Celecoxib pharmacogenetics and pediatric adenotonsillectomy: a double-blinded randomized controlled study

Pharmacogénétique du célecoxib et adéno-amygdalectomie pédiatrique: une étude randomisée contrôlée en aveugle

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Abstract

Background Pediatric adenotonsillectomy (A&T) is associated with prolonged pain and functional limitation. Celecoxib is an effective analgesic in adult surgery patients; however, its analgesic efficacy on pain and functional recovery in pediatric A&T patients is unknown.

Methods During 2009-2012, children (age 2-18 yr) scheduled for elective A&T were enrolled in a single-centre double-blind randomized controlled trial. Study participants received either oral placebo or celecoxib 6 mg·kg\(^{-1}\) preoperatively, followed by 3 mg·kg\(^{-1}\) twice daily for five doses. The primary outcome was the mean “worst 24-hr pain” scores during postoperative days (PODs) 0-2 on a 100-mm visual analogue scale (VAS). Secondary outcomes for PODs 0-7 included co-analgesic consumption, adverse events, and functional recovery. The impact of the CYP2C9*3 allele – associated with reduced celecoxib hepatic metabolism – on recovery was considered.

Results Of the 282 children enrolled, 195 (celecoxib = 101, placebo = 94) were included in the primary outcome analysis. While on treatment, children receiving celecoxib experienced a modest reduction in the average pain experienced over PODs 0-2 (7 mm on a VAS; 95% confidence interval [CI]: 0.3 to 14; \(P = 0.04\)) and a “clinically significant” reduction (≥10 mm on a VAS; \(P = 0.01\)) on PODs 0 and 1. During PODs 0-2, the mean acetaminophen consumption was lower in the celecoxib group vs the placebo group (78 mg·kg\(^{-1}\); 95% CI: 68 to 89 mg·kg\(^{-1}\)).

Author contributions Kimmo Murto conceptualized and designed the study and drafted the initial manuscript. Christine Lamontagne, Johnna MacCormick, David Rosen, and Regis Vaillancourt contributed to study conception and design. Kimmo Murto, Christine Lamontagne, Johnna MacCormick, Kelly-Ann Ramakko, and David Rosen supervised data collection. Christine Lamontagne, Johnna MacCormick, David Rosen, Colleen McFaul, Kelly-Ann Ramakko, and Mary Aglipay reviewed and revised the manuscript. Colleen McFaul assisted in the design of the data collection instruments and the initial analyses and interpretation. Kelly-Ann Ramakko designed the data collection instruments and coordinated the data collection. Mary Aglipay developed the randomization sequence and carried out the initial analyses and interpretation. Regis Vaillancourt developed and deployed the celecoxib suspension and placebo and reviewed the final manuscript.

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Adenotonsillectomy (A&T) is the most common pediatric ambulatory surgery in North America, and “suspected” obstructive sleep apnea (OSA) is the primary indication. These children experience severe acute pain for the first three postoperative days (PODs), followed by prolonged pain and functional limitation lasting more than one week. Poor pain control can lead to increased hospital visits, negative behaviour, impaired food intake, dehydration, and sleep disturbance. Children commonly receive acetaminophen and an opioid. Typically, parents are instructed to administer analgesics “as needed” (prn), with the understanding that the literature is at clinical equipoise regarding “around-the-clock” (ATC) vs prn dosing to manage pain. Although nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in treating mild to moderate pain as sole agents, their addition as a co-analgesic is controversial because of concerns regarding an increased risk for secondary hemorrhage. While they have been shown to reduce nausea and vomiting, decrease opioid requirements, and act synergistically with acetaminophen, the proper dose and dose frequency of NSAIDs in combination with acetaminophen beyond 24 hr is unknown.

Despite the above efforts to manage pain, a previous quality assurance study in our hospital indicated that 70% of children continued to experience moderate-to-severe pain for the first week after A&T (unpublished data), which was consistent with other pediatric studies. Functional recovery was prolonged as well. To complicate matters, OSA predisposes children to perioperative opioid-induced respiratory depression, brain injury, and death. It is clear that current analgesic practices do not adequately address post A&T pain. Oral celecoxib, a NSAID, is a cyclooxygenase-2-specific inhibitor that preserves platelet function. It is an effective opiate-sparing perioperative co-analgesic in adults and has a good safety profile with less gastrointestinal ulceration and hemorrhage than other
NSAIDs. In North America, the United States has approved the use of celecoxib in the pediatric population for the management of juvenile idiopathic arthritis, using a twice-daily (approximately 3 mg·kg\(^{-1}\)) dosing regimen. As there is minimal pharmacokinetic literature to guide the dosing of celecoxib in children, we have adopted this twice-daily dosing regimen – following a loading dose (6 mg·kg\(^{-1}\)) – in an attempt to address the unmet pain needs of our pediatric postoperative A&T patients, albeit in the absence of objective data on efficacy. We undertook this study with the specific aim to determine if the addition of twice-daily oral celecoxib dosing to standard of care for pediatric A&T could: 1) reduce acute postoperative pain; 2) decrease co-analgesic requirements; and 3) improve functional recovery. In exploratory analysis, we also evaluated the role of the hepatic cytochrome \(P450\) 2C9 \((CYP2C9^*3)\) allele, a genetic marker of reduced celecoxib metabolism, on drug efficacy and adverse events.

Methods

Study design

A double-blind randomized controlled trial of oral celecoxib or placebo following tonsillectomy or A&T in children was conducted in a Canadian pediatric tertiary care centre. The study protocol was approved by both the institutional ethics review board and Health Canada.

Participants

Children (age 2-18 yr) scheduled for elective surgery were enrolled over a three-year period (2009-2012). Exclusion criteria included patients with extremes in body mass index (< 10\(^{th}\) or > 95\(^{th}\) percentile), abnormal renal or hepatic blood work, moderate-to-severe OSA documented in a sleep lab, any contraindication to NSAIDs, allergy to sulfa drugs, risk of pregnancy, recently received \(CYP2C9\) inhibitors or inducers, language barrier to English or French, and parent/participant cognitive impairment.

Study protocol

Children were allocated to oral celecoxib or placebo in blocks of two and four according to a computer-generated randomization schedule provided by an independent statistician. Standard pediatric fasting guidelines were followed. 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. Prior to randomization, a blinded pharmacist prepared oral suspensions of celecoxib (10 mg·mL\(^{-1}\)) in numbered 100 mL opaque amber bottles according to the randomization schedule. The placebo contained OraBlend\(^{\circledR}\) and a calcium carbonate excipient that is identical in appearance, smell, and taste to the study drug. The bottles were stored in the day surgery refrigerator.

A clinical research assistant (CRA) recruited participants at a clinic visit prior to surgery. Enrolment occurred on the day of surgery, and written caregiver consent and child (≥ eight years) assent were obtained prior to study participation. Before surgery, baseline data were collected from caregivers and children aged ≥ five years using a package of age-appropriate validated questionnaires to measure pain, fatigue (Multidimensional Fatigue Scale version 1.0), and quality of life (QOL) (Pediatric Quality of Life Inventory\(^{\text{TM}}\) in the preceding week. Within one hour prior to surgery, a day-surgery nurse removed the next sequentially numbered study bottle from the refrigerator and administered the appropriate volume·kg\(^{-1}\) dose (maximum 550 mg celecoxib). All patients received oral acetaminophen 30 mg·kg\(^{-1}\) (maximum 1,300 mg) and \(pm\) oral midazolam 0.5 mg·kg\(^{-1}\) (maximum 20 mg) prior to surgery.

During surgery, participants underwent a standardized surgical and anesthetic technique (Appendix 1, available as Electronic Supplementary Material), including administration of intravenous fluids, inhalational agent, morphine, dexamethasone, and ondansetron. Required genetic and screening blood work was drawn post induction. At the end of surgery, the surgeon rated surgical hemostasis, and suction blood loss was recorded. In the postanesthesia care unit (PACU), six trained nursing staff provided standardized monitoring and administered fluids, analgesics, and antiemetics. Validated tools were used to assess pain in the PACU (modified Children’s Hospital of Eastern Ontario Pain Scale [CHEOPS] for ages two to six years; numerical rating score for ages seven to 18 yr) and delirium on emergence from anesthesia (Pediatric Anesthesia Emergence Delirium [PAED] scale). Admission to hospital was by request of the attending surgeon or related to complications. All investigators, attending hospital staff, caregivers, and children were blinded to the allocation.

At discharge, the caregivers were instructed to administer a volume·kg\(^{-1}\) oral dose of the study agent the evening of surgery and then twice daily for four subsequent doses. In addition, parents were instructed to provide \(pm\) oral acetaminophen 15 mg·kg\(^{-1}\) every four to six hours and rescue morphine (range 0.05-0.2 mg·kg\(^{-1}\), maximum 10 mg) every three to four hours according to standard postoperative instructions provided by the
Caregivers and children $\geq$ five years were instructed to complete, once daily, a diary for PODs 0-7. The assessed outcome measures are detailed below. On PODs 1 and 2, a CRA contacted the families to encourage study drug and diary compliance and made further contact on PODs 7 and 14 for questionnaire completion and return of unused study medication. Five months after study closure, the medical charts of all study participants were screened for postoperative visits related to bleeding and liver or renal dysfunction and cross-referenced with the survey results.

Outcomes

The primary outcome measure was the average of “worst pain in the last 24 hr” (WP24HR) scores reported and recorded by parents once daily over PODs 0-2 and self-reported by children $\geq$ five years. We used a validated, age-appropriate, anchored 100-mm visual analogue scale (VAS) that was modified to reflect pain in the last 24 hr (vs seven days), where 0 (associated with a figure and wording) indicated “no pain” and 100 was similarly displayed to indicate “severe pain”.$^{30}$ Participants younger than five years were evaluated using the validated postoperative parental pain measure modified to reflect worst 24-hr pain (vs at the moment) by assessing the presence of 15 behaviours or signs on a checklist. This result was translated to a VAS score as per previous work.$^{35}$

Secondary outcomes for PODs 0-7 included once-daily WP24HR scores and VAS pain scores at rest and with swallowing, as well as co-analgesic consumption, adverse events, recovery of QOL and fatigue, and caregiver satisfaction. A survey on POD 14 captured the frequency of and indications for contact with a healthcare worker, bleeding events (by type), and the severity and overall satisfaction with care. A blinded Data and Safety Monitoring Committee comprised of two physicians and a statistician implemented and reviewed a planned interim analysis of serious adverse events (SAEs), recruitment data, demographics, and the primary study outcome ($n = 100$ patients). Study stopping criteria were based on a clinically determined imbalance of SAEs between the study groups. The impact of the $CYP2C9^{*3}$ genotype on identical outcomes was explored for patients who received celecoxib.

Statistical analysis

Sample size

Based on our previous experience of a 70% rate of moderate-to-worst pain ever following A&T and anticipating an absolute 20% reduction to a 50% rate in WP24HR scores over PODs 0-2 with celecoxib, a sample size of 190 participants (95 per treatment group) would be required to have 80% power, assuming a type 1 error of 5%. To account for dropouts, an initial sample size of 210 participants was established, but interim analysis revealed a higher (25-30%) dropout rate, dictating an increase to 282 participants. A minimum clinically meaningful difference in WP24HR was defined as $\geq$ 10 mm on a VAS or a 10-20% reduction in pain based on previous adult$^{36}$ and pediatric literature.$^{16,17,26,37-39}$

Analysis

Participant profiles were summarized by treatment group using descriptive statistics. Mean pain scores were compared using a Student’s $t$ test. Linear mixed models were conducted using the robust Huber-White estimate of standard error and restricted maximum likelihood (REML) estimation to compare WP24HR scores for PODs 0-7 between treatment groups, and then separately for POD while on the study medication (i.e., PODs 0-2). A first-order autoregressive model adjusting for age was used to determine differences in pain between groups over time. Between-group comparisons for continuous secondary outcomes were conducted using Student’s $t$ tests. To evaluate between-group differences in dimensions of QOL and fatigue, adjusting for age and scores at baseline, a repeated measures analysis of covariance model was fitted using the linear mixed-effects model (MIXED) procedure in SPSS$^{16}$ with REML estimation and Bonferroni corrections. The proportion of children experiencing PACU PAED scores $> 12$ and the proportion of those experiencing pain scores $> 40$ mm on a VAS were compared between groups using Fisher’s exact tests. Total PACU opioid consumption was compared between groups using a non-parametric (Mann-Whitney U) test. A Chi Square test was used to carry out a planned interim analysis of adverse events ($n = 100$ patients) to evaluate the safety and toxicity of celecoxib, and the analysis was performed again at the end of the study. In exploratory analysis, patients in the celecoxib arm, with and without the $CYP2C9^{*3}$ allele, were compared in terms of pain scores, need for co-analgesics, frequency and severity of adverse events, and functional recovery as described above. Data were analyzed with IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA).

Results

Participants and enrolment

The interim analysis was inconclusive; therefore, the study continued to its target accrual. There were 1,029 subjects screened for the study and 282 participants were enrolled.
The losses to follow-up and diary non-response were similar between treatment arms (31 vs 38). Baseline characteristics did not differ between the two study groups or between study completers and those lost to follow-up post randomization (Tables 1 and 2). Among patients who returned their diaries (n = 206), drug compliance was 96%. The gene frequency of the \( CYP2C9^*3 \) allele was 7.4% and satisfied the Hardy-Weinberg equilibrium equation indicating no difference between the expected and observed frequency of the \( CYP2C9^*3 \) allele.40

Outcomes

The intra-class correlation coefficients (ICC) between parent and child self-reports (five to 18 yr) of pain were very good (ICC: 0.75-0.82); therefore, we elected to use parent reports of pain and functional recovery for data consistency. Age was found to be an important predictor of pain, and therefore, we controlled for pain in the final analysis. Treatment with celecoxib resulted in a modest 11% reduction in the WP24HR score averaged over PODs 0-2 (7 mm on VAS; 95% CI: 0.3 to 14; \( P = 0.04 \)),
Table 1  Demographics and baseline characteristics of children scheduled for elective T&A, by study group

| Characteristic                                                                 | Study Group, n (%) | Placebo (n = 141) |
|--------------------------------------------------------------------------------|-------------------|-------------------|
| **Age, yr, mean (SD)**                                                         | 7.9 (4.2)         | 7.2 (3.4)         |
| **Age group**                                                                 |                   |                   |
| 2-4                                                                            | 43 (30.5)         | 46 (32.6)         |
| 5-7                                                                            | 45 (31.9)         | 46 (32.6)         |
| 8-12                                                                           | 31 (22.0)         | 38 (27.0)         |
| 13-18                                                                          | 22 (15.6)         | 11 (7.8)          |
| **Female sex**                                                                 | 81 (57.5)         | 70 (49.7)         |
| **BMI percentile, mean (SD)**                                                  | 59 (25)           | 56 (26)           |
| **Surgery type**                                                               |                   |                   |
| Tonsillectomy                                                                  | 34 (24.1)         | 42 (29.8)         |
| Adenotonsillectomy                                                             | 107 (75.9)        | 99 (70.2)         |
| **Duration of anesthesia (min), median [IQR]**                                  | 45 [35-50]        | 45 [40-55]        |
| **Surgical-blood loss (mL), median [IQR]**                                     | 5 [0.75-10]       | 5 [1-10]          |
| **American Society of Anesthesiologists classification**                       |                   |                   |
| I                                                                              | 64 (45.4)         | 57 (40.4)         |
| II                                                                             | 56 (39.7)         | 75 (53.2)         |
| III                                                                            | 21 (14.9)         | 9 (6.4)           |
| **PedQL™ QOL functional dimension scores for preceding week, Median [IQR]**    |                   |                   |
| Physical                                                                       | 91 [78-100]       | 94 [88-100]       |
| Emotional                                                                      | 70 [55-85]        | 75 [60-85]        |
| Social                                                                         | 90 [80-100]       | 95 [80-100]       |
| School                                                                         | 80 [61-92]        | 82 [67-95]        |
| **PedQL™ Fatigue-related functional dimension scores for preceding week, median [IQR]** |                   |                   |
| General                                                                        | 79 [67-93]        | 88 [75-96]        |
| Sleep & rest                                                                   | 75 [63-88]        | 79 [67-92]        |
| Cognitive                                                                      | 79 [63-96]        | 79 [67-92]        |
| **PedQL™ Pain score (100 mm VAS) for preceding week, median [IQR]**            | 7 [0-21]          | 2 [0-21]          |
| **Ethnicity**                                                                  |                   |                   |
| Caucasian                                                                      | 95 (67.4)         | 88 (62.5)         |
| Black / African American                                                       | 5 (3.6)           | 2 (1.4)           |
| Hispanic                                                                       | 2 (1.4)           | 2 (1.4)           |
| South Asian                                                                    | 0 (0)             | 3 (2.1)           |
| East Asian                                                                     | 2 (1.4)           | 3 (2.1)           |
| Not specified                                                                  | 37 (26.2)         | 43 (30.5)         |
| **CYP2C9 genotype**                                                            |                   |                   |
| *1 / *3                                                                        | 13 (9.2)          | 18 (12.8)         |
| *2 / *3                                                                        | 5 (3.5)           | 2 (1.4)           |
| *3 / *3                                                                        | 0 (0)             | 1 (0.7)           |
| *1 / *1                                                                        | 86 (61.0)         | 84 (59.6)         |
| *1 / *2                                                                        | 30 (21.3)         | 28 (19.9)         |
| *2 / *2                                                                        | 0 (0)             | 4 (2.8)           |
| Undetermined                                                                   | 7 (5.0)           | 4 (2.8)           |

BMI = body mass index; CYP2C9 = cytochrome P450 2C9 liver enzyme; IQR = interquartile range; QOL = quality of life; SD = standard deviation; T&A = adenotonsillectomy; VAS = visual analogue scale; *1 = wild-type allele; *2 = 430C>T allele; *3 = 1075A>C allele

† Unless otherwise indicated
Table 2  Demographics and baseline characteristics of children scheduled for elective T&A, completers vs non-completers

| Characteristic                                      | Study Group, n (%)†                  |
|-----------------------------------------------------|--------------------------------------|
|                                                     | Completers (n = 195) | Non-completers (n = 87) |
| Age, yr, mean (SD)                                  | 7.6 (3.6)                | 7.4 (4.2)                |
| Age group                                           |                        |                         |
| 2-4                                                 | 56 (28.7)               | 33 (37.9)               |
| 5-7                                                 | 67 (34.4)               | 24 (27.6)               |
| 8-12                                                | 52 (26.7)               | 17 (19.6)               |
| 13-18                                               | 20 (10.2)               | 13 (14.9)               |
| Female sex                                          | 103 (52.8)              | 48 (55.2)               |
| BMI percentile, mean (SD)                           | 59 (25)                 | 55 (28)                 |
| Surgery type                                        |                        |                         |
| Tonsillectomy                                       | 56 (28.7)               | 20 (23.0)               |
| Adenotonsillectomy                                  | 139 (71.3)              | 64 (77.0)               |
| Duration of anesthesia (min), median [IQR]          | 45 [40-50]              | 45 [35-55]              |
| Surgical-blood loss (mL), median [IQR]              | 5 [1-10]                | 5 [1-10]                |
| American Society of Anesthesiologists classification|                        |                         |
| I                                                    | 87 (44.6)               | 34 (39.1)               |
| II                                                   | 87 (44.6)               | 44 (50.6)               |
| III                                                  | 21 (10.8)               | 9 (10.3)                |
| PedsQL™ QOL functional dimension scores for preceding week, Median [IQR] | | |
| Physical                                             | 91 [78-100]             | 94 [73-98]              |
| Emotional                                           | 70 [55-85]              | 60 [58-78]              |
| Social                                               | 90 [80-100]             | 90 [83-98]              |
| School                                              | 83 [65-95]              | 79 [75-96]              |
| PedsQL™ Fatigue-related functional dimension scores for preceding week, median [IQR] | | |
| General                                              | 83 [71-96]              | 88 [71-96]              |
| Sleep & rest                                         | 75 [63-90]              | 79 [67-92]              |
| Cognitive                                            | 79 [67-92]              | 79 [63-100]             |
| PedsQL™ Pain score (100 mm VAS) for preceding week, median [IQR] | | |
| Ethnicity                                            |                         |                         |
| Caucasian                                            | 150 (76.9)              | 33 (37.9)               |
| Black / African American                             | 7 (3.6)                 | 0 (0)                   |
| Hispanic                                             | 3 (1.5)                 | 1 (1.2)                 |
| South Asian                                          | 3 (1.5)                 | 0 (0)                   |
| East Asian                                           | 5 (2.6)                 | 0 (0)                   |
| Not specified                                        | 27 (13.9)               | 53 (60.9)               |
| CYP2C9 genotype                                      |                         |                         |
| *1 / *3                                              | 27 (13.9)               | 4 (4.6)                 |
| *2 / *3                                              | 5 (2.6)                 | 2 (2.3)                 |
| *3 / *3                                              | 0 (0)                   | 1 (1.2)                 |
| *1 / *1                                              | 110 (56.4)              | 60 (68.9)               |
| *1 / *2                                              | 43 (22.1)               | 15 (17.2)               |
| *2 / *2                                              | 3 (1.5)                 | 1 (1.2)                 |
| Undetermined                                         | 7 (3.5)                 | 4 (4.6)                 |

BMI = body mass index; IQR = interquartile range; QOL = quality of life; SD = standard deviation; T&A = adenotonsillectomy; VAS = visual analogue scale; CYP2C9 = cytochrome P450 2C9 liver enzyme; *1 = wild-type allele; *2 = 430C>T allele; *3 = 1075A>C allele
† Unless otherwise indicated
comprised of minimal clinically meaningful reductions in WP24HR scores of 12 mm (95% CI: 3 to 22; \(P = 0.01\)) and 10 mm (95% CI: 3 to 17; \(P < 0.01\)) reported on POD 0 and 1, respectively (Fig. 2 and Table 3). Interestingly, after celecoxib was stopped, participants had a 14% increase in WP24HR on POD 3 compared with placebo (61 mm; 95% CI: 56 to 66 \(\text{vs}\) 53 mm; 95% CI: 46 to 59, respectively; \(P = 0.06\)); pain scores for the rest of the week were not statistically different (\(P > 0.10\)). Celecoxib provided a modest reduction (16-19%) in “pain with swallowing” and “pain at rest” on POD 0-1 and POD 0, respectively (Table 3). The proportion of celecoxib patients \(\text{vs}\) placebo patients with PACU pain scores \(>40\) mm (65\% \(\text{vs}\) 69\%, respectively; \(P = 0.61\)) and PAED scores \(>12\) (21\% \(\text{vs}\) 15\%, respectively; \(P = 0.28\)) did not differ significantly. Likewise, total opioid consumption did not differ between groups (\(P > 0.50\)).

Acetaminophen consumption on PODs 0-2 was significantly lower in the celecoxib group than in the placebo group (78 mg·kg\(^{-1}\); 95% CI: 68 to 89 \(\text{vs}\) 97 mg·kg\(^{-1}\); 95% CI: 85 to 109 respectively; \(P = 0.03\)) and morphine consumption was also lower (0.56 mg·kg\(^{-1}\); 95% CI: 0.47 to 0.65 \(\text{vs}\) 0.70 mg·kg\(^{-1}\); 95% CI: 0.59 to 0.81, respectively; \(P = 0.06\)); the number of morphine-free patients did not differ between groups. Cumulative co-analgesic consumption and the type and frequency of adverse advents for POD 0-7, including bleeding, did not differ between groups (Table 4). Functional recovery at POD 7 was similar between groups (Table 5). The follow-up survey response rate on POD 14 was 72%. The rate of any contact with a healthcare worker during this time interval was 38\% and was similar between the two groups. Pain and not drinking (i.e., dynamic pain) accounted for the majority of contacts (53\%), while nausea/vomiting and

**Table 3** Parent report of post-adenotonsillectomy pain score on 100-mm VAS for postoperative days 0-2, by study group (\(n = 195\))

|                | “Worst pain” in previous 24 hr mm (95% CI) | “Pain with swallowing” mm (95% CI) | “Pain at rest” mm (95% CI) |
|----------------|----------------------------------------|---------------------------------|---------------------------|
|                | Celecoxib: Placebo | \(P\) value | Celecoxib: Placebo | \(P\) value | Celecoxib: Placebo | \(P\) value |
| POD 0          | 50 (44 to 57) \(\text{vs}\) 62 (56 to 69) | 0.01 | 48 (42 to 54) \(\text{vs}\) 57 (51 to 63) | 0.03 | 47 (42 to 52) \(\text{vs}\) 56 (50 to 62) | 0.02 |
| POD 1          | 64 (59 to 70) \(\text{vs}\) 75 (69 to 80) | < 0.01 | 50 (44 to 55) \(\text{vs}\) 62 (55 to 68) | < 0.01 | 51 (45 to 56) \(\text{vs}\) 57 (51 to 62) | 0.12 |
| POD 2          | 63 (58 to 68) \(\text{vs}\) 64 (59 to 70) | 0.70 | 48 (42 to 53) \(\text{vs}\) 53 (47 to 58) | 0.21 | 49 (43 to 54) \(\text{vs}\) 48 (42 to 53) | 0.84 |

\(CI = \text{confidence interval; POD = postoperative day; VAS = visual analogue scale}\)
bleeding accounted for 12% and 9% of contacts, respectively. Parent satisfaction did not differ between groups.

Among celecoxib patients who returned diaries and were compliant with the study medication (\(n=98\)), 14 patients were heterozygous for CYP2C9*3 (H*3-slow metabolizer) and 84 were absent for the allele (A*3-normal metabolizer). Demographics were similar between these subgroups (Appendix 2; available as Electronic Supplementary Material). Pain scores among the 93 patients (13 celecoxib H*3 and 80 celecoxib A*3) who provided at least three WP24HR scores during PODs 0-7 are presented in Fig. 3. On POD 7 alone, a significant 48% reduction in WP24HR score was reported: celecoxib group: 23 mm on a VAS; 95% CI: 8 to 39 vs placebo group: 44 mm; 95% CI: 38 to 50; \(P=0.02\). There was no difference in total co-analgesic consumption for PODs 0-7.

**Table 4** Frequency of at least one adverse event experienced for postoperative days 0-7 time interval, by study group

| Adverse Event                        | Celecoxib (\(n=107\)) | Placebo (\(n=99\)) | Difference in proportion with adverse event (Celecoxib-Placebo) (absolute % difference, 95% CI)† |
|--------------------------------------|------------------------|---------------------|------------------------------------------------------------------------------------------------|
| Nausea & vomiting                    | 60 (56.1)              | 55 (55.6)           | 0.5 (−13 to 14)                                                                                   |
| Stomach ache                         | 59 (55.1)              | 50 (50.5)           | 4 (−9 to 18)                                                                                     |
| Diarrhea                             | 7 (6.5)                | 9 (9.1)             | −2 (−11 to 5)                                                                                    |
| Dizziness                            | 45 (42.1)              | 41 (41.4)           | 0.6 (−13 to 14)                                                                                  |
| Difficulty breathing                 | 13 (12.2)              | 19 (19.2)           | −7 (−17 to 3)                                                                                    |
| Rash                                 | 5 (4.7)                | 3 (3.0)             | 2 (−4 to 8)                                                                                      |
| Headache                             | 33 (30.8)              | 35 (35.4)           | −5 (−17 to 8)                                                                                    |
| Hospital visit for bleeding          | 8 (5.7)*               | 7 (5.0)*            | 0.4 (−7 to 8)                                                                                    |
| Bleeding requiring surgery           | 3 (2.1)*               | 2 (1.4)*            | 0.7 (−4 to 6)                                                                                    |

*Proportion based on \(n=141\) representing review of all study participant charts five months after study completion and cross-referenced with questionnaire responses

A significant difference in the severity (rated as moderate to severe) of adverse events experienced between study groups was reported only for headache (11 vs 21 patients; \(P=0.05\)).

† Used the Wilson score method for the confidence interval for the difference between independent proportions (Newcombe, 1998)

**Table 5** Parent-reported mean score for dimensions of quality of life and fatigue at postoperative day 7, by study group

|                | Celecoxib Mean (95% CI) | Placebo Mean (95% CI) | \(P\) value |
|----------------|-------------------------|-----------------------|-------------|
| **QOL Related Dimensions of Function** |                         |                       |             |
| Physical       | 57 (52 to 63)           | 58 (53 to 63)         | 0.83        |
| Emotional      | 72 (68 to 76)           | 70 (66 to 75)         | 0.55        |
| Social         | 82 (79 to 85)           | 83 (79 to 86)         | 0.80        |
| School         | 73 (68 to 78)           | 66 (59 to 73)         | 0.12        |
| **Fatigue-Related Dimensions of Function** |                         |                       |             |
| General        | 54 (49 to 59)           | 54 (49 to 59)         | 0.89        |
| Sleep/Rest     | 58 (54 to 63)           | 55 (50 to 60)         | 0.36        |
| Cognitive      | 77 (74 to 80)           | 76 (72 to 81)         | 0.74        |

CI = confidence interval; QOL = quality of life

Bleeds were similar following A&T, as was the incidence and severity of adverse events (Appendix 3; available as Electronic Supplementary Material). Regarding QOL, the celecoxib H*3 children experienced a better physical (\(P<0.01\)) and emotional dimension of recovery (\(P=0.04\)) (Appendix 4; available as Electronic Supplementary Material). Fatigue and parent satisfaction did not differ between groups.

**Discussion**

Compared with placebo, a three-day course of an oral celecoxib suspension resulted in a modest but clinically meaningful reduction in early post A&T pain, as shown by reduced pain scores and co-analgesic consumption. Studies evaluating celecoxib in a pediatric perioperative setting are
lacking; however, adult studies evaluating celecoxib dosing for a minimum of three days have shown delayed but improved analgesia.41-43 Similarly, we found that children experienced pain relief within the first 24 hr of surgery, although it was delayed until after PACU discharge, reflecting a comparable time to achieve maximum plasma concentration (three to four hours) seen in adults.41-44

The observed pattern of pain reduction followed by pain rebound on celecoxib withdrawal suggests that an adult-based dosing regimen was inappropriate. The pain profile of those children who received placebo was nearly identical to other pediatric A&T studies,3,16 but unlike adults,41,43 a short twice-daily course of celecoxib did not provide either sustained or extended analgesia after withdrawal. The pharmacokinetics of celecoxib in children is different from that in adults. The half-life is reduced (five hr vs 11 hr) and clearance is doubled.25,44 In adults, twice-daily dosing results in stable plasma levels above an analgesic threshold. In children with identical dosing, we observed brief attainment of this analgesic threshold followed by labile pain scores presumably reflecting sub-analgesic blood levels occurring even before the drug was stopped. Adults report prolonged pain relief with celecoxib after a single dose23 or following a short course,45 presumably due to an increased half-life and reduced clearance when compared with children. In the present study, pain rebound after celecoxib withdrawal was likely a result of both a rapid clearance of celecoxib and relative co-analgesic under prescribing. Based on our current study, we would recommend more frequent dosing. The observation that celecoxib “slow” metabolizers – when compared with “normal” metabolizers – appeared to avoid pain rebound while receiving an adult dosing regimen (Fig. 3) supports this recommendation.

Celecoxib was well tolerated. The reported rates of adverse events and the functional recovery profile are similar to those in the literature. Nevertheless, the rate of vomiting for PODs 0-7 was higher than the 30% reported by others,45,46 possibly due to the higher frequency of reporting in our study. In the celecoxib group, the incidence of hemorrhage and the need for surgery were less than reported elsewhere.47 Pain was the most common reason for postoperative contact with a healthcare worker and is consistent with other studies.3,16,17,46 The duration of QOL impairment in our study was similar to other pediatric3 and adult A&T populations.43 Nevertheless, compared with other adult surgical populations,41,42 we found that celecoxib did not improve functional recovery at POD 7. This finding may be due to the greater amount of pain associated with A&T vs laparoscopic and plastic surgery and the delayed timing of the assessment in relation to ingesting the drug. Although the frequency and severity of celecoxib-related adverse events were independent of the CYP2C9 genotype, “slow” compared

Fig. 3 Parent report of “worst pain” recorded in previous 24 hr for postoperative days 0-7 in children aged two to 18 yr, by CYP2C9 sub-study group. Error bars represent standard error of the mean. *P < 0.02. Dashed line = threshold for moderate pain on 100-mm visual analogue scale
with “normal” metabolizers showed improved physical and emotional recovery at POD 7; however, our numbers are small.

This study has limitations. Many parents refused to participate. A number of factors may account for the high refusal rate, including the length of the study (two weeks), the extent of the outcome assessments, and unease to administer a drug not approved to manage postoperative pain in children. Pain following A&T lasts longer than one week. The short course of celecoxib was intended to cover early intense pain, optimize compliance, limit the risk of NSAID-related bleeding,9-12 and hopefully provide extended pain relief as seen in adults.21,43 It is possible that greater analgesic effect may have occurred by combining celecoxib with ATC acetaminophen. The primary outcome, a once-daily global report of pain over 24 hr, may have been subjected to recall bias; however, it paralleled other real-time pain measurements in terms of relative magnitude and pattern. The pattern was identical to previous pediatric findings using multiple validated daily assessments.3,16 Moreover, a single global assessment for severe pain is clinically meaningful and is less likely to miss severe pain resulting from measurements at predetermined intervals or associated with recent analgesic ingestion.48 Pain self-report is preferred, but strong correlation between child and parent reports was shown. Tools for young (< five years) children are not robust,26 and self-report analysis (not shown) resulted in similar study conclusions. Although the dropout rates were considerable, they likely do not affect the validity of our findings because: 1) baseline characteristics, including genotype (with ethnicity inferred), were similar between study completers and dropouts; 2) dropout numbers were balanced between treatment arms; and 3) rates were comparable with other pediatric A&T trials.5,7,8,49,50 Our theories related to CYP2C9*3 “slow metabolizer” genotype, underdosing, and rapid or delayed clearance of celecoxib are speculative because we did not measure plasma levels and analgesic concentrations are unknown. Finally, the study is underpowered to conclude that celecoxib is safe or that the CYP2C9 genotype influences analgesia and functional recovery.

Of interest to those involved with the perioperative care of children, celecoxib was able to reduce pain and co-analgesic consumption while administered. The patient population studied was typical of a community setting where celecoxib may be an attractive and potentially opioid-sparing alternative that does not suffer from the same safety concerns as codeine, a commonly prescribed opioid.51 A reduction in opioid consumption is welcome in a surgical population where the prevalence of OSA is higher than normal. Finally, preliminary evidence to suggest improved analgesia and functional recovery for heterozygotes with the CYP2C9*3 allele brings us closer to realizing the utility of personalized medicine to influence clinical outcomes.

In conclusion, perioperative oral celecoxib provides modest early pain relief for children undergoing A&T. It is well tolerated and has a relatively rapid onset of action. Analgesic efficacy, however, may be limited when dosed according to adult guidelines that do not account for its shorter half-life and faster clearance in children. Our findings indicate that an increase in dose, dose frequency, and duration of treatment of at least seven days warrant future study in the pediatric perioperative setting. Preliminary findings suggest that the CYP2C9*3 allele confers improved celecoxib analgesic efficacy and functional recovery without an associated increase in adverse events.

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