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REPORTS OF ORIGINAL INVESTIGATIONS

Impact of celecoxib on inflammation during cancer surgery: a randomized clinical trial

Impact du célécoxib sur l'inflammation pendant les chirurgies du cancer: une étude clinique randomisée

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Abstract

Purpose *During cancer surgery, prostaglandin-mediated inflammation may promote and activate micrometastatic disease with a consequent increase in long-term cancer recurrence. Cyclooxygenase-2 inhibitors, known to have anti-proliferative properties, may offset such perioperative perturbation. We investigated the effectiveness of these agents to minimize inflammatory changes during cancer surgery.*

Methods *Following ethics approval, 32 patients who were to undergo major intracavity cancer surgery were enrolled in this prospective, randomized, clinical trial. The treatment group received 400 mg celecoxib preoperatively followed by five 200 mg 12-hourly doses. The control group received no anti-inflammatory agents. Inflammatory and immunomodulatory end points were measured serially. The primary end points were the measured plasma and urinary prostaglandin E metabolite (PGE_M) levels 48 hours following surgery. Secondary endpoints included interleukin levels, leucocyte profile, and clinical end points.*

Results *No differences in the 48-hr plasma or urinary PGE_M levels were observed between the celecoxib and control groups. Linear mixed modeling, used to accommodate differences in baseline PGE_M levels, showed that celecoxib (cf. control) administration lowered plasma PGE_M over the entire 48-hr period following surgery (β-coefficient = -0.38 pg.ml^{-1}; 95% confidence interval: -0.69 to -0.06; $P = 0.021$). Celecoxib administration also lowered postoperative pain scores.*

Discussion *Standard dosing of the cyclooxygenase-2 inhibitor celecoxib slightly reduced perioperative cyclooxygenase activity during cancer surgery. Given cyclooxygenase's role in cancer pathways, we recommend dose-finding studies be undertaken before prospective clinical trials are conducted testing the currently unsubstantiated hypothesis that perioperative anti-inflammatory administration improves long-term cancer outcomes. This trial was registered at: Australian New Zealand Clinical Trial Registry: ACTRN12615000041550; www.anzctr.org.au*

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Résumé

Objectif *Pendant les chirurgies du cancer, l'inflammation médiée par les prostaglandines pourrait favoriser et activer une maladie micrométastatique avec une augmentation conséquente de la récurrence du cancer à long terme. Les inhibiteurs de la cyclo-oxygénase-2, dont on connaît les propriétés antiprolifératives, pourraient compenser une telle perturbation périopératoire. Nous avons étudié l'efficacité de ces agents pour minimiser les changements inflammatoires pendant les chirurgies du cancer.*

Méthode *Après avoir obtenu le consentement du Comité d'éthique, 32 patients devant subir une chirurgie ouverte majeure pour un cancer ont été enrôlés dans cette étude clinique prospective et randomisée. Le groupe traitement a reçu 400 mg de célécoxib avant l'opération, puis cinq doses de 200 mg aux 12 heures. Le groupe témoin n'a reçu aucun agent anti-inflammatoire. Les critères d'évaluation d'inflammation et d'immunomodulation ont été mesurés en série. Les critères d'évaluation principaux étaient les taux de métabolites des prostaglandines E (PGE_M) mesurés dans le plasma et dans l'urine 48 h après la chirurgie. Les critères d'évaluation secondaires comprenaient les taux d'interleukine, le profil leucocytaire ainsi que des critères d'évaluation cliniques.*

Résultats *Aucune différence n'a été observée dans les taux de PGE_M dans le plasma ou l'urine à 48 h entre le groupe célécoxib et le groupe témoin. Un modèle linéaire mixte, utilisé pour tenir compte des différences dans les taux de base de PGE_M, a démontré que l'administration de célécoxib réduisait les PGE_M dans le plasma tout au long de la période de 48 h suivant la chirurgie (coefficient $\beta = -0{,}38$; intervalle de confiance 95 % : $-0{,}69$ à $-0{,}06$; $P = 0{,}021$). L'administration de célécoxib a également réduit les scores de douleur postopératoires.*

Discussion *Une posologie standard de l'inhibiteur de cyclo-oxygénase 2 qu'est le célécoxib a légèrement réduit l'activité périopératoire de la cyclo-oxygénase pendant une chirurgie du cancer. Étant donné le rôle de la cyclo-oxygénase dans les voies de développement du cancer, nous recommandons de tester l'hypothèse, actuellement non vérifiée, selon laquelle l'administration périopératoire d'anti-inflammatoires améliorerait les pronostics oncologiques à long terme, avant de réaliser des études cliniques prospectives. Cette étude est enregistrée au : Registre australien et néozélandais des études cliniques : ACTRN12615000041550; www.anzctr.org.au*

Perioperative surgical stress up-regulates patients' adrenergic-inflammatory pathways. These changes are linked with cancer progression and are potentially mediated by increasing the susceptibility for activation or initiation of micrometastatic disease.[1–4] This hypothesis is supported by animal studies[5] and retrospective clinical studies that associated interventions that reduced the perioperative stress response with improved cancer outcomes, including spinal anesthesia,[6] epidural analgesia,[7] non-steroidal anti-inflammatory drugs (NSAIDs),[8] and beta-blockade.[9]

Perioperative inflammation increases cyclooxygenase (COX) activity, thereby elevating prostaglandin (PG) and cytokine levels.[10,11] Prostaglandins promote cancer processes[12] by facilitating tumour growth,[13] tumour invasion,[14] and lymphatic-mediated metastasis.[15] High COX-2 expression in lung,[16] breast,[17] colon,[18] and cervical[14] tumours is associated with poor survival. As a correlation exists between surgical-site and systemic prostaglandin E (PGE) levels,[19] elevated plasma PGE may be a useful biomarker throughout the perioperative period of cancer surgery as an indicator of adequate blockade of inflammatory processes. Prostaglandin E metabolite (PGE_M) - a promising cancer biomarker of treatment response and recurrence risk[20] - is more easily analyzed than the rapidly metabolized plasma PGE_2, but is untested as a marker of perioperative inflammatory response in the cancer surgery setting.[20,21]

Observational studies have reported that perioperatively administered NSAIDs are associated with improved disease-free survival.[8,22] Potential mechanisms include prevention of micrometastatic disease activation via reduced inflammation.[2]

In animals, COX-2 inhibitors (in contrast to non-selective COX inhibitors) prevent cancer progression.[5,23] Cyclooxygenase-2 inhibitors' capacity to mitigate surgery-induced inflammation and specific cancer markers of immunosuppression requires further study. The present trial undertook serial measurement of inflammatory markers (plasma PGE_M [$pPGE_M$] and urinary PGE_M [$uPGE_M$]) during the perioperative period of cancer surgery. Our primary hypothesis was that the selective COX-2 inhibitor celecoxib would suppress an anticipated perioperative increase in these inflammatory markers. The primary endpoints were $pPGE_M$ and $uPGE_M$ levels 48 hours following surgery commencement, capturing the period of peak perioperative inflammatory response.[11] Secondary end points included plasma cytokine concentrations, leucocyte profile changes, and clinical end points.

Methods

This institutionally approved (13/06, Peter MacCallum Cancer Centre Human Research Ethics Committee, St. Andrews Place, Melbourne, Australia, January 2015), prospectively registered, proof-of-concept mechanistic

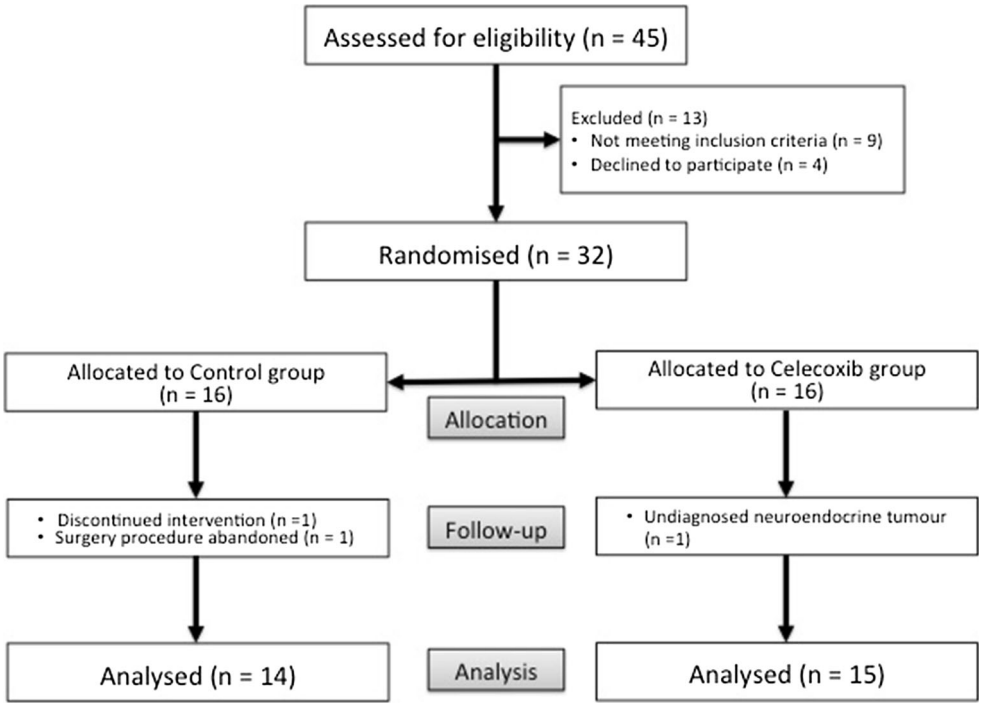

Fig. 1 Study profile

study was conducted with data collection during January to August 2015 at the Peter MacCallum Cancer Centre, Melbourne, Australia. Following attainment of written informed consent, patients were randomized (1:1) to celecoxib or control (no NSAID) groups on the day of surgery using the closed double envelope technique (prepared independently and administered by the institution's Biostatistics and Clinical Trials Centre), and were unblinded throughout the study.

Study criteria and recruitment

Patients more than 18 years of age with a cancer diagnosis undergoing (non-laparoscopic) intra-abdominal or intra-thoracic surgery were eligible for this study. Exclusion criteria included contraindications to celecoxib, acute inflammatory condition (sepsis, infection), pregnancy or lactation, concurrent use of oral corticosteroid treatment or NSAID/acetylsalicylic acid (within a week prior to study entry), presence of a neuroendocrine tumour, hepatic impairment (aspartate transaminase >240 $\mu \cdot L^{-1}$, alanine transaminase >110 $\mu \cdot L^{-1}$), and/or renal impairment (creatinine >150 $\mu mol \cdot L^{-1}$).

Group allocation, dosing, and anesthetic management

A study investigator obtained informed consent and performed patient registration, group allocation (randomization), and the collection of baseline demographic data including exposure to neoadjuvant (preoperative) chemotherapy (12 weeks prior to surgery). Patients underwent routine clinical evaluation including a detailed medical history, clinical examination, standard preoperative blood testing, and electrocardiography.

Patients randomized to celecoxib received a 400 mg oral loading dose one hour prior to surgery and subsequently 200 mg (oral) every 12 hours for five doses postoperatively (a total of six dosing events). The control group received no NSAID throughout the perioperative period. General anesthesia was induced with propofol 1.5-2 $mg \cdot kg^{-1}$ and rocuronium 0.5-0.75 $mg \cdot kg^{-1}$. The patients were ventilated with sevoflurane (1.5%-2.2% sevoflurane in a mixture with air/oxygen: 60/40). Opioid administration (fentanyl or morphine) was left to the discretion of the treating anesthesiologist (a non-investigator). Intraoperative steroid medications were avoided. Local anesthesia infiltration was permitted.

Immune mediators measured and laboratory analyses

Venous blood samples were obtained at baseline (preoperative) and six-, 24-, and 48-hr following the commencement of surgery. Samples were analyzed for markers of inflammation: PGE_M, cytokine concentrations (interleukin [IL]-6, IL-10), and the IL-6/IL-10 ratio.[24] Immunosuppression was analyzed by evaluating the platelet/lymphocyte ratio[25] because of its predictive role in cancer-related mortality. Urinary PGE_M was analyzed from urine samples obtained at baseline and 48-hr following surgery. All samples were immediately taken to a dedicated on-site laboratory, centrifuged, and the plasma frozen (−80°C) until analyzed.

Table 1 Baseline patient and surgical characteristics

	Control (14)	Celecoxib (15)
Comorbidities		
Age (yr)	62 (54-72)	60 (52-71)
Gender (Male)	7	12
ASA II/III	9/5	10/5
Smoking (previous 12 weeks)	1	1
Neoadjuvant chemotherapy	6	6
Past History:		
- Coronary artery disease	0	0
- Cardiac failure	0	0
- Asthma	1	3
- Diabetes	1	1
Medication:		
- ACEI/Angiotensin II receptor antagonist	6	6
- Diuretic	1	0
- Beta blocker	3	3
Surgery		
Surgery, Thoracic/ Laparotomy	6 (3 partial lobectomy, 3 lobectomy), 8 (5 segmental hepatectomy, 2 hemi-hepatectomy, 1 abdominal wall repair)	7 (4 partial lobectomy, 2 lobectomy, 1 pleurodesis), 7 (4 segmental hepatectomy, 2 hemi-hepatectomy, 1 abdominal wall repair)
Duration of surgery (minutes)	145 (112-175)	148 (125-190)
Compliance with treatment allocation	100%	100%
Postoperative complications		
POMS-5	6	4
POMS-30	0	0
Clavien-Dindo I	2	3
Clavien-Dindo II	5	4
Clavien-Dindo III/IV	1	0

Values are expressed as median (IQR) or as numbers for categorical variables. ACEI = angiotensin-converting enzyme inhibitor; ASA = American Society of Anesthesiologists; POMS = postoperative morbidity survey

All laboratory testing was performed on de-identified samples to ensure blinding of scientists to group allocation. The $pPGE_M$ and $uPGE_M$ were measured using a PGE_M enzyme immunoassay kit according to the manufacturer's instructions (Cayman Chemical, MI, USA). Cytokine analysis was performed using the BD Cytometric Multiplexed Bead-Based Immunoassay (BD Biosciences, San Jose, CA, USA) in accordance with the manufacturer's instructions. Leucocytes were counted using Cell-Dyn Sapphire (Abbott, IL, USA).

Clinical monitoring and data collection

Clinical review and assessment of patients' visual analogue scores (VAS) regarding the perception of static and dynamic pain were assessed twice daily prior to each dosing event. Data were compiled pertaining to the Clavien-Dindo severity grading system of postoperative complications and the postoperative morbidity survey (POMS) on postoperative days 5 and 30.[26] Data were analyzed at the study's conclusion.

Statistical analysis

A pre-trial power calculation was based on a previous study of anti-inflammatory use in a non-cancer surgical population that found preoperative celecoxib halved PGE production.[19] Using a two-sided significance level of 5%, it was calculated that 30 patients would provide 85% power to detect a 10 $pg{\cdot}mL^{-1}$ reduction in $pPGE_M$ (from 50 $pg{\cdot}mL^{-1}$) at 48 hr after surgery (assuming a standard deviation of 9 $pg{\cdot}mL^{-1}$). Hence, we recruited 32 patients.

All data were tested for normality using the Kolmogorov-Smirnov test. Normally distributed data are presented as the mean (SD) and non-normally distributed data as the median (interquartile range). Where the

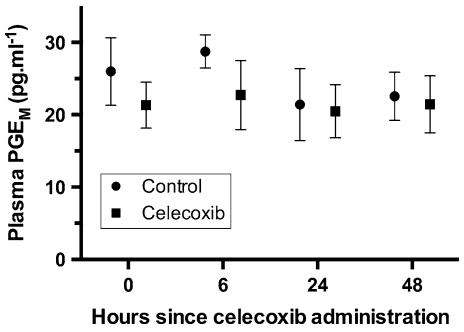

Fig. 2 Perioperative plasma prostaglandin E metabolite ($pPGE_M$) concentrations in patients receiving celecoxib compared with control. Data are presented as the mean with 95% confidence interval

assumption of normal distribution was confirmed, an independent two-sample *t*-test was used. Otherwise a Mann-Whitney U test was performed. Categorical data were analyzed using the two-tailed Fisher's exact test. Safety end points and complications (RIFLE-classified kidney injury) are reported as frequency. As this study has a proof-of-concept design, analysis was planned *per protocol* if patients were compliant with at least five of the six dosing events to which they were randomized.

In addition to the planned analysis of the primary endpoint using a univariate analysis, *post hoc* linear mixed models using unstructured covariance for repeated measures and random effects were used to assess the effect of celecoxib on PGE_M (plasma and urinary concentrations, primary end points), cytokine concentrations, and leucocyte profiles (secondary endpoints) over the entire 48-hr perioperative period after adjusting for the fixed effect of biologically plausible confounding. Predictors that were entered into the fixed effects portion of the model included age, sex, duration of operation, site of operation (abdominal *vs* thoracic), use of neoadjuvant chemotherapy, beta-blockers, and an interaction term between celecoxib and the use of neoadjuvant chemotherapy. Predictors were then removed in a stepwise fashion starting with the predictors that had the largest *P* value to obtain a parsimonious model. Covariates were no longer removed if the reduced model was associated with a larger Schwarz's Bayesian Criterion (BIC). All statistical analyses were conducted using SPSS for Windows (version 23, IBM, Armonk, NY, USA), and $P < 0.05$ was considered to indicate statistical significance.

Results

The study was stopped following the recruitment and follow-up (30 days following surgery) of the planned 32 patients. A per-protocol analysis was conducted following exclusion of three patients (Fig. 1). One patient in the control group suffered a pain crisis and was assessed by the treating team as requiring NSAID treatment; one patient's (celecoxib group) surgical procedure was abandoned after induction of general anesthesia due to disease progression; and one patient's (celecoxib group) tumour was found to be neuroendocrine in origin after initiation of surgery. The two study groups were similar in baseline characteristics and perioperative parameters (Table 1).

Cyclooxygenase activity and PGE_M production

By the 48-hr time point, there were no significant differences between the celecoxib and control groups regarding the unadjusted mean $pPGE_M$ concentration (21.5 *vs* 22.6 pg·mL^{-1}; $P = 0.65$, Fig. 2) or the $uPGE_M$ concentration (8.4 *vs* 9.9 pg·mL^{-1}; $P = 0.66$) (Table 2). The six-hour mean $pPGE_M$ concentration, however, was lower in the celecoxib group (22.7 *vs* 28.8 pg·mL^{-1}; $P = 0.02$).

A linear mixed model was utilized to account for baseline differences in the PGE_M concentrations for the observations at each time point and to examine the effect of celecoxib on $pPGE_M$ over the entire 48-hr perioperative period. It demonstrated that celecoxib lowered the $pPGE_M$ concentrations over the 48-hr perioperative period compared with that of the control group (β-coefficient = −0.38 pg·mL^{-1}; 95% confidence interval [CI]: −0.69 to −0.06 pg·mL^{-1}; $P = 0.02$, Table 3).

Factors including age, sex, surgical site, and duration of the operation were not significantly associated with changes in $pPGE_M$ concentrations and so were removed during the modeling process. Further removal of neoadjuvant chemotherapy ($P = 0.62$) from the final linear mixed model resulted in an inferior model according to the information criterion (BIC = 320), but use of celecoxib remained significantly associated with reduced $pPGE_M$ concentration compared with that of the control group. In a separate model, no covariates (including celecoxib) were associated with changes in $uPGE_M$ concentration.

Cytokines and immune cell profile

Markers of an inflammatory response to surgery (thrombocytosis, lymphopenia, elevated IL-6/IL-10 ratio) were elevated in the control group (*cf.* celecoxib) at specific time points (Table 2). During linear mixed model testing, however, celecoxib prevented only the thrombocytosis that was observed in the control group (β-coefficient = 35.4 × 10^9·L^{-1}; 95% CI: −70 to −0.3 × 10^9·L^{-1}; $P = 0.049$), after adjusting for use of neoadjuvant chemotherapy ($P = 0.11$). The use of celecoxib was not significantly associated with changes in IL-6 ($P = 0.669$),

Table 2 Prostaglandin and interleukin concentrations, leucocyte numbers, immune cell ratios

	Control group (n = 14)	Celecoxib group (n = 15)	Difference (95% CI)	P-Value
$pPGE_M$ ($pg \cdot mL^{-1}$)				
- Baseline	26.0 (8.1)	21.3 (5.7)	4.7 (−0.8 to 10.1)	0.09
- 6 hr	28.8 (4.1)	22.7 (8.3)	6.1 (0.9 to 11.2)	0.02
- 24 hr	21.4 (8.6)	20.5 (6.6)	0.9 (−5.0 to 6.8)	0.75
- 48 hr	22.6 (5.8)	21.5 (7.1)	0.1 (−3.8 to 6.0)	0.65
$uPGE_M$ ($pg \cdot mL^{-1}$)				
- Baseline	12.4 (11.9)	12.3 (9.9)	0.1 (−8.3 to 8.5)	0.98
- 48 hr	9.9 (8.2)	8.4 (9.9)	1.5 (−5.4 to 8.4)	0.66
Interleukin-6 ($pg \cdot mL^{-1}$)				
- Baseline	89 [1-480]	86 [1-1156]	3 (−508 to 202)	0.62
- 6 hr	31943 [17295-82779]	49611 [15031-71639]	−17668 (−37819 to 27548)	0.72
- 24 hr	56292 [2394-206206]	39927 [24854-79994]	16365 (−30746 to 119322)	0.97
- 48 hr	19193 [6328-88941]	16122 [7019-53256]	3071 (−13260 to 36018)	0.71
Interleukin-10 ($pg \cdot mL^{-1}$)				
- Baseline	5 [1-91]	66 [20-122]	−61 (0 to 70)	0.06
- 6 hr	696 [170-881]	401 [170-6095]	295 (−4944 to 473)	0.83
- 24 hr	133 [77-667]	733 ([233-1822]	−600 (−937 to 26)	0.06
- 48 hr	109 [8-285]	148 [62-576]	−53 (−349 to 65)	0.27
Interleukin-6:10				
- Baseline	4 [1-72]	1 [0-29]	3 (−16 to 23)	0.35
- 6 hr	69 [57-160]	56 [17-136]	13 (−42 to 67)	0.25
- 24 hr	204 [113-851]	76 [34-340]	128 (6 to 508)	0.04
- 48 hr	363 [56-1966]	113 [45-1067]	250 (−69 to 581)	0.25
White Cell Count ($x10^9 \cdot L^{-1}$)				
- Baseline	5.8 [4.6-7.8]	6.9 [5.1-7.4]	−1.1 (−1.7 to 1.1)	0.80
- 6 hr	11.1 [8.4-11.8]	10.6 [8.9-11.7]	0.5 (−2.0 to 2.1)	0.78
- 24 hr	11.0 [7.2-12.9]	8.5 [7.3-11.2]	2.5 (−1.0 to 4.1)	0.41
- 48 hr	8.1 [6.6-11.4]	7.8 [5.5-9.4]	0.3 (−1.2 to 3.1)	0.44
Lymphocytes ($x10^9 \cdot L^{-1}$)				
- Baseline	1.4 [0.9-2.0]	1.5 [1.1-2.3]	−0.2 (−0.8 to 0.4)	0.46
- 6 hr	0.8 [0.7-1.3]	1.6 [1.1-2.3]	−0.8 (−1.2 to −0.1)	0.04
- 24 hr	1.2 [0.9-1.7]	1.2 [0.8-1.5]	0.1 (−0.3 to 0.4)	0.83
- 48 hr	1.5 [0.8-1.9]	1.2 [0.8-1.8]	0.3 (−0.5 to 0.6)	0.92
Platelets ($x10^9 \cdot L^{-1}$)				
- Baseline	224 [195-238]	209 [189-256]	15 (−47 to 33)	0.99
- 6 hr	296 [198-314]	210 [172-267]	86 (−20 to 119)	0.12
- 24 hr	274 [186-296]	186 [140-209]	88 (28 to 122)	0.01
- 48 hr	225 [175-273]	165 [123-207]	60 (−1 to 84)	0.05
PLR				
- Baseline	177 [104-248]	135 [83-235]	42 (−48 to 98)	0.50
- 6 hr	249 [222-446]	123 [81-222]	126 (61 to 256)	0.01
- 24 hr	221 [158-329]	155 [122-177]	66 (−4 to 154)	0.06
- 48 hr	186 [135-235]	131 [81-207]	55 (−33 to 98)	0.18

$pPGE_M$ and $uPGE_M$ are expressed as mean (standard deviation), all other data are presented as median [interquartile range]. CI = confidence interval; PLR = platelet/lymphocyte ratio; $pPGE_M$ = plasma prostaglandin-E metabolite; $uPGE_M$ = urinary prostaglandin-E metabolite

Table 3 Linear mixed model showing the predictors of $pPGE_M$ concentrations during the entire 48-hr perioperative period

Variable	β-coefficient (95% CI)	*P*-value
Time (reference to baseline)		
- 6 hr	0.21 (−0.80 to 0.49)	0.15
- 24 hr	−0.27 (−0.55 to 0.03)	0.07
- 48 hr	−0.16 (−0.35 to 0.14)	0.31
Celecoxib treatment		
- No	*Reference group*	
- Yes	−0.38 (−0.70 to −0.06)	0.02
Neoadjuvant chemotherapy exposure		
- No	*Reference group*	
- Yes	−0.08 (−0.40 to 0.24)	0.62

CI = confidence interval; $pPGE_M$ = plasma prostaglandin-E metabolite. Sex, age, surgical site, duration of operation, use of beta-blockers were removed during the modeling process without increasing the Schwarz's Bayesian Criterion (BIC). The BIC of the final model was 298. A positive β-coefficient indicates a positive association between each predictor and an elevated $pPGE_M$; celecoxib treatment was associated with a lower $pPGE_M$ over the entire 48-hr perioperative period

IL-10 (P = 0.42), white blood cell count (P = 0.62), lymphocyte count (P = 0.94), or the platelet/lymphocyte ratio (P = 0.07).

Twelve patients (six controls, six with celecoxib treatment) were given neoadjuvant chemotherapy, which was associated with a lower lymphocyte count (β-coefficient = $-0.53 \times 10^9 \cdot L^{-1}$; 95% CI: -0.92 to $-0.15 \times 10^9 \cdot L^{-1}$; P = 0.01) and a higher platelet/lymphocyte ratio (β-coefficient = 126; 95% CI: 83 to 169; P = 0.001).

Pain and clinical outcomes

Celecoxib resulted in significantly lower static (rest) and dynamic (movement) VAS pain scores at 48 hr following surgery (Fig. 3). The POMS at postoperative days 5 and 30 (POMS-5 and POMS-30, respectively) did not differ between the two groups (Table 1). One control patient developed sepsis necessitating inotropic supportive care following surgery. No postoperative mortality occurred.

Discussion

When compared with no NSAID administration, perioperative dosing of the selective COX-2 inhibitor celecoxib resulted in a slight reduction ($pPGE_M$) in COX activity throughout the first 48 hr of the perioperative period following cancer surgery, although there was no difference between the two groups regarding the $uPGE_M$ concentration. Most of the difference in $pPGE_M$ between the groups was seen during the early perioperative phase. The clinical significance of such a small difference in a surrogate marker of inflammation is currently unknown.

The importance of prostaglandins in cancer pathophysiology[13,15] and progression[14,16] has led to the use of PGE_M as a cancer biomarker.[27,28] As unregulated COX activity during cancer surgery has been hypothesized to affect patients' long-term cancer outcomes,[8] our study has shown that $pPGE_M$ can be measured and is slightly inhibited by celecoxib perioperatively.

The role of celecoxib as an adjunctive aid to chemotherapy has been demonstrated in non-surgical settings[29] and was found to be most efficacious for obtaining complete PGE_M suppression at high (800-1600 mg daily)[30,31] dosage.[32] In the present study, we observed only modest suppression of COX activity by celecoxib. This may have been due to neoadjuvant chemotherapy's dysregulation of the post-transcriptional modification of COX-2 messenger RNA,[33] limiting celecoxib's effectiveness.[20] Alternatively, celecoxib either does not achieve profound PGE_M suppression perioperatively or can do so only at a higher dosage.

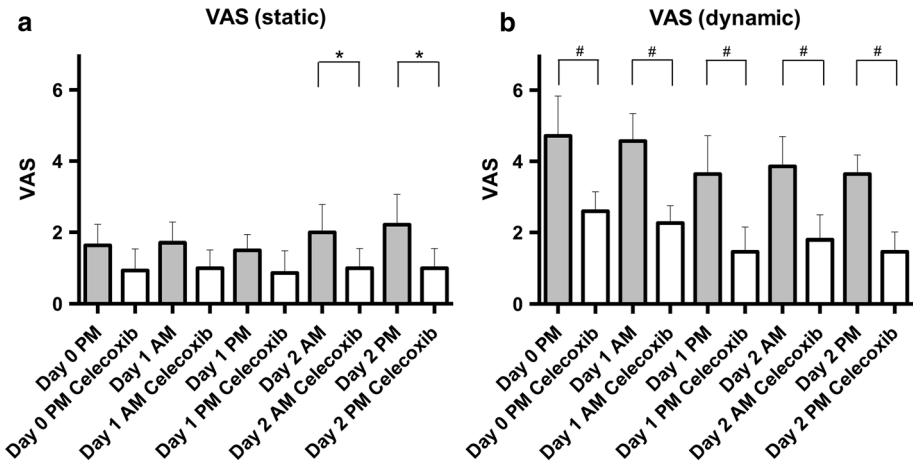

Fig. 3 Perioperative visual analogue scores. Celecoxib improved patients' twice-daily report of static (3a) and dynamic (3b) pain scores. Data are presented as the mean with 95% confidence interval. VAS = visual analogue score; *$P <$ 0.05, #$P < 0.01$

To characterize celecoxib's effectiveness as a perioperative anti-inflammatory agent more broadly, inflammatory (IL-6) and 'anti-inflammatory' (IL-10) cytokine concentrations were measured as secondary end points.[34] These cytokines are relevant to cancer processes through their regulation of T-helper cell differentiation and natural killer cell activity.[2] An elevated IL-6/IL-10 ratio is associated with excessive inflammatory response[24] and cancer progression.[35] Although celecoxib prevented an elevated IL-6/IL-10 ratio at 24 hr, it did not correlate with changes in the clinical end points (although our study was underpowered to assess such an association).

Several studies have reported that altered perioperative immune function (lymphopenia, elevated platelet/lymphocyte ratio) is associated with poor cancer survival.[25,36] Our study found that celecoxib prevented thrombocytosis (an acute-phase response), lymphopenia, and hence an elevation of the platelet/lymphocyte ratio during the early perioperative period. Of interest for future study is whether celecoxib preserves lymphocyte subpopulations (e.g. natural killer cells), which are vital anti-cancer effector cells.

As our study's primary end points were biochemical surrogates, a considered decision was made not to employ a placebo-based control. However, the lack of patient blinding confounds the interpretation of celecoxib's improvement in the VAS scores – a secondary endpoint. In this small proof-of-concept study, the risk of a type I statistical error remains high, and one should be cautioned not to over-interpret the study's findings. Importantly, although celecoxib slightly reduced a COX biomarker ($pPGE_M$) and was associated with improved VAS scores, the study was not powered to detect any improvements in clinical end points, particularly in reference to cancer outcomes.

In summary, this study found that standard dosing of the selective COX-2 anti-inflammatory drug celecoxib produced slight perioperative inhibition of COX as assessed by $pPGE_M$ levels. Thus, $pPGE_M$ may become a useful biomarker for determining effective COX blockade, particularly during the perioperative period following cancer surgery where anti-inflammatory techniques are postulated to improve patients' cancer outcomes. Currently, there is no strong evidence that an anti-inflammatory perioperative regimen could have an impact on long-term cancer outcomes. We suggest, then, that before large-scale trials investigating a potential benefit of perioperative NSAIDs on improved long-term cancer outcomes are contemplated, future studies first need to consider the optimal perioperative dosing strategy for NSAIDs.

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