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Effect of intravenous parecoxib on post-craniotomy pain

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Editor's key points

- The role of cyclooxygenase-2 (COX-2) inhibitors as analgesics in neurosurgical procedures is unclear.
- There is evidence from other areas that COX-2 inhibitors may be opioid sparing in the postoperative period.
- This current study found no benefit from using i.v. parecoxib, a COX-2 inhibitor, in reducing opioid consumption after craniotomy.
- Using parecoxib did not change the incidence or severity of side-effects, such as postoperative nausea and vomiting.
- There is a need for further studies to develop an evidence base for best pratcice post-craniotomy analgesia.

Background. Pain management in craniotomy patients is challenging, with mild-to-moderate pain intensity, moderate-to-high risk of postoperative nausea and vomiting (PONV), and potentially catastrophic consequences of analgesic-related side-effects. The aim of this study was to determine whether i.v. parecoxib administered at dural closure during craniotomy decreased total morphine consumption and morphine-related side-effects compared with placebo.

Methods. One hundred adult patients presenting for supratentorial craniotomy under propofol/remifentanil anaesthesia were randomized to receive parecoxib, 40 mg i.v., or placebo in a double-blind manner. All patients received local anaesthetic scalp infiltration, regular i.v. paracetamol, nurse-administered morphine in the post-anaesthesia care unit (PACU) until verbal analogue pain scores were $\leq$4/10 and patient-controlled morphine thereafter. Morphine consumption, pain intensity, and analgesia-related side-effects were recorded during the first 24 h after operation.

Results. Ninety-six patients (49 control and 47 parecoxib) were included in the analyses. Fifty-nine (61%) patients received morphine in the PACU and only one patient (control) did not receive any morphine in the postoperative period. There were no significant differences between the two groups in morphine consumption [20 (range: 0–102) *vs* 16 (range: 1–92) mg; P=0.38], pain intensity [excellent/very good pain relief in 78% of parecoxib patients; 74% of control patients (P=0.72)] or analgesia-related side-effects (PONV in 51% of parecoxib patients; 56% of control patients; P=0.55) in the first 24 h after operation. No major morbidity was recorded.

Conclusions. Our study demonstrated no clinical benefit to adding i.v. parecoxib to local anaesthetic scalp infiltration, i.v. paracetamol, and patient-controlled i.v. morphine after supratentorial craniotomy.

Trial Registration: ClinicalTrials.gov registry NCT00455117; Australian Clinical Trials Registry ACTRN12605000600640

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Pain management in craniotomy patients is challenging, because pain intensity is typically mild to moderate, the risk of postoperative nausea and vomiting (PONV) is moderate to high, and the consequences of analgesic-related side-effects may be catastrophic.[1] In addition to being non-sedative, cyclooxygenase-2 (COX-2) inhibitors have no effect on platelet aggregation and therefore may be suitable for use when the risks associated with bleeding are high.[2] Systematic reviews support the analgesic efficacy of i.v. parecoxib alone[3] or in combination with morphine patient-controlled analgesia (PCA)[4] for the pain associated with a variety of procedures, but only one previous study has examined the use of parecoxib in craniotomy.

Jones and colleagues[5] evaluated the effect of parecoxib, 40 mg i.v., in craniotomy patients receiving local anaesthetic scalp infiltration and nurse-administered intramuscular (i.m.) morphine. Morphine consumption at 24 h was similar in the placebo and parecoxib groups (mean 16.6 *vs* 15.1 mg) and the differences in pain intensity demonstrated at 6 h were clinically insignificant. However, as Jones and colleagues observed, PCA (rather than nurse-administered) morphine is the optimal method of determining a morphine-sparing effect in studies of analgesic efficacy. The aim of our study was to determine

whether parecoxib, 40 mg i.v., administered at dural closure during supratentorial craniotomy decreased total morphine consumption in the first 24 h after operation compared with placebo.

Methods

With approval from the research ethics committee at the Royal Melbourne Hospital, patients presenting for supratentorial craniotomy were approached and written informed consent was obtained. Eligible patients were aged 18–65 yr and were of ASA physical status I–III. Exclusion criteria included ischaemic heart disease, cerebrovascular disease, asthma, renal impairment (serum creatinine concentration >100 μmol litre^{-1}), allergy to any of the study medications, chronic pain, chronic opioid or benzodiazepine use, heavy alcohol intake, angiotensin-converting enzyme inhibitor or diuretic use, administration of paracetamol within 8 h of induction of anaesthesia or inability to communicate in English due to impaired conscious state (Glasgow Coma Score <15), cognitive deficit, intellectual disability, or language barrier.

Patients were randomized to receive parecoxib, 40 mg i.v. in 2 ml saline, or a placebo of 2 ml saline at dural closure. Computer-generated randomization results were concealed in opaque envelopes until consent had been obtained. The randomization was stratified by gender. The study medication was prepared by an anaesthetist who was not involved with the case. The patients, attending anaesthetists, surgeons, and postoperative observers were blind to group allocation.

Baseline patient characteristic data were collected. I.V. and intra-arterial access was established before induction, and routine monitoring was commenced. General anaesthesia was induced with propofol and remifentanil, and tracheal intubation was facilitated with atracurium. The pharmacokinetic–dynamic models of Schnider and colleagues[6] (for propofol; initial target 2–5 μg ml^{-1}) and Minto and colleagues[7] (for remifentanil; initial target 2–6 ng ml^{-1}) were implemented in effect-site control. Anaesthesia was titrated subsequently to a bispectral index (BIS-XP Version 4.0) between 40 and 60 (if BIS monitoring was not precluded by the surgical approach). The patients' lungs were ventilated with oxygen and air to normocapnia. The patients' scalps were infiltrated with bupivacaine 0.5% with epinephrine 5 μg ml^{-1} (maximum 20 ml) before skin incision. Dexamethasone was administered at surgeon request. Core temperature was measured in the distal oesophagus and forced air warming was used to maintain normothermia. At dural closure, the study medication was administered and paracetamol, 1 g i.v., was infused. Muscle relaxation was reversed with neostigmine 2.5 mg i.v. and glycopyrrolate 0.4 mg i.v., the trachea was extubated, and the patient was transferred to the post-anaesthesia care unit (PACU).

Postoperative pain was initially treated with nurse-administered i.v. morphine, with PCA morphine commenced when a verbal analogue scale (VAS) for pain was ≤ 4 out of 10. Paracetamol, 1 g i.v., was administered 6 hourly. No other analgesic drugs were administered.

Morphine consumption was measured at PACU discharge and 24 h. Pain scores, PONV scores, sedation scores, systolic arterial pressures, heart rates, and ventilatory frequencies were recorded at 0, 1, 2, 4, 8, and 24 h. Pain (resting and dynamic) was rated by patients using the 10-point VAS. PONV was rated by patients as: 0, absent; 1, nausea not requiring treatment; 2, nausea requiring treatment; and 3, vomiting. Sedation was rated by attending nurses as: 0, awake and alert; 1, easy to rouse with verbal commands; 2, drowsy, roused only by touch; or 3, somnolent, roused only by pain. At 24 h, patients rated the effectiveness of their pain regimen on a five-point scale (1, excellent; 2, good; 3, satisfactory; 4, poor; and 5, very poor). Major morbidity (including myocardial infarction, thrombo-embolic stroke, intracranial haemorrhage, significant blood loss, and renal failure) was recorded from the patient's chart.

The primary outcome was 24 h morphine consumption. Stoneham and colleagues[8] reported that median PCA morphine consumption in craniotomy patients was 17 mg in 24 h. Variability in morphine use is high and so we used an SD of 8 mg in our sample size calculation. The likely reduction in morphine consumption with the addition of parecoxib is in the order of 30%.[9] The sample size required for each group therefore was 41 patients ($\alpha=0.05$; power$=0.8$). To account for dropouts, we therefore recruited 100 patients, with 50 patients in each group.

Data were analysed on an intention-to-treat basis using Stata 10.1 (Stata Corporation, College Station, TX, USA). Continuous variables were graphed to determine their distribution. Normally distributed variables were described using mean and SD and compared using unpaired two-tailed *t*-tests. Skewed variables were described using median and range (or inter-quartile range) and compared using Wilcoxon's rank sum tests. Categorical variables were described using number (%) and compared using χ^2 or Fisher's exact test. Repeated-measures analysis of variance (normally distributed data) or Friedman's test (skewed data) were used to compare resting and dynamic pain scores, PONV scores, sedation scores, systolic arterial pressures, heart rates, and ventilatory frequencies over time between the two groups. A value of $P<0.05$ was considered to be statistically significant.

Results

One hundred patients were recruited. One patient's surgery was cancelled after randomization and three patients withdrew from the study after operation, leaving 96 patients (49 in the control group and 47 in the parecoxib group; Fig. 1). The groups were comparable at baseline (Table 1).

Fifty-nine (61%) patients received morphine in the PACU [26 (53%) in the parecoxib group and 33 (70%) in the control group; $P=0.08$] and only one patient (randomized to control) did not receive any morphine in the postoperative period. There was no significant difference in median

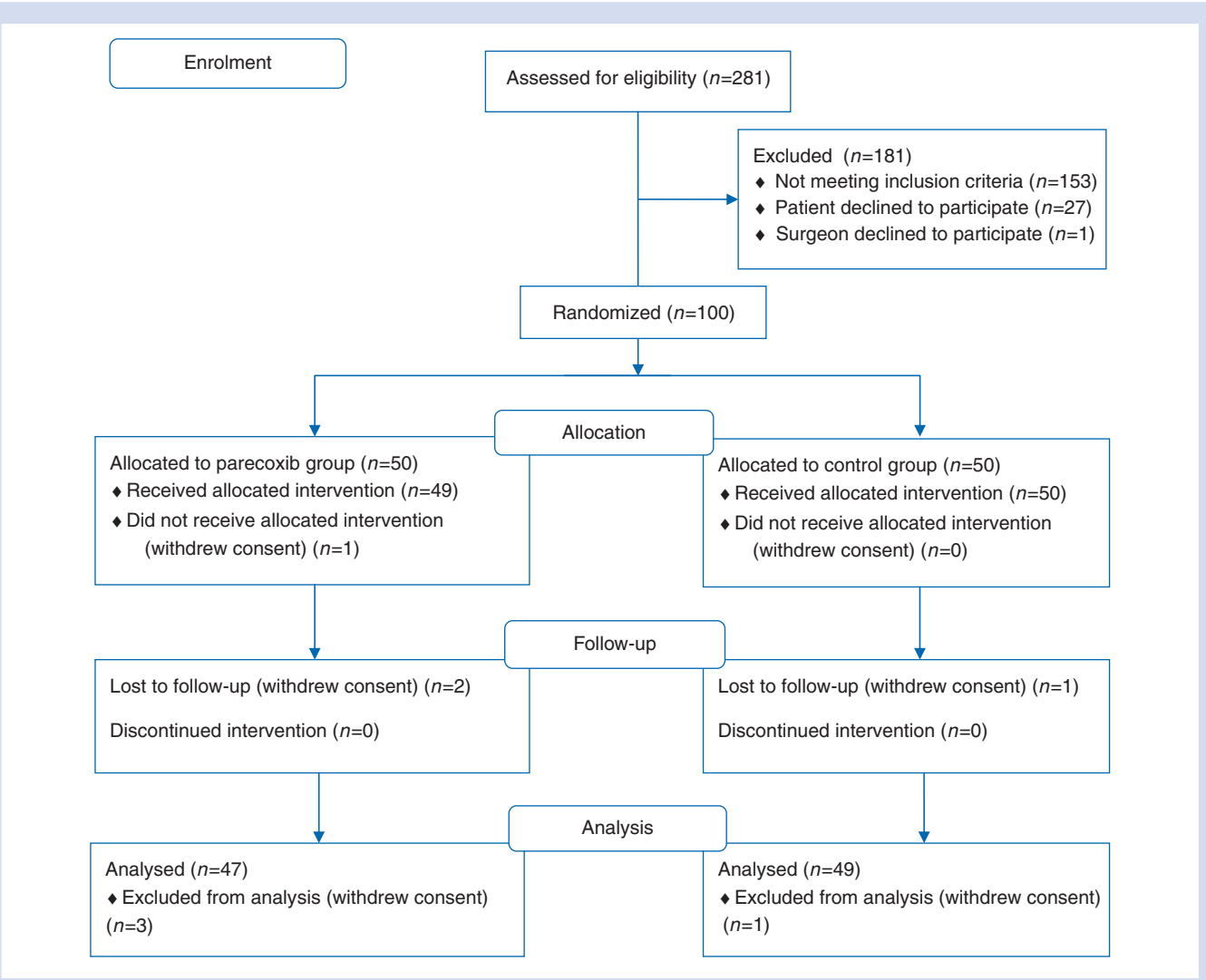

Fig 1 CONSORT diagram.

Table 1 Baseline characteristics. Data are expressed as mean (range), mean (SD) or number (%). ASA, American Society of Anesthesiologists

Characteristic	Control ($n=49$)	Parecoxib ($n=47$)
Age (yr)	46 (20–65)	41 (18–65)
Weight (kg)	72 (18)	75 (16)
Sex (female)	26 (53)	25 (53)
ASA physical status		
1	6 (12)	11 (23)
2	34 (70)	29 (62)
3	9 (18)	7 (15)
Pathology		
Tumour	36 (73)	30 (64)
Vascular	7 (14)	6 (13)
Other	6 (12)	11 (23)

morphine consumption in the first 24 h after operation between the two groups [20 (range: 0–102) *vs* 16 (range: 1–92) mg; $P=0.38$] (Table 2).

Systolic arterial pressures, heart rates, and ventilatory frequencies varied over the 24 h period within groups, but there was no difference between groups in resting or dynamic pain, PONV, or sedation scores (Table 3 and Fig. 2). Excellent or very good pain relief was achieved in 38 (78%) parecoxib patients and 35 (74%) control patients ($P=0.72$). Fifty-two patients (54%) had at least one episode of nausea within 24 h of surgery, but only seven patients vomited. No death or major morbidity was recorded.

Discussion

In our study, i.v. parecoxib, 40 mg i.v., had no effect on morphine consumption, pain intensity, or analgesic-related side-effects in the first 24 h after supratentorial craniotomy. This

result is consistent with the result of Jones and colleagues,[5] despite differences in study design. In addition to using PCA rather than nurse-administered morphine, we limited our study to supratentorial surgery, as infratentorial surgery may be associated with more pain;[10] confined anaesthetic maintenance to propofol, as volatile anaesthetics may be associated with more PONV;[11] did not impose morphine dose limitations (except for a 5 min lockout), as this may confound estimation of morphine consumption; and administered paracetamol regularly and measured dynamic and resting pain scores. We conclude that there is no clinical benefit to adding parecoxib to local anaesthetic scalp infiltration, i.v. paracetamol, and PCA morphine after supratentorial craniotomy.

Table 2 Intraoperative and postoperative data. Data are expressed as median (range) or number (%). PACU, post-anaesthesia care unit; PCA, patient-controlled analgesia

Characteristic	Control	Parecoxib	*P*-value
Induction, wound closure (min)	195 (97–614)	188 (73–520)	0.62
Wound closure, eyes open (min)	15 (0–80)	15 (0–65)	0.72
Wound closure, PACU discharge (min)	100 (67–247)	90 (40–162)	0.64
Dexamethasone administered	42 (86)	41 (87)	0.87
Dexamethasone dose (mg)	12 (4–20)	8 (4–20)	0.03
Bispectral index monitoring used	24 (49)	20 (43)	0.53
Morphine administered in PACU	26 (53)	33 (70)	0.08
Morphine administration in PACU (mg)	5 (1–14)	6 (1–14)	0.88
Morphine administration via PCA (mg)	18 (0–97)	11 (0–86)	0.32
Morphine total (mg)	20 (0–102)	16 (1–92)	0.38
Postoperative nausea and/or vomiting	28 (56)	24 (51)	0.55
Excellent or very good pain relief	38 (78)	35 (74)	0.72

These results contrast with two studies on the use of oral non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors in craniotomy patients. Tanskanen and colleagues[12] randomized patients to paracetamol or ketoprofen as an adjuvant to PCA oxycodone. Oxycodone consumption (19.6 *vs* 37.1 mg) and pain scores (5/100 *vs* 22/100) were significantly lower in the ketoprofen group. Rahimi and colleagues[13] conducted a randomized trial in which rofecoxib was offered in addition to nurse-administered oral or i.v. opioids and paracetamol. They reported that rofecoxib patients had significantly lower pain scores than opioid-only patients (3.8/10 *vs* 5.3/10). These studies were small, and in the case of Rahimi and colleagues, uncontrolled.

Our results also contrast with previous research in the non-craniotomy setting. In their systematic review, Elia and colleagues[4] reported that NSAIDs and COX-2 inhibitors reduced PCA morphine consumption by 15–55%. The median 24 h morphine consumption in the control groups in these studies was 49 mg. They demonstrated a small improvement in pain intensity and morphine-related side-effects in the NSAID groups only. The effect of COX-2 inhibitors on pain intensity and side-effects was unclear, as there were too few studies and inconsistent measurement tools were used. Both drug classes were associated with adverse effects, but the risks of these were small and their relevance to 'single-shot' administration is debatable.[4]

The reason for the different results in these studies and ours may relate to pain intensity after supratentorial craniotomy. The median pain scores in our control group were only

Table 3 Postoperative characteristics. Results are presented as median (inter-quartile range) or mean (SD). *Friedman test. **Repeated-measures analysis of variance. PONV, postoperative nausea and vomiting; PONV was rated by patients as: 0, absent; 1, nausea not requiring treatment; 2, nausea requiring treatment; and 3, vomiting. Sedation was rated by attending nurses as: 1, awake and alert; 2, easy to rouse with verbal commands; 3, drowsy, roused only by touch; 4, somnolent, roused only by pain

		0 h	1 h	2 h	4 h	12 h	24 h	*P*-value
PONV score	Control	—	1 (1–1)	1 (1–2)	1 (1–2)	1 (1–1)	1 (1–1)	
	Parecoxib	—	1 (1–1)	1 (1–2)	1 (1–2)	1 (1–1)	1 (1–1)	1.0*
Sedation score	Control	2 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–0)	
	Parecoxib	2 (2–4)	1 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–0)	1.0*
Systolic arterial pressure (mm Hg)	Control	145 (24)	139 (22)	127 (16)	125 (15)	121 (14)	122 (17)	
	Parecoxib	139 (20)	133 (17)	126 (14)	122 (15)	122 (14)	121 (15)	Between groups 0.26; within groups <0.0001**
Heart rate (beats min^{-1})	Control	76 (16)	72 (14)	78 (16)	76 (17)	72 (17)	76 (13)	
	Parecoxib	74 (17)	70 (16)	75 (16)	73 (17)	72 (14)	74 (15)	Between groups 0.50; within groups 0.0003**
Ventilatory frequency (bpm)	Control	15 (3)	15 (2)	15 (3)	15 (2)	16 (2)	16 (2)	
	Parecoxib	15 (3)	15 (2)	16 (2)	16 (3)	16 (2)	16 (2)	Between groups 0.06; within groups 0.002**

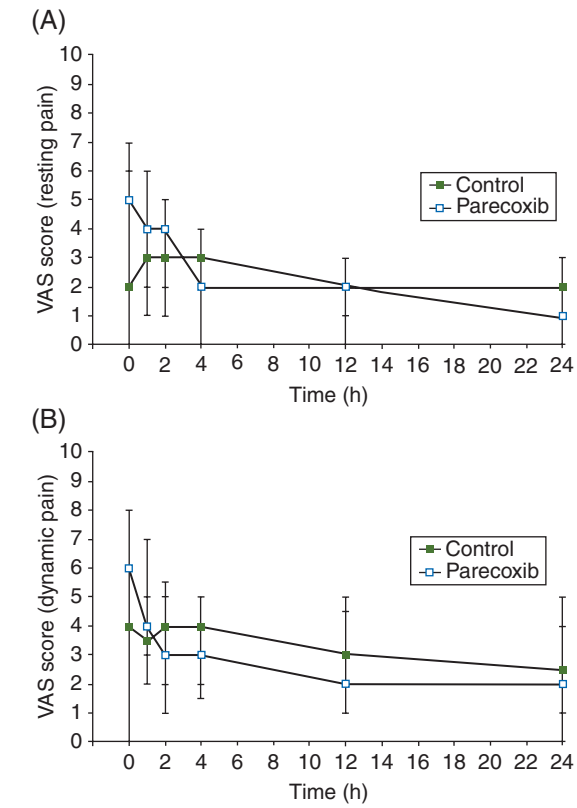

Fig 2 VAS score for resting pain (A) and dynamic pain (B) in patients receiving parecoxib and placebo. Data are presented as median (inter-quartile range).

3/10 at 1 h and only 2/10 at 24 h after operation. These results are consistent with previous studies with similar intraoperative and postoperative analgesic protocols, including regular paracetamol administration.[5 14 15] Baseline pain intensity is crucial to sensitivity of analgesic studies, and it is difficult to prove a benefit of an analgesic in terms of morphine-sparing if there is little or no pain ('no pain, no gain').[16] Furthermore, the variability in pain scores was great: the range of pain scores at 1 h was 0–8 and at 24 h was 0–7 in our study (once again consistent with previous studies).[5 14 15] It may be that selective administration of COX-2 inhibitors as 'rescue' analgesics when high morphine requirement is identified in the PACU may be a worthwhile approach, but this would require investigation with a properly designed trial.

PCA morphine with regular paracetamol and intraoperative local anaesthetic scalp infiltration appears to be an effective analgesic regimen for supratentorial craniotomy. Although not widely used,[17] PCA is a safe and effective method of treating pain after craniotomy.[8 12 15] Morphine consumption is generally lower than that reported in non-craniotomy settings,[4] although a direct comparison has not been made, and morphine consumption in our study was consistent with previous studies in similar settings.[5 15] Paracetamol given in addition to PCA opioids is proven to reduce opioid consumption, although it has not been proven to decrease opioid-related side-effects.[18] Finally, scalp infiltration with bupivacaine results in lower pain scores 1 h after operation as well as having benefits intraoperatively.[19]

Our study has several limitations. First, we did not include prophylactic anti-emetics in our protocol even though craniotomy is associated with a high rate of PONV.[14 20] Nevertheless, 85% of our patients received dexamethasone (a proven anti-emetic)[11] for surgical indications and the incidence of vomiting (8%) was consistent with previous studies in which prophylactic anti-emetics were given.[5 20] Dexamethasone dose was higher in the control group but doses were supra-maximal for PONV in both groups.[11] Secondly, even though we restricted the surgical approach to supratentorial, this allowed a variety of operations to be included that undoubtedly produced a range of postoperative pain.[10] However, restricting the operation further, to frontal approaches only, for example, would have reduced the feasibility and generalizability of the trial. Thirdly, our sample size calculation did not anticipate the extent of variability in morphine requirement that eventuated in our study. Statistically significant, but possibly clinically unimportant, differences in morphine requirement therefore may have been missed. Finally, our study and others were too small to identify the risk of rare but important side-effects such as bleeding, renal failure, and myocardial infarction. Systematic review may be the only way to establish these risks firmly.

There is no consensus about postoperative pain management in craniotomy patients. A recent survey of British neurosurgical centres revealed that only 23% of units had a standardized analgesic protocol, whereas 52% of the units used NSAIDs, some prescribing them regularly.[17] On the basis of the foregoing discussion, it seems likely that these protocols were not entirely evidence-based. We agree with these authors that adequately powered randomized controlled trials are required to address the safety and efficacy issues in pain management after craniotomy.

In conclusion, our study demonstrated no clinical benefit to adding i.v. parecoxib to local anaesthetic scalp infiltration, i.v. paracetamol, and PCA morphine after supratentorial craniotomy. On this basis, we do not believe that the use of prophylactic i.v. parecoxib in craniotomy patients is justified.

Conflict of interest

None declared.

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