A single preoperative dose of diclofenac reduces the intensity of acute postcraniotomy headache and decreases analgesic requirements over five postoperative days in adults: A single center, randomized, blinded trial

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ABSTRACT

Objective: Postcraniotomy headache causes considerable pain and can be difficult to treat. We therefore tested the hypothesis that a single 100-mg preoperative dose of diclofenac reduces the intensity of postcraniotomy headache, and reduces analgesic requirements.

Methods: 200 patients having elective craniotomies were randomly assigned to diclofenac (n = 100) or control (n = 100). Pain severity was assessed by an independent observer using a 10-cm-long visual analog scale the evening of surgery, and on the 1st and 5th postoperative days. Analgesics given during the first five postoperative days were converted to intramuscular morphine equivalents. Results were compared using Mann-Whitney-tests; P < 0.05 was considered statistically significant.

Results: Baseline and surgical characteristics were comparable in the diclofenac and control groups. Visual analog pain scores were slightly, but significantly lower with diclofenac at all times (means and 95% confidence intervals): the evening of surgery, 2.47 (1.8–3.1) vs. 4.37 (5.0–3.7), (P < 0.001); first postoperative day, 3.98 (3.4–4.6) vs. 5.6 (4.9–6.2) cm (P < 0.001) and 5th postoperative day: 2.8 (2.2–3.4) vs. 4.0 ± (3.3–4.7) cm (P = 0.013). Diclofenac reduced systemic analgesic requirements over the initial five postoperative days (mean and 95% CI): 3.3 (2.6–3.9) vs. 4.3 (3.5–5.1) mg morphine equivalents (P < 0.05).

Conclusions: Preoperative diclofenac administration reduces postcraniotomy headache and postoperative analgesic requirements—a benefit that persisted throughout five postoperative days.

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1. Introduction

According to the International Headache Society, acute postcraniotomy headache (PCH) is defined as a headache of variable intensity, being most serious at the site of surgical intervention and developing within 7 days after craniotomy. Typically, pain resolves within 3 months [1]. The headache is mainly nociceptive in nature and largely results from surgical damage to pericranial muscle and soft tissue [2,3].

De Benedittis first recognized that the incidence of PCH is as high as 60%, and that two-third of craniotomy patients report moderate to severe headaches [4]. Subsequent studies have shown that the incidence of PCH is underestimated both by physicians and nurses [5–7]. The past decade has seen publication of many studies assessing the efficacy and safety of preoperative, intraoperative, and postoperative treatments. Nonetheless, two recent systematic reviews concluded that “no firm recommendations on analgesia following craniotomy can be given” [8,9].

Most previous clinical studies assessed the effect of intraoperative and postoperative treatments, such as local infiltration of the surgical site before craniotomy and administration of different analgesics after craniotomies [8–10]. In contrast, there are limited data on the efficacy of preoperatively administered analgesics on the incidence and severity of postcraniotomy headache. As postcraniotomy headache is believed to be nociceptive in nature, it is conceivable that preoperative...
administration of non-steroidal anti-inflammatory agents decreases local inflammation and consequent sensitization and pain windup during craniotomy. We therefore tested the hypothesis that a single preoperative oral dose of diclofenac in adults reduces the severity of acute postcraniotomy headache, and decreases the need for opioid analgesia.

2. Patients and methods

This study was conducted with approval from the University of Debrecen Medical Ethics Committee and the National Medical Ethics Committee (registration number: 5481/2013/EKU, responsible person: József Szentmiklósi; Department of Pharmacology, University of Debrecen, 98, Nagyerdei krt, Debrecen, Hungary; Phone: +36 52411600) and written consent from all patients. The study was registered in Clinical Trials.gov (Registration number: NCT01907984, Principal investigator: Csilla Molnár). We enrolled consecutive adults having elective craniotomies for brain tumors at the Department of Neurosurgery, University of Debrecen. Only patients who were alert preoperatively were included. Patients taking non-steroidal anti-inflammatory agents prior to surgery and with preoperative aphasia were excluded.

Before starting the study, we evaluated postoperative pain in 54 craniotomy patients [11]. Pain was assessed using 10-cm-long visual analog scores (VAS) preoperatively, on the first postoperative morning, and on the fifth postoperative morning. Cumulative postoperative pain scores were computed, and averaged $14.3 \pm 9.3$ cm. Based on an anticipated 20% decrease of the cumulative VAS score, we estimated that 182 patients would provide 90% power at $P = 0.05$.

Revised analgesic doses necessary to maintain VAS scores $\leq 3$ cm. Results are presented as means and 95% confidence intervals; $P = 0.05$ was considered statistically significant.

3. Results

A total of 200 patients were enrolled. Baseline and surgical characteristics of the treatment groups were similar (Table 1).

VAS scores were comparable preoperatively, but were significantly lower on the evening after surgery and on the first and fifth postoperative days in patients randomized to diclofenac (Fig. 2). The distribution of postcraniotomy headache of different severity in the entire population showed, that in the diclofenac group more patients reported on “no pain” or “mild pain” throughout the study period except for the 5th postoperative day (Table 2).

None of our patients required postoperative opioids. Doses of other analgesics were nonetheless converted to intramuscular morphine equivalents to facilitate comparison. The mean morphine equivalent analgesic doses necessary to maintain VAS scores $\leq 3$ cm was lower in the diclofenac than control group: $3.3 \pm 2.6$ mg vs. $4.3 \pm 3.5$ mg, $P = 0.044$.

Fig. 3 depicts the VAS scores observed after supratentorial surgical interventions. In this subgroup of patients, preventive diclofenac was predominantly effective in the early postoperative period, whereas on the 5th postoperative day it was no longer superior. In contrast, administration of diclofenac resulted in a more effective pain relief in patients.
who had infratentorial interventions and benefit was maintained in the late postoperative period (Fig. 4).

No postoperative surgical bleeding, gastrointestinal complications, or kidney dysfunction was observed in any of our patients during the initial five postoperative days.

4. Discussion

In patients undergoing elective craniotomy oral premedication with diclofenac 100 mg, given 1 h before surgery, reduces postcraniotomy headache. In the largest case series, two-thirds of the patients reported moderate-to-severe headache after craniotomy [4]. A more recent study indicated that 55% of craniotomy patients report moderate-to-severe pain in the first 24 h [13]. Our results are consistent with previous reports, with 52% of the diclofenac patients and 73% of the control patients reporting moderate-to-severe pain the day after surgery. Postcraniotomy headache was thus common, despite scalp infiltration with local anesthetic, which provides a distinct but transient benefit [3,14].

Surgery causes tissue injury and inflammation that stimulates nociceptors. Nociception, in turn, provokes central sensitization, wind-up, and activation of brain structures involved in pain perception [9]. Reducing the initial nociceptive stimulus may thus reduce postprocedural pain which is the basis for preemptive analgesia, a concept introduced by Wall in the late 1980s [15].

Non-steroidal anti-inflammatory agents have proven to be effective for preemptive analgesia in various types of surgery [16]. Acute postcraniotomy headache appears to include components of site-of-injury and tension-type headaches [2,9]. We found that preoperative administration of just a single dose of the non-steroidal inflammatory agent diclofenac slightly reduced both the incidence and the severity of acute postcraniotomy headache. Furthermore, the benefit persisted throughout five postoperative days which far exceeds the few hours over which the drug is normally analgesic. Effective preventive analgesia is thus the most likely explanation for our results.

Although there are reports on the usefulness of preemptive analgesia in animal models [17,18], its clinical efficacy remains debatable. Previous reviews of Moiniche [19] and Dahl [20] concluded that although in some studies it appeared to be effective, preemptive analgesia generally was not superior to postoperative pain relief in terms of reduced pain scores. More recently, Ong et al. conducted a meta-analysis of 3261 published cases and concluded that preemptive local anesthetic infiltration and systemic NSAID administration may improve analgesic consumption and time to first analgesic administration without influencing postoperative pain scores [21]. None of these reviews included neurosurgical studies.

Infratentorial craniotomies are apparently more likely to provoke chronic postcraniotomy headaches than supratentorial procedures [3,4]. Interestingly, preventive treatment with diclofenac was more effective for infratentorial than supratentorial operations. Although a causal relationship has yet to be established, intense acute surgical pain is highly associated with chronic incisional pain [3]. Superior efficacy of diclofenac for infratentorial procedures thus appears fortuitous, and may help to reduce persistent incisional pain. Unfortunately, we were unable to evaluate the incidence of chronic postcraniotomy headache.

Table 2

Distribution of postcraniotomy headache according to severity. A number of cases are presented. P-value indicates differences between "no pain + mild pain" vs. "moderate + severe pain" cases in diclofenac and control groups.

<table>
<thead>
<tr>
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<th>0 Mild (VAS 1–3)</th>
<th>Moderate (VAS 4–6)</th>
<th>Severe (VAS 7–10)</th>
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<td><strong>5th postoperative day</strong></td>
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<tr>
<td>Control</td>
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<td>Diclofenac</td>
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Fig. 2. Median VAS scores in patients randomized to diclofenac (open circles) or vs. no treatment (filled squares); error bars show 95% confidence intervals.

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Distribution of postcraniotomy headache according to severity. A number of cases are presented. P-value indicates differences between "no pain + mild pain" vs. "moderate + severe pain" cases in diclofenac and control groups.

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and can thus only speculate about potential long-term benefit; an important limitation in the present study.

The incidence of postcraniotomy hematoma is about 2%, with 88% of the bleeding occurring within 6 h after surgery [22]. Non-steroidal anti-inflammatory drugs are often avoided in neurosurgery for fear of increasing bleeding risk [23] or started 6–24 h postoperatively [24,25]. No intracranial or gastrointestinal bleedings were detected in any of our 200 patients, but our study was not even vaguely powered for these rare (but serious) complications.

In summary, a single preoperative dose of diclofenac reduced the severity of acute postcraniotomy headache, and decreased analgesic requirements over a five-day period in adults. These data suggest that preventive analgesia provides a small, but distinct benefit and might be considered in patients having craniotomies.

Conflict of interest

The authors have no conflict of interest to report.

References