, n (%)	15 (20)	24 (16)	
> 95th percentile, n (%)	5 (7)	15 (10)	
Surgical procedure, n (%)			
Adenotonsillectomy	67 (88)	128 (84)	0.42
Tonsillectomy	9 (12)	24 (16)	0.42
Cold technique	15 (20)	20 (13)	0.19
Respiratory disorders, n (%)	75 (99)	142 (93)	0.08
Asthma	20 (26)	42 (28)	
Bronchitis	5 (7)	8 (5)	
Recent lung infection	9 (12)	4 (3)	
Confirmed sleep apnea	37 (49)	85 (56)	
Suspected sleep apnea	33 (43)	53 (35)	
Cardiovascular disorders, n (%)†	6 (8)	10 (7)	0.71
Neuromuscular disorders, n (%)‡	6 (8)	13 (9)	0.87
Hematological disorders, n (%)§	0 (0)	6 (4)	0.30
Hemoglobin at admission, g/L, mean (min)¶	137 (137)	123 (111)	
Comorbidities with increased risk of respiratory depression, n (%)	0 (0)	5 (3)	0.11
Down syndrome	0 (0)	3 (2)	
Patau syndrome	0 (0)	1 (1)	
Prader-Willi syndrome	0 (0)	1 (1)	
Medication with an analgesic effect at home before surgery, n (%)	2 (3)	2 (1)	0.48
Nonsteroidal anti-inflammatory drugs#	1 (1)	2 (1)	
Corticosteroids**	1 (1)	0 (0)	
History of problems with anesthesia, n (%)††	4 (5)	4 (3)	0.31
Postoperative stay, hr, mean (±SD)	34 (±19)	32 (±17)	0.35
Duration of anesthesia, min, mean (median)‡‡	34 (30)	38 (32)	0.07
Blood loss in the operating room, mL, mean (median)§§	12 (3)	19 (7)	0.04
Analgesic medication in the recovery room, n (%)	38 (50)	68 (45)	0.40
Dexamethasone	1 (1)	2 (1)	
Opioids	39 (51)	69 (45)	
Ketorolac	0 (0)	0 (0)	

* Calculated for patients older than 1 yr with documented weight and height (53 subjects in the celecoxib group and 106 subjects in the control group).
† At least 1 among heart murmur, congenital malformation, valve disease, arrhythmia.
‡ At least 1 among epilepsy/convulsions, hypotonia, developmental delay, Spina bifida, cerebral palsy/paralysis, ataxia, muscular dystrophy.
§ At least 1 among anemia, Von Willebrand, hemophilia, Factor V Leiden.
¶ Data available for only 1 celecoxib patient and 6 matched subjects.
# Naproxen (celecoxib group), acetylsalicylic acid and indomethacin (matched group). Discontinued during hospitalization.
** Hydrocortisone. Continued during hospitalization.
†† The nature of the problem with anesthesia could not be specified.
‡‡ Missing data for 1 celecoxib patient and 1 matched subject.
§§ Missing data for 1 matched subject.

Figure 2. Post-operative opioid use following adenotonsillectomy per 24-hr hospitalization period. (A) Oral morphine equivalent daily dose received by patients in the celecoxib + opioids and control groups (MEDD). (B) Frequency of opioid administration in the celecoxib + opioids and control groups.



* Statistically non-significant difference for the mean MEDD when compared to opioids group at 0–24 hr (0.15 mg/kg/day vs 0.20 mg/kg/day, p = 0.05).

† Statistically significant difference for the mean MEDD when compared to opioids group at 0–24 hr (0.12 mg/kg/day vs 0.20 mg/kg/day, p = 0.002) and at 25–48 hr (0.02 mg/kg/day vs 0.09 mg/kg/day, p = 0.001); statistically non-significant difference at 49 hr and beyond (0.00 mg/kg/day vs 0.04 mg/kg/day, p = 0.20).

‡ Statistically non-significant difference for the mean MEDD when compared with opioids group at 0–24 hr (0.27 mg/kg/dose vs 0.20 mg/kg/dose, p = 0.09); statistically significant difference at 25–48 hr (0.25 mg/kg/day vs 0.09 mg/kg/day, p < 0.01) and at 49 hr and beyond (0.14 mg/kg/day vs 0.04 mg/kg/day, p = 0.01).

§ Statistically significant difference for the mean daily number of opioids doses received when compared with opioids group at 0–24 hr (1.7 doses/24 hr vs 2.2 doses/24 hr, p = 0.006).

¶ Statistically significant difference for the mean daily number of opioids doses received when compared with opioids group at 0–24 hr (1.4 doses/24 hr vs 2.2 doses/24 hr, p = 0.0001) and at 25–48 hr (0.3 doses/24 hr vs 1.1 doses/24 hr, p = 0.0007).

Statistically non-significant difference for the mean daily number of opioids doses received when compared with opioids group at 0–24 hr (2.6 doses/24 hr vs 2.2 doses/24 hr, p = 0.07); statistically significant difference at 25–48 hr (2.6 doses/24 hr vs 1.1 doses/24 hr, p < 0.01) and at 49 hr and beyond (1.4 doses/24 hr vs 0.5 doses/24 hr, p = 0.01).

Discussion

To our knowledge, our study is the first to highlight the potential role of early introduction (< 24 hours) of celecoxib in reducing opioids use and length of hospital stay in pediatric patients undergoing AT that required hospitalization for 3 days or less. Only one other study

Table 2. Celecoxib Administration in Postoperative Hospitalized Children Following Adenotonsillectomy

Administration of Celecoxib	Group	p value
	Celecoxib + Opioids (n = 76)	
Time to administration time after recovery room, n (%)		
0–24 hr	60 (79)	
25–48 hr	11 (14)	
49 hr and more	5 (7)	
Administration of a loading dose, n (%)	0 (0)	
Dose received by age group, mg/kg/dose, mean (±SD)		
1–4 yr old	3.2 (±0.5)	0.001*
5–7 yr old	2.5 (±0.6)	0.03†
8–12 yr old	2.7 (±1.1)	
13–17 yr old	1.4 (±0.5)	
Doses administered per day, mean (±SD)		
0–24 hr	1.4 (±1.0)	
25–48 hr	1.0 (±0.9)	
49 hr and more	0.8 (±0.8)	
Dose received by subjects who started celecoxib in 0–24 hr, mg/kg/dose, mean (±SD)		
0–24 hr	2.9 (±0.7)	
25–48 hr	3.0 (±0.5)	
49 hr and more	2.9 (±1.2)	

* Dose for the 1- to 4-yr-old group is statistically higher than for the 5–7 and 13- to 17-year-old groups.
† 5 to 7-yr-olds have a statistically higher dose than the 13- to 17-yr-old group.

has evaluated celecoxib for pain management after AT in children, but this study only included patients managed in the outpatient setting. Murto et al[25] presented in 2015, a prospective study using celecoxib (6 mg/kg preoperatively followed by a dose of 3 mg/kg, twice daily for 5 days vs placebo) in an outpatient setting with hospitalization as needed. In their study, patients with extreme body mass indexes and moderate-severe obstructive sleep apnea were excluded. They found a non-significant decrease in post-AT morphine consumption with celecoxib (0.56 mg/kg vs 0.70 mg/kg from day 0 to day 2 post-operation), when administered to the children in the outpatient setting by their parents.[25] These authors concluded that oral celecoxib provided a modest pain relief but that an increase in the dosage and frequency of administration of celecoxib should be evaluated in a future study.[25] The role of celecoxib to reduce opioid use had also been studied in the postoperative period of an adult population.[29]

Considering the recommended pediatric weight-based oral morphine doses for acute pain (0.1 to 0.3 mg/kg every 3 to 4 hours for patients without increased risk of respiratory depression), morphine exposure observed in our study was low (0.15 mg/kg/day vs 0.20 mg/kg/day at 0–24 hours) and included patients who were prescribed an as needed opioid but did not receive it, which may be explained by 1. increased risk of respiratory depression in hospitalized AT patients and 2. the trained hospital staff being aware of the added risk of opioid-induced respiratory depression.[1,30] In our study, daily opioid consumption at 25 to 48 hours and at 49 hours and beyond was lower than 0.10 mg/kg/day for both controls and subjects who started celecoxib within the first 24 hours post-operation. This could be explained by their short length of stay (32 hours vs 27 hours) and the fact that most patients were probably discharged at the beginning of the 25- to 48-hour period.

The reduced opioid requirement and shorter length of hospital stay when celecoxib was started within the first 24 hours could indicate a link between its initiation time and its anti-inflammatory effect following surgery. The expression of COX-2 is mediated by an increase in inflammatory cytokines, which peaks at about 18 to 24 hours post-operation.[31,32] Therefore, the introduction of celecoxib during this period could maximize its efficacy, which could explain why patients who received it after the initial 24 hours post-operation had higher opioid use and an extended length of stay compared to patients who initiated it at 0 to 24 hours post-operation. This also possibly explains the increased administration of dexamethasone beyond the initial 24 hours of hospitalization in the celecoxib group: about 64% of patients who received dexamethasone at 25 to 48 hours post-operation and 100% of patients who received dexamethasone at 49 hours post-operation and beyond had not started celecoxib during the first 24 hours. On the other hand, if celecoxib was not prescribed within the first 24 hours, celecoxib could have been initiated if the post-operative evolution was unfavorable, for example in case of uncontrolled pain or persistent difficulty eating or drinking fluids, which could explain why patients who started celecoxib after 24 hours received more dexamethasone, more opioids and had a longer length of stay than controls and those who started it before 24 hours.

In the present study, the mean daily dose of celecoxib on the first day post-AT received by patients who started within 24 hours post-operation was 5.0 mg/kg/day (mean dose of 2.9 mg/kg administered at a mean frequency of 1.7 doses/day), which may have positively influenced the course and duration of their hospitalization. This dosing ranges within the recommended dose for juvenile rheumatoid arthritis (2–5 mg/kg/dose).[33]

Table 3. Postoperative Adverse Effects in Children Hospitalized After Adenotonsillectomy

Adverse Effects*	Groups		p value
	Celecoxib + Opioids (n = 76)	Controls (n = 152)	
Bleeding during the postoperative stay, n (%) Bleeding requiring readmission to the operating room during the postoperative stay Bleeding after celecoxib initiation	4 (5) 1 (1) 0 (0)	10 (7) 0 (0) —	0.4
Emergency room consultation for bleeding within 10 days of discharge, n (%)	0 (0)	3 (2)	0.24
Hospitalization for bleeding within 10 days of discharge, n (%)	3 (4)	7 (5)	0.71
Diarrhea, n (%)	1 (1)	5 (3)	0.38
Abdominal pain, n (%)	4 (5)	8 (5)	1.00
Gastroesophageal dyspepsia or reflux, n (%)	0 (0)	1 (1)	0.48
Headaches, n (%)	0 (0)	1 (1)	0.48
Skin rash, n (%)	4 (5)	3 (2)	0.17
Nausea, n (%)	8 (11)	14 (9)	0.75
Vomiting, n (%)	19 (25)	39 (26)	0.91
Ondansetron administration, n (%) Number of administrations during hospitalization, mean (±SD)	14 (18) 1.64 (±1)	18 (12) 1.15 (±0)	0.18
Dimenhydrinate administration, n (%) Number of administrations during hospitalization, average (standard deviation)	7 (9) 1.4 (±1)	13 (9) 1.2 (±0)	0.87
Constipation, n (%)†	2 (3)	2 (1)	0.48
Oxygen administration for respiratory desaturation during hospitalization, n (%)†‡	6 (8)	22 (15)	0.26
Maximum systolic blood pressure recorded during hospitalization, mm Hg, mean (median)	125 (124)	127 (125)	0.23
Minimum systolic blood pressure recorded during hospitalization, mm Hg, mean (median)	88 (88)	91 (90)	0.10

* Adverse effects occurring at least once during the recovery in the postoperative period.
† Adverse effects of special interest associated with taking opioids.
‡ Patients exposed to opioids in the hospital. The timing of desaturation to opioids intake could not be documented.

Furthermore, the mean dose of celecoxib prescribed for 1- to 12-year-old children (2.5–3.2 mg/kg/dose) was similar to that described by Murto et al[25] (3 mg/kg/dose). However, the 13- to 17-year-olds were prescribed a dosage recommended for adults (100–200 mg/day), which may explain the lower dose relative to body weight (1.4 mg/kg/dose). The mean frequency of celecoxib administration in celecoxib + opioids group varied from 0.8 to 1.4 doses/day depending on the period of hospitalization, which was still lower than the 2 doses/day regimen in the study by Murto et al.[25] These differences may be attributed to the lack of standardization of celecoxib dosage, whether to be used "regularly" or "as needed," or of the time of initiation. Furthermore, data were collected through 24-hour periods following discharge from the recovery room; hence, the initiation of celecoxib at the end of a 24-hour period or the patient's departure at the beginning of this interval may have influenced the number of daily doses collected for the whole celecoxib + opioids group.

The pain scores collected in the present study did not decrease significantly with celecoxib administration from post-operative days 0 to 2, unlike the previous study by Murto et al.[25] More patients in the celecoxib group received dexamethasone during their stay, which may have influenced the results. However, the mean pain scores recorded in our study were always below 2, lower than those reported in the literature (about 4

or higher) for both adults and pediatric patients post AT.[25,29,34,35] This may be explained by the inconsistency in our institution's pain scores documentation and pain timing assessment, associated with the study's retrospective nature. It should also be noted that some scales used to assess pain at our institution (FPS-R and FLACC-scale) are not used in adults and are different from the one used in Murto et al[25] study for young patients (Modified Children's Hospital of Eastern Ontario Pain Scale), which limits the comparison of pain scores. Another possible explanation of the minor change in pain scores could be the underreporting of pain in children under 12 years of age, who accounted for 97% of our study sample.[36]

The findings on the occurrence of adverse events and postoperative bleeding were similar in both groups and consistent with celecoxib safety data reported in other post-AT studies, both in pediatric and adult populations.[25,29,34] However, bleeding rates were higher in our study (5.3% and 6.6% during hospitalization) when compared with the standards reported by the American Academy of Otolaryngology-Head and Neck Surgery (0.2%–2.2% at 0–24 hours and 0.1%–3.0% after 24 hours).[37] This may be attributed to: 1) A closer watch and a more systematic reporting by the medical personnel; 2) The retrospective nature of the study, all the bleeding reports were collected without taking into account their actual clinical impact; and 3) The possible selection of more severe cases that required hospitalization. Regardless, no bleeding that occurred during the hospital stay were documented after the introduction of celecoxib. The results for medical consultation for bleeding in the week following the procedure as reported by Murto et al[25] (5.7% vs 5.0%) were comparable with our control group (4.6%) but higher than those for the celecoxib group (0%). Some patients may have consulted elsewhere, and this may cause a bias in this study. The incidence of nausea (10%) and vomiting (25%) was similar in both groups in our study. These results are consistent with the incidence of celecoxib-related vomiting documented in the literature (about 30%).[38,39]

This study has some limitations. The retrospective design introduces risk of information bias, undocumented information, missing data for some patients and unmeasured sources of confounding from other factors. Our cohort is not representative of all patients undergoing AT because we did not evaluate any outpatient cases. Since celecoxib is only available in oral form, patients receiving celecoxib following AT should be able to swallow, which could lead to selection bias by including patients with less postoperative pain in the celecoxib + opioids group. The dosing and timing of celecoxib at our center was not standardized, maybe due to a lack of recommendations in the literature. Although the choice of pain assessment scale is standardized according to patient age in our institution, it was not possible to know which one was used due to the retrospective design. These scales remain measuring tools that could possibly be influenced by subjective evaluation of the caregivers. Another limitation is that all adverse events reported in the medical notes were collected without a causal link being established. It was therefore not possible to distinguish whether the adverse events were caused by celecoxib or opioids. The presence of other cofounding factors cannot be excluded. Renal and liver functions were not collected. These could have an impact on the occurrence of adverse events, since celecoxib and opioids are metabolized by liver and eliminated at renal level. Also, since the study included only hospitalized children, opioid use, pain, and adverse events at home could not be assessed and were not included in analysis, which may cause a detection bias. Future studies may include the outpatient recovery phase for assessing celecoxib efficacy. Our sample size of patients receiving celecoxib for more than 24 hours after surgery and our subgroup analysis were underpowered. Finally, analysis were not adjusted to account multiplicity, which increases risks of α-error.

Nonetheless, our study population is adequately representative of the children undergoing AT, which allows the results to be useful for most children, aged 1 to 17 years, hospitalized after this procedure and able to take oral medications.

Conclusion

In this study, celecoxib administration following AT reduced both opioid use during hospitalization and the duration of hospital stay, without additional side effects or bleeding, when started within the first 24 hours post-operatively. These results are clinically interesting, but limited by the retrospective design and the small sample size. A randomized controlled trial in post-AT hospitalized children is needed to confirm the results of this study. Considering the potential efficacy of celecoxib with early initiation, future studies should assess the importance of initiating NSAIDs pre-operatively.

Article Information

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