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REPORTS OF ORIGINAL INVESTIGATIONS

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

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

Kimmo Murto, MD · Christine Lamontagne, MD · Colleen McFaul, MD · Johnna MacCormick, MD · Kelly-Ann Ramakko, BSc · Mary Aglipay, MSc · David Rosen, MD · Regis Vaillancourt, PharmD

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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*

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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K. Murto, MD (✉) · C. Lamontagne, MD · K.-A. Ramakko, BSc · D. Rosen, MD
Department of Anesthesiology, Children's Hospital of Eastern Ontario (CHEO), University of Ottawa, 401 Smyth Rd., Ottawa, ON K1H 8L1, Canada
e-mail: Kmurto@cheo.on.ca

K. Murto, MD · M. Aglipay, MSc
Clinical Research Unit (CRU), Children's Hospital of Eastern Ontario (CHEO) Research Institute (RI), Ottawa, ON, Canada

C. McFaul, MD
Department of Anesthesiology, University of Ottawa, Ottawa, ON, Canada

J. MacCormick, MD
Department of Otolaryngology, Children's Hospital of Eastern Ontario (CHEO), University of Ottawa, Ottawa, ON, Canada

R. Vaillancourt, PharmD
Department of Pharmacy, Children's Hospital of Eastern Ontario (CHEO), Ottawa, ON, Canada

*vs 97 mg·kg^{-1}; 95% CI: 85 to 109, respectively; P = 0.03). No differences in adverse events, functional recovery, or satisfaction were observed by POD 7. The CYP2C9*3 allele was associated with less pain and improved functional recovery.*

Conclusions *A three-day course of oral celecoxib reduces early pain and co-analgesic consumption; however, an increase in dose, dose frequency, and duration of dose may be required for sustained pain relief in the pediatric setting. The CYP2C9*3 allele may influence recovery. This trial was registered at: ClinicalTrials.gov: NCT00849966.*

Résumé

Contexte *L'adéno-amygdalectomie (AA) est associée à des douleurs et des limites fonctionnelles prolongées. Le célécoxib est un agent analgésique efficace chez les patients chirurgicaux adultes; toutefois, son efficacité analgésique pour le contrôle de la douleur et la récupération fonctionnelle chez les patients pédiatriques subissant une AA est inconnue.*

Méthode *Entre 2009 et 2012, des enfants (âgés de 2 à 18 ans) devant subir une AA non urgente ont été recrutés pour participer à une étude randomisée contrôlée à double insu réalisée dans un seul centre. Les participants à l'étude ont reçu soit un placebo oral, soit 6 mg·kg^{-1} de célécoxib avant l'opération, suivi par cinq doses de 3 mg·kg^{-1} deux fois par jour. Le critère d'évaluation principal était les scores moyens de « pire douleur durant 24 h » pendant les jours postopératoires (JPO) 0-2 sur une échelle visuelle analogique (EVA) de 100 mm. Les critères secondaires pour les JPO 0-7 comprenaient la consommation d'autres analgésiques, les effets secondaires néfastes et la récupération fonctionnelle. L'impact de l'allèle CYP2C9*3 – associé à un métabolisme hépatique réduit du célécoxib – lors du rétablissement a été pris en compte.*

Résultats *Parmi les 282 enfants recrutés, 195 (célécoxib = 101, placebo = 94) ont été inclus dans l'analyse du critère d'évaluation principal. Pendant le traitement, les enfants recevant du célécoxib ont fait état d'une réduction modeste de la douleur moyenne ressentie au cours des JPO 0-2 (7 mm sur une EVA; intervalle de confiance [IC] 95 %: 0,3 à 14; P = 0,04) et d'une réduction « significative d'un point de vue clinique » (≥ 10 mm sur une EVA; P ≤ 0,01) au JPO 0 et 1. Au cours des JPO 0-2, la consommation moyenne d'acétaminophène était moindre dans le groupe célécoxib que dans le groupe placebo (78 mg·kg^{-1}; IC 95 %: 68 à 89 vs 97 mg·kg^{-1}; IC 95 %: 85 à 109, respectivement; P = 0,03). Aucune différence n'a été observée en matière d'effets secondaires néfastes, de récupération fonctionnelle ou de satisfaction jusqu'au jour 7. L'allèle CYP2C9*3 a été associé à une réduction de la douleur ainsi qu'à une récupération fonctionnelle améliorée.*

Conclusion *Un traitement de trois jours avec du célécoxib par voie orale réduit la douleur précoce et la consommation d'autres agents analgésiques; toutefois, une augmentation de la dose, de la fréquence de dosage et de la durée de dosage pourrait être nécessaire pour un soulagement continu de la douleur dans un contexte pédiatrique. L'allèle CYP2C9*3 pourrait avoir un impact sur la récupération. Cette étude a été enregistrée au: ClinicalTrials.gov: NCT00849966.*

Adenotonsillectomy (A&T) is the most common pediatric ambulatory surgery in North America,[1] and "suspected" obstructive sleep apnea (OSA) is the primary indication.[2] 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.[3] Poor pain control can lead to increased hospital visits, negative behaviour, impaired food intake, dehydration, and sleep disturbance.[4-6] 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.[7,8] 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.[9-12] While they have been shown to reduce nausea and vomiting, decrease opioid requirements,[13] and act synergistically with acetaminophen, the proper dose and dose frequency of NSAIDS in combination with acetaminophen beyond 24 hr is unknown.[14]

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.[3,15-17] Functional recovery was prolonged as well. To complicate matters, OSA predisposes children to perioperative opioid-induced respiratory depression, brain injury, and death.[18,19] 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.[20] It is an effective opiate-sparing perioperative co-analgesic in adults[21] and has a good safety profile with less gastrointestinal ulceration and hemorrhage than other

NSAIDs.[22] 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,[23-25] 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.[26] In exploratory analysis, we also evaluated the role of the hepatic cytochrome *P450 2C9 1075A>C* (*CYP2C9*3*) allele, a genetic marker of reduced celecoxib metabolism, on drug efficacy and adverse events.[27,28]

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 sulfonamides, 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[29] according to the randomization schedule. The placebo contained OraBlend® 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 PedsQL™ questionnaires to measure pain, fatigue (Multidimensional Fatigue Scale version 1.0), and quality of life (QOL) (Pediatric Quality of Life Inventory™) in the preceding week.[30-33] 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 *prn* 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).[34] 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 *prn* 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

surgeon. Inpatients underwent an identical protocol. Caregivers and children ≥ 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 ≥ 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 ≥ 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® 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

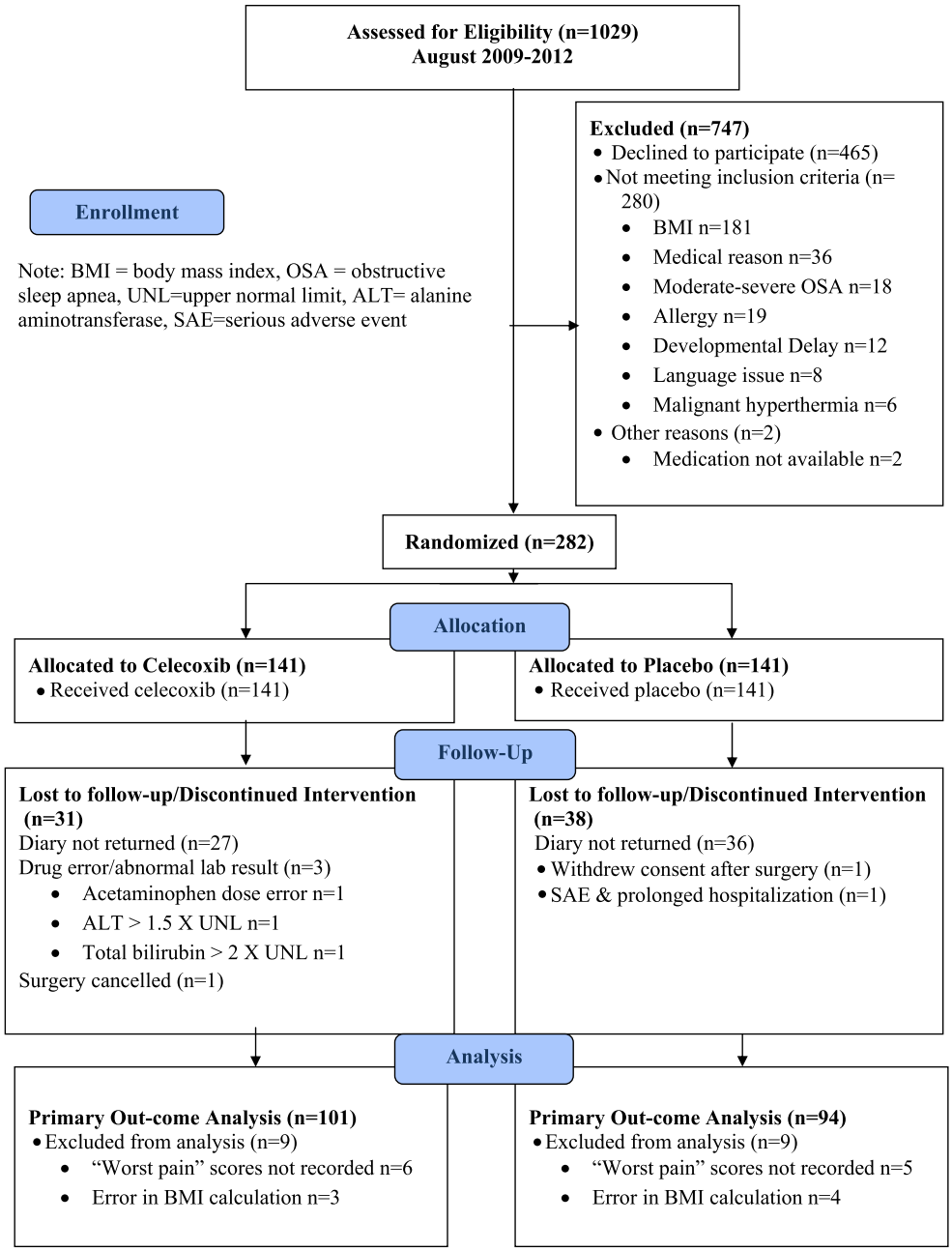

Fig. 1 Flow of patients through the trial

(141 participants/group) (Fig. 1). 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* (%)[†]	
	Celecoxib (*n* = 141)	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)
PedsQL™ 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]
PedsQL™ 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]
PedsQL™ 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]	3 [0-25]	6 [0-30]
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

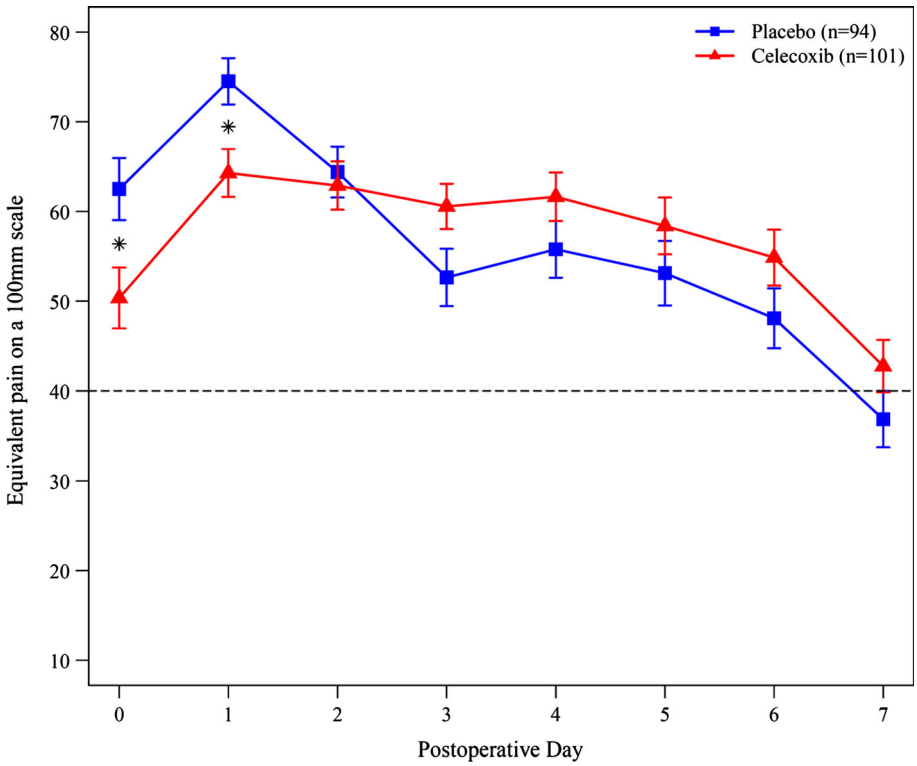

Fig. 2 Parent report of "worst pain" recorded in previous 24 hr for postoperative days 0-7 in children aged two to 18 yr, by study group. Error bars represent standard error of the mean. *$P < 0.02$. Dashed line = threshold for moderate pain on 100-mm visual analogue scale

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: 56-66 *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 *vs* placebo patients with PACU pain scores > 40 mm (65% *vs* 69%, respectively; $P = 0.61$) and PAED scores > 12 (21% *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 $mg \cdot kg^{-1}$; 95% CI: 68 to 89 *vs* 97 $mg \cdot kg^{-1}$; 95% CI: 85 to 109 respectively; $P = 0.03$) and morphine consumption was also lower (0.56 $mg \cdot kg^{-1}$; 95% CI: 0.47 to 0.65 *vs* 0.70 $mg \cdot kg^{-1}$; 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)	62 (56 to 69)	0.01	48 (42 to 54)	57 (51 to 63)	0.03	47 (42 to 52)	56 (50 to 62)	0.02
POD 1	64 (59 to 70)	75 (69 to 80)	< 0.01	50 (44 to 55)	62 (55 to 68)	< 0.01	51 (45 to 56)	57 (51 to 62)	0.12
POD 2	63 (58 to 68)	64 (59 to 70)	0.70	48 (42 to 53)	53 (47 to 58)	0.21	49 (43 to 54)	48 (42 to 53)	0.84

CI = confidence interval; POD = postoperative day; VAS = visual analogue scale

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

Adverse Event	Celecoxib ($n = 107$) n (%)	Placebo ($n = 99$) n (%)	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

	n	Celecoxib Mean (95% CI)	Placebo Mean (95% CI)	P value
QOL Related Dimensions of Function				
Physical	187	57 (52 to 63)	58 (53 to 63)	0.83
Emotional	192	72 (68 to 76)	70 (66 to 75)	0.55
Social	183	82 (79 to 85)	83 (79 to 86)	0.80
School	109	73 (68 to 78)	66 (59 to 73)	0.12
Fatigue-Related Dimensions of Function				
General	192	54 (49 to 59)	54 (49 to 59)	0.89
Sleep/Rest	192	58 (54 to 63)	55 (50 to 60)	0.36
Cognitive	191	77 (74 to 80)	76 (72 to 81)	0.74

CI = confidence interval; QOL = quality of life

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. 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

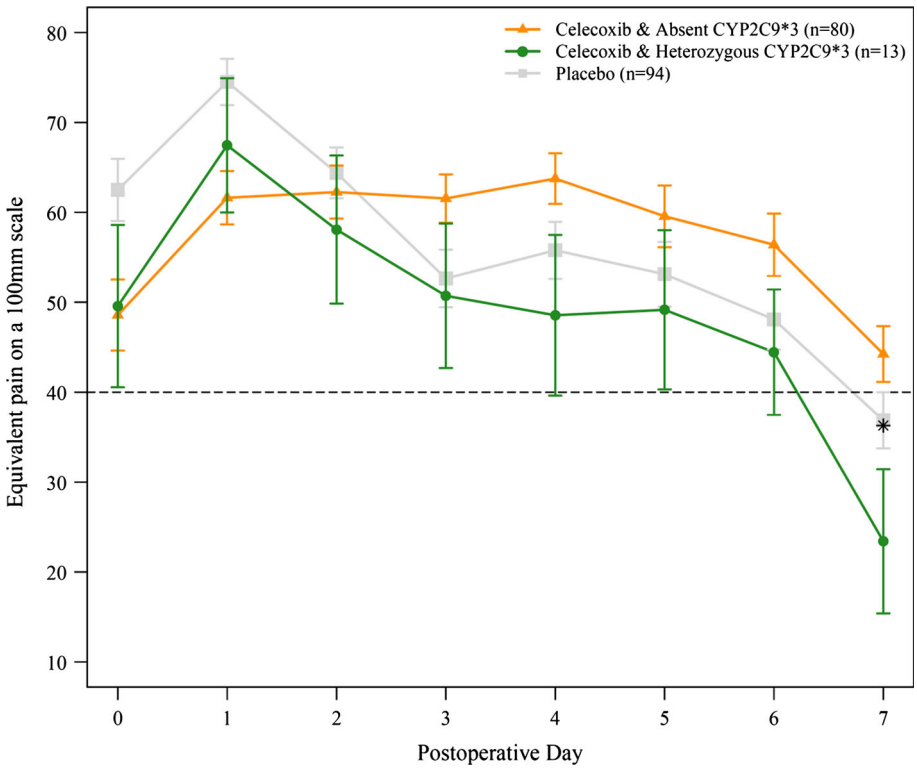

Fig. 3 Parent report of "worst pain" recorded in previous 24 hr for postoperative days 0-7 in children aged two to 18 yr, by *CYP2C9* sub-study group. Error bars represent standard error of the mean. $*P < 0.02$. Dashed line = threshold for moderate pain on 100-mm visual analogue scale

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 dose[21] or following a short course,[43] 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 pediatric[3] 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

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.[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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References

1. *Cullen KA*, *Hall MJ*, *Golosinskly A*. Ambulatory surgery in the United States, 2006. Natl Health Stat Report 2009; 28: 1-25.
2. *Erickson BK*, *Larson DR*, *St Sauver JL*, *Meverden RA*, *Orvidas LJ*. Changes in incidence and indications of tonsillectomy and adenotonsillectomy, 1970-2005. Otolaryngol Head Neck Surg 2009; 140: 894-901.
3. *Stewart DW*, *Ragg PG*, *Sheppard S*, *Chalkiadis GA*. The severity and duration of postoperative pain and analgesia requirements in children after tonsillectomy, orchidopexy, or inguinal hernia repair. Paediatr Anaesth 2012; 22: 136-43.
4. *Kotiniemi LH*, *Ryhanen PT*, *Moilanen IK*. Behavioral changes following routine ENT operations in two-to-ten-year-old children. Pediatr Anaesth 1996; 6: 45-9.

5. *Sommer M*, *de Rijke JM*, *van Kleef M*, *et al*. Predictors of acute postoperative pain after elective surgery. Clin J Pain 2010; 26: 87-94.
6. *Colclasure JB*, *Graham SS*. Complications of outpatient tonsillectomy and adenoidectomy: a review of 3,340 cases. Ear Nose Throat J 1990; 69: 155-60.
7. *Sutters KA*, *Miaskowski C*, *Holdridge-Zeuner D*, *et al*. A randomized clinical trial of the effectiveness of a scheduled oral analgesic dosing regimen for the management of postoperative pain in children following tonsillectomy. Pain 2004; 110: 49-55.
8. *Sutters KA*, *Miaskowski C*, *Holdridge-Zeuner D*, *et al*. A randomized clinical trial of the efficacy of scheduled dosing of acetaminophen and hydrocodone for the management of postoperative pain in children after tonsillectomy. Clin J Pain 2010; 26: 95-103.
9. *Moniche S*, *Romsing J*, *Dahl JB*, *Tramer MR*. Nonsteroidal antiinflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. Anesth Analg 2003; 96: 68-77.
10. *Marret E*, *Flahault A*, *Samama CM*, *Bonnet F*. Effects of postoperative, nonsteroidal, antiinflammatory drugs on bleeding risk after tonsillectomy: meta-analysis of randomized, controlled trials. Anesthesiology 2003; 98: 1497-502.
11. *Lewis SR, Nicholson A, Cardwell ME, Siviter G, Smith AF*. Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. Cochrane Database Syst Rev 2013; 7: CD003591.
12. *Riggin L*, *Ramakrishna J*, *Sommer DD*, *Koren G*. A 2013 updated systematic review & meta-analysis of 36 randomized controlled trials; no apparent effects of non steroidal anti-inflammatory agents on the risk of bleeding after tonsillectomy. Clin Otolaryngol 2013; 38: 115-29.
13. *Michelet D*, *Andreu-Gallien J*, *Bensalah T*, *et al*. A meta-analysis of the use of nonsteroidal antiinflammatory drugs for pediatric postoperative pain. Anesth Analg 2012; 114: 393-406.
14. *Hannam J*, *Anderson BJ*. Explaining the acetaminophen-ibuprofen analgesic interaction using a response surface model. Paediatr Anaesth 2011; 21: 1234-40.
15. *Fortier MA*, *MacLaren JE*, *Martin SR*, *Perret-Karimi D*, *Kain ZN*. Pediatric pain after ambulatory surgery: where's the medication? Pediatrics 2009; 124: e588-95.
16. *Salonen A*, *Kokki H*, *Nuutinen J*. The effect of ketoprofen on recovery after tonsillectomy in children: a 3-week follow-up study. Int J Pediatr Otorhinolaryngol 2002; 62: 143-50.
17. *Warnock FF*, *Lander J*. Pain progression, intensity and outcomes following tonsillectomy. Pain 1998; 75: 37-45.
18. *Brown KA*. Outcome, risk, and error and the child with obstructive sleep apnea. Paediatr Anaesth 2011; 21: 771-80.
19. *Cote CJ*, *Posner KL*, *Domino KB*. Death or neurologic injury after tonsillectomy in children with a focus on obstructive sleep apnea: Houston, we have a problem! Anesth Analg 2014; 118: 1276-83.
20. *Leese PT*, *Hubbard RC*, *Karim A*, *Isakson PC*, *Yu SS*, *Geis GS*. Effects of celecoxib, a novel cyclooxygenase-2 inhibitor, on platelet function in healthy adults: a randomized, controlled trial. J Clin Pharmacol 2000; 40: 124-32.
21. *Derry S, Moore RA*. Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database Syst Rev 2012; 3: CD004233.
22. *Essex MN*, *Zhang RY*, *Berger MF*, *Upadhyay S*, *Park PW*. Safety of celecoxib compared with placebo and non-selective NSAIDs: cumulative meta-analysis of 89 randomized controlled trials. Expert Opin Drug Saf 2013; 12: 465-77.
23. *Young D*. FDA advisers endorse Celebrex for juvenile rheumatoid arthritis: lack of studies in children raises safety concerns. Am J Health Syst Pharm 2007; 64: 11-2.
24. *Foeldvari I*, *Szer IS*, *Zemel LS*, *et al*. A prospective study comparing celecoxib with naproxen in children with juvenile rheumatoid arthritis. J Rheumatol 2009; 36: 174-82.
25. *Stempak D*, *Gammon J*, *Klein J*, *Koren G*, *Baruchel S*. Single-dose and steady-state pharmacokinetics of celecoxib in children. Clin Pharmacol Ther 2002; 72: 490-7.
26. *McGrath PJ*, *Walco GA*, *Turk DC*, *et al*. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. J Pain 2008; 9: 771-83.
27. *Stempak D*, *Bukaveckas BL*, *Linder M*, *Koren G*, *Baruchel S*. Cytochrome P450 2C9 genotype: impact on celecoxib safety and pharmacokinetics in a pediatric patient. Clin Pharmacol Ther 2005; 78: 309-10.
28. *Tang C*, *Shou M*, *Rushmore TH*, *et al*. In-vitro metabolism of celecoxib, a cyclooxygenase-2 inhibitor, by allelic variant forms of human liver microsomal cytochrome P450 2C9: correlation with CYP2C9 genotype and in-vivo pharmacokinetics. Pharmacogenetics 2001; 11: 223-35.
29. *Donnelly RF*, *Pascuet E*, *Ma C*, *Vaillancourt R*. Stability of celecoxib oral suspension. Can J Hosp Pharm 2009; 62: 464-8.
30. *Gragg RA*, *Rapoff MA*, *Danovsky MB*, *et al*. Assessing chronic musculoskeletal pain associated with rheumatic disease: further validation of the pediatric pain questionnaire. J Pediatr Psychol 1996; 21: 237-50.
31. *Huguet A*, *Stinson JN*, *McGrath PJ*. Measurement of self-reported pain intensity in children and adolescents. J Psychosom Res 2010; 68: 329-36.
32. *Varni JW*, *Burwinkle TM*, *Szer IS*. The PedsQL Multidimensional Fatigue Scale in pediatric rheumatology: reliability and validity. J Rheumatol 2004; 31: 2494-500.
33. *Varni JW*, *Burwinkle TM*, *Seid M*, *Skarr D*. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr 2003; 3: 329-41.
34. *Sikich N*, *Lerman J*. Development and psychometric evaluation of the pediatric anesthesia emergence delirium score. Anesthesiology 2004; 100: 1138-45.
35. *Chambers CT*, *Finley GA*, *McGrath PJ*, *Walsh TM*. The parents' postoperative pain measure: replication and extension to 2-6-year-old children. Pain 2003; 105: 437-43.
36. *Kelly AM*. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? Acad Emerg Med 1998; 5: 1086-90.
37. *Birnie KA*, *McGrath PJ*, *Chambers CT*. When does pain matter? Acknowledging the subjectivity of clinical significance. Pain 2012; 153: 2311-4.
38. *Powell CV*, *Kelly AM*, *Williams A*. Determining the minimally clinically significant difference in visual analogue pain score for children. Ann Emerg Med 2001; 37: 28-31.
39. *Von Baeyer CL*. Children's self-reports of pain intensity: scale selection, limitations and interpretation. Pain Res Manag 2006; 11: 157-62.
40. *Lotsch J*. Basic genetic statistics are necessary in studies of functional associations in anesthesiology. Anesthesiology 2007; 107: 168-9.
41. *Sun T*, *Sacan O*, *White PF*, *Coleman J*, *Rohrich RJ*, *Kenkel JM*. Perioperative versus postoperative celecoxib on patient outcomes after major plastic surgery procedures. Anesth Analg 2008; 106: 950-8.
42. *White PF*, *Sacan O*, *Tufanogullari B*, *Eng M*, *Nuangchamnong N*, *Ogunnaike B*. Effect of short-term postoperative celecoxib

administration on patient outcome after outpatient laparoscopic surgery. Can J Anesth 2007; 54: 342-8.
43. *Nikanne E*, *Kokki H*, *Salo J*, *Linna TJ*. Celecoxib and ketoprofen for pain management during tonsillectomy: a placebo-controlled clinical trial. Otolaryngol Head Neck Surg 2005; 132: 287-94.
44. *Krishnaswami S*, *Hutmacher MM*, *Robbins JL*, *Bello A*, *West C*, *Bloom BJ*. Dosing celecoxib in pediatric patients with juvenile rheumatoid arthritis. J Clin Pharmacol 2012; 52: 1134-49.
45. *Stanko D*, *Bergesio R*, *Davies K*, *Hegarty M*, *von Ungern-Sternberg BS*. Postoperative pain, nausea and vomiting following adeno-tonsillectomy - a long-term follow-up. Paediatr Anaesth 2013; 23: 690-6.
46. *Kotiniemi LH*, *Ryhanen PT*, *Valanne J*, *Jokela R*, *Mustonen A*, *Poukkula E*. Postoperative symptoms at home following day-case surgery in children: a multicentre survey of 551 children. Anaesthesia 1997; 52: 963-9.
47. *Sarny S*, *Ossimitz G*, *Habermann W*, *Stammberger H*. Hemorrhage following tonsil surgery: a multicenter prospective study. Laryngoscope 2011; 121: 2553-60.
48. *Landau R*, *Schwinn D*. Genotyping without phenotyping: does it really matter? Anesth Analg 2013; 116: 8-10.
49. *Bean-Lijewski JD*, *Kruitbosch SH*, *Hutchinson L*, *Browne B*. Post-tonsillectomy pain management in children: can we do better? Otolaryngol Head Neck Surg 2007; 137: 545-51.
50. *Romsing J*, *Hertel S*, *Harder A*, *Rasmussen M*. Examination of acetaminophen for outpatient management of postoperative pain in children. Paediatr Anaesth 1998; 8: 235-9.
51. *Racoosin JA*, *Roberson DW*, *Pacanowski MA*, *Nielsen DR*. New evidence about an old drug—risk with codeine after adenotonsillectomy. N Engl J Med 2013; 368: 2155-7.