Background. Pain after craniotomy is often under-treated. Opiates carry distinct disadvantages. Non-steroidal anti-inflammatory drugs have an anti-platelet action and carry a bleeding risk. Cyclo-oxygenase 2 inhibitors such as parecoxib are not associated with a bleeding risk and would be welcome analgesics if shown to be effective.

Methods. In a prospective double-blind, randomized, placebo-controlled study, we investigated the analgesic effect of a single dose of parecoxib 40 mg given at dural closure in 82 patients undergoing elective craniotomies. Remifentanil was used intraoperatively, and i.v. morphine was titrated to the requirement in the post-anaesthetic unit. On the ward, i.m. morphine 5 mg as required and regular acetaminophen was prescribed. Morphine use and visual analogue pain scores were recorded at 1, 6, 12, and 24 h after surgery.

Results. Parecoxib reduced pain scores at 6 h and morphine use at 6 and 12 h after operation. However, overall, it had only minimal impact on postoperative analgesia. We found a wide variability in analgesic requirements where 11% of patients required no opioids and 16% required more than 15 mg i.v. morphine 1 h after the surgery.

Conclusions. We found only limited evidence to support parecoxib as an analgesic after craniotomy.

Keywords: analgesia, postoperative; neurosurgery; non-steroidal anti-inflammatory drugs

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Methods

This was a prospective, double-blind, randomized, placebo-controlled study. Approval was obtained from the Institutional Research Ethics Committee. Patients aged more than 18 yr, undergoing elective craniotomy, were recruited. Exclusion criteria included confusion, contraindication to NSAIDs, and a history of chronic pain or regular opioid consumption. After obtaining written informed consent, patients were educated in the use of the visual analogue slide ruler.

Patients were allocated to receive either parecoxib 40 mg or saline at closure of dura. Allocation was via the computer-generated permuted block randomization. A syringe containing parecoxib or saline was prepared by a third party and labelled study drug. Patient, anaesthetist, and investigators were blinded to the syringe content.

Opioids and clonidine were avoided as premedications. Remifentanil with either propofol or volatile agents were used for anaesthesia. Bupivacaine 0.5% with epinephrine (1:200 000) was administered by the neurosurgeons along the planned incision. Dexamethasone 0.1 mg kg$^{-1}$ was given to all the patients. Morphine was avoided until the patient was extubated. Morphine could be administered before PACU if judged clinically appropriate by the anaesthetist. No nitrous oxide, acetaminophen, clonidine, tramadol, NSAIDs, or scalp blocks were to be used perioperatively. Incision length and position were noted.

In PACU, morphine was administered as required to a verbal pain score (numeric scale of 0–10) 3 or less, sedation score 2 or less (Table 1), or maximum morphine dose up to 15 mg. All patients were prescribed acetaminophen 1 g regularly every 6 h and morphine 5 mg i.m. if required every 3 h. No codeine, tramadol, oral opioids, or NSAIDs were to be given in the first 24 h.

After 1 h in recovery and after operation at 6, 12, and 24 h, patients were formally assessed for visual analogue pain score, sedation score, nausea and vomiting score, and global satisfaction score. In recovery, total morphine use at 1 h and antihypertensives and antiemetics, if given, were noted. On the ward, timing and amount of morphine and antiemetics used were noted.

Formal assessment was made by the PACU nursing staff in PACU, and by the acute pain team consisting of either a pain nurse or anaesthetic registrar after operation in the ward.

The number of patients in each group was determined based on previous experience of morphine use in PACU at our institution and a standard deviation of 7.8 mg derived from this. We assumed that a 50% reduction of PACU morphine dose from 10 to 5 mg would represent a significant clinical difference with respect to unwanted side-effects of morphine. On this basis and assuming a type 1 error protection of 0.05 and a power of 0.8, 39 patients were required in each group. This was increased to 41 in each group to allow for post-randomization withdrawal or significant protocol violation. Data were analysed using Student’s $t$-test for continuous variables and $\chi^2$ or Fisher’s exact test for nominal variables. The software used was Statview v4.5 (Abacus Concepts, CA, USA). A $P$-value of <0.05 was taken to indicate statistical significance. Data are presented as mean (SD) for patient characteristic data or mean (SEM) (Table 2).

Results

Eighty-two patients were enrolled in the study. Two were excluded because a craniotomy was not performed.

There were no differences between the groups with regards to age, gender, duration of surgery, or blood loss. There was no difference in the type of surgery, incision length, or surgical grading of likely pain. There was a difference in weight, with the parecoxib group being heavier.

Protocol deviations resulted in intraoperative morphine (2–10 mg), clonidine (150–300 µg), or both being given to 13 patients, although their distribution was similar across the treatment groups.

There were no significant differences in the time spent in PACU [mean (SEM) 119 (6) min parecoxib, 114 (7) min saline, $P=0.56$].

Visual analogue scale (VAS) scores were similar at all time points except at 6 h, where the parecoxib group had significantly lower VAS scores ($P<0.01$, Fig. 1).

Morphine analgesia was required by the majority of patients in PACU (89%), with no significant difference in dose requirements between the groups [parecoxib 11.1 (1.1) mg, saline 9.8 (1.0) mg, $P=0.40$]. The 95% confidence interval for the difference in morphine required in PACU between the two groups is −2.7 to 4.3. For the remainder of the 24 h postoperative period, ~50% of patients in each group (19 parecoxib and 21 saline) required additional
The degree of sedation in PACU was marginally lower with parecoxib patients, with only 40% of patients having a score of 2 or higher compared with 57% of those in the saline group, this difference was not statistically significant ($P=0.14$). There was no correlation between morphine dose and sedation score ($r^2=0.041$, $P=0.08$).

There was a low overall incidence of nausea and vomiting (14%) and there were no differences in the incidence or severity of nausea and vomiting between the groups.

Overall, patients rated their satisfaction as high.

### Discussion

This study demonstrates that a single intraoperative dose of parecoxib in patients having a craniotomy reduced pain scores at 6 h and morphine use from 6 to 12 h after operation, but overall had only minimal impact on postoperative analgesia.

De Benedittis and colleagues$^3$ reported that 47% of patients experienced moderate to severe postoperative pain after craniotomy. He concluded that the reputation for decreased analgesia requirement was actually due to the reluctance of neurosurgeons to adequately treat craniotomy pain for fear of respiratory and cerebral depression. Regardless, an effective non-opioid analgesic would find a welcome role in the current management of craniotomy pain. However, we found only limited evidence to support the use of parecoxib after craniotomy.

Parecoxib is a COXIB with no effect on platelets or bleeding time. Although much attention has been drawn to the risk of these agents in patients with cardiovascular thromboembolic disease, parecoxib has been shown to be safe in the perioperative period in non-cardiac surgery.$^{12}$ COXIBs are known to be effective perioperative analgesics for a range of surgical procedures with documented morphine-sparing effects between 30% and 50%. Tanskanen and colleagues$^3$ published one of the few papers examining NSAIDs for analgesia after craniotomy. They showed regular ketoprofen commenced an hour after operation, when compared with acetaminophen alone, decreased PCA oxycodone by 47% over the first 24 h. Therefore, we were surprised that a greater analgesic effect was not demonstrated for intraoperative parecoxib. There may be a number of explanations for this.

When designing this study, PACU morphine dose was thought to be the most significant outcome as it could translate a lower morphine dose to the effects such as lower sedation score, less nausea, and shorter PACU stay. Unlike some other studies where a benefit was seen in the immediate postoperative period, our study failed to show a benefit until the 6–12 h period which is arguably less important. This may in part relate to the move from using intraoperative opioids such as fentanyl to remifentanil, an ultra-short-acting opioid which induces acute opioid tolerance$^{14}$ and hyperalgesia$^{15}$ in the early postoperative period. As morphine is rendered relatively ineffective as an analgesic in PACU, it follows that the amount of morphine administered became misleading as a guide to analgesic quality between the groups. However, there was no significant difference in VAS scores in PACU which we would expect with the addition of an effective analgesic. Perhaps, the hyperalgesia seen with remifentanil in some way attenuates the analgesic benefit expected with COXIBs?

Interestingly, a recent cross-over study by Troster and colleagues$^6$ found that parecoxib given before remifentanil infusion, but not during, produced a clinically relevant reduction in opioid-induced hyperalgesia in volunteers. It is thought that opioid tolerance in part is related to up-regulation of prostaglandins at central sites$^{17}$ which can be prevented by early COX inhibition but is ineffective once prostaglandins sensitize the nociceptive system.

As previously noted, we found a wide variability in pain after craniotomy; 11% of patients required no opioid after operation whereas 16% required more than 15 mg
morphine in the PACU. The average morphine requirement in PACU was 9.9 mg at 1 h. Similarly on the ward, 50% of patients received at least one dose of morphine and 25% had multiple doses. Our findings lend weight to the growing evidence that pain after craniotomy can be persistent and difficult to treat.

Pain after craniotomy is prominently superficial and thought to arise from surgical incision and reflection of muscle underlying the scalp rather than the brain itself. It is stated that subfrontal and temporal approaches may be more painful than others. On the other hand, a study by Quiney and colleagues in 1996 on post-craniotomy pain in 52 patients found that there was no significant difference in postoperative codeine phosphate requirement between temporal, frontal, parietal, or occipital craniotomy; however, there was a trend towards an increased analgesic requirement in the temporal group. Also, female and younger patients tend to have more pain. While we did not control for these factors, there were no differences between the groups with regards to age, sex, type of incision, length of incision, and length of surgery or surgical assessment of likely pain. There was a clinically small difference between the groups in weight which would possibly bias in favour of lower morphine requirements in the saline group. Intraoperative use of morphine and clonidine were discouraged but left to the discretion of the anaesthetist. There were no differences between the groups in their use.

After discharge from PACU, patients were given regular oral acetaminophen and morphine i.m. as required. This method of morphine administration has obvious limitations as a tool to distinguish analgesic requirements between patients. Nurse administration of analgesia via the i.m. route is an involved process requiring patient request, two nurses, and an invasive procedure for administration, all well known to limit the ease at which morphine can be delivered. With a set dose of 5 mg, the ability to titrate to need is impaired. We would have preferred to use a patient-controlled analgesia (PCA), but were met with resistance from our neurosurgical colleagues despite demonstrated safety post-craniotomy. Given that morphine i.m. reflected our practice at that time (now increasingly oral oxycodeone), it seemed a valid compromise. i.v. morphine was used in PACU where we felt our greatest benefit would be demonstrated.

In conclusion, we found only limited evidence to support parecoxib as an analgesic after craniotomy. Given there were decreased VAS scores at 6 h and morphine reduction at 6–12 h after operation, further investigation may reveal subgroups of patients in whom a stronger benefit may be seen.

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