TREATMENT OF POSTOPERATIVE PAIN WITH DICLOFENAC IN UVULopalatopharyngoplasty

H. EJNELL, R. BJÖRKMÁN, L. WÄHLANDER AND J. HEDNER

SUMMARY

Diclofenac sodium suppositories 150–200 mg/day were compared with placebo in a double-blind study during the first 3 days after uvulopalatopharyngoplasty in 40 patients with habitual snoring or obstructive sleep apnoea syndrome. Consumption of rescue analgesics (paracetamol suppositories) and pain assessed by a visual analogue scale were significantly less in the diclofenac group. Bleeding time (modified Ivy's test) and reported side effects did not differ between the two groups.

KEY WORDS

Analgesics • non-steroidal, diclofenac. Pain. postoperative Surgery • uvulopalatopharyngoplasty

Non-steroidal anti-inflammatory drugs (NSAID) are prescribed commonly in mild to moderate pain. The NSAID, diclofenac, has been shown to have an analgesic effect in several situations, such as postoperative pain after tonsillectomy, tooth extraction and hip joint surgery. The mechanisms of action are thought to involve inhibition of prostaglandin synthesis, but other possible mechanisms, such as an interaction with central opioid systems, have been suggested.

Postoperative analgesic treatment of patients with habitual snoring or obstructive sleep apnoea syndrome (OSAS), or both, after uvulopalatopharyngoplasty (UPPP) poses specific problems. OSAS patients have repetitive nocturnal respiratory pauses, leading sometimes to severe hypoxaemia accompanied by hypercapnia and sleep fragmentation. Daytime complications include hypersomnolence, systemic hypertension and, in severe cases, pulmonary hypertension and cardiac failure. Moreover, OSAS patients may present with a pathologically low ventilatory response to hypoxia and hypercapnia, possibly as a result of chronic nocturnal exposure to alveolar hypoventilation. UPPP is a surgical technique to treat habitual snorers or OSAS; it includes concomitant tonsillectomy and results in perioperative bleeding and postoperative pain. Opioid analgesics may be less well tolerated because of respiratory depressant effects in OSAS patients.

The aim of this study was to evaluate the use of a non-opioid analgesic drug, diclofenac, for treating pain after UPPP.

The study comprised a double-blind, placebo-controlled investigation comparing diclofenac sodium suppository (Voltaren) with a placebo. Paracetamol suppository 500 mg (Panodil) was allowed ad libitum up to a maximum dose of 4 g/24 h as rescue medication during the study period. Patients were studied for 3 days after operation and allocated randomly to each group using a list of random numbers. After obtaining informed consent, we studied 40 consecutive patients of either sex, aged 20–75 yr, suffering from severe habitual snoring or previously diagnosed OSAS. All patients had undergone an overnight study in the sleep laboratory. Mean desaturation index (number of oxygen desaturations ≥ 4% per hour of estimated sleep time) was 9.6 (SD 10.7). The study was approved by the Committee of Ethics of the Medical Faculty, University of Göteborg and by the National Board of Health and Welfare.

Patients with asthma or known or suspected sensitivity to acetylsalicylic acid or other NSAID, or those receiving other forms of treatment which could affect pain assessment, were excluded from the trial. Patients with significant coexisting illness, including gastric ulcer, cardiac, hepatic or renal disease, a blood or coagulation disorder, and those receiving treatment with anticoagulants or lithium were excluded. Other exclusions included a history of alcohol or drug abuse or signs of alcohol-induced organ damage, mental dysfunction or other factors limiting the ability to co-operate. Patients were allowed to withdraw from the study at any time for any reason. One hour before operation, the patient received one diclofenac suppository (50 mg) or corresponding placebo, together with morphine 0.15 mg kg⁻¹ i.m. and hyoscine 0.006 mg kg⁻¹ i.m. Anaesthesia was induced with thiopentone 3 mg kg⁻¹ i.v., followed by pancuronium 0.05–0.08 mg/kg body weight (or suxamethonium 0.25 mg kg⁻¹ followed by pancuronium, when needed). The lungs were ventilated to normocapnia with 50–70% nitrous oxide in oxygen and anaesthesia was supplemented with fentanyl 3 μg kg⁻¹ i.v. and, in appropriate patients, 1–3% isoflurane. Per- and post-

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POSTOPERATIVE PAIN AND DICLOFENAC

Table I. Patient characteristics and clinical data (frequency or mean (SD) [range])

<table>
<thead>
<tr>
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<th>Diclofenac (n = 19)</th>
<th>Placebo (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>16/3</td>
<td>20/1</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.0 [20-62]</td>
<td>42.4 [25-58]</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>86.3 (15.7) [63-115]</td>
<td>84.0 (8.0) [72-97]</td>
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<tr>
<td>Duration of operation (min)</td>
<td>33.3 (6.2) [20-45]</td>
<td>33.8 (6.7) [25-45]</td>
</tr>
<tr>
<td>Estimated perioperative bleeding (ml)</td>
<td>140.3 (72.0) [25-250]</td>
<td>142.9 (87.0) [50-400]</td>
</tr>
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</table>

Operative bleeding was assessed from the volume of blood in the suction device. Blood loss towards the oesophagus was avoided by tamponade.

Bleeding times were assessed with disposable Simplates, using a vertical incision on the volar aspect of the forearm [13] by the same person on all occasions, before operation, 1 h after operation and 2 h after administration of suppository on day 3. A biopsy from resected uvular tissue was obtained from all patients and frozen at −20 °C for subsequent measurement of diclofenac concentration [14]. At the same time, a plasma sample was obtained via an indwelling i.v. cannula during the operation (1.5–2.5 h after administration of suppository) for the measurement of serum diclofenac concentration. The sample was left at room temperature and, after 1 h, the serum fraction was removed and stored frozen until analysis. All patients received phenoxymethyl penicillin (1 g twice daily, orally) during the first 7 days after operation.

During the postoperative period, diclofenac or corresponding placebo was given as suppositories three times daily (100 mg, 50 mg and 50 mg) at 06:00, 12:00 and 20:00. Pain was assessed using a Visual Analogue Scale (VAS) [15], with a range of 0–100 indicating “no pain” and “worst possible pain”, respectively. On the day of operation, assessments were made immediately after operation and at 14:00, 15:00, 20:00 and 21:00. Assessments on day 1 and 2 were made at 06:00, 08:00, 12:00, 14:00, 20:00 and 21:00 and on the third day after operation at 06:00.

After the study was terminated on day 3, all patients were prescribed diclofenac suppositories 50 mg three times daily for 7 days. Subsequently, the following question was asked: “Which medication did you prefer in terms of analgesic effectiveness, the one given in hospital or the one given after the period

![Graph showing cumulative consumption of paracetamol in patients receiving diclofenac or placebo.](image)

**Fig. 1.** Mean (SEM) cumulative consumption of paracetamol in patients receiving diclofenac (•; n = 19) or placebo (□; n = 21) on postoperative days 0, 1 and 2. *P < 0.05; **P < 0.01.

![Graph showing pain scores by VAS before and after administration of suppository.](image)

**Fig. 2.** Mean (SEM) pain scores by VAS before and after administration of suppository (• = diclofenac 50 mg or placebo; □ = diclofenac 100 mg or placebo) throughout the study period. Numbers on horizontal axis represent time of day at which VAS evaluations were made. □ = Diclofenac group; ▲ = placebo group. *P < 0.05; **P < 0.01.
We studied 40 patients of mean age 44.5 yr; 19 received diclofenac and 21 placebo. There were no significant differences between the groups in sex, age, weight, duration of operation or peroperative blood loss. Mean apnoea index (SEM) based on estimated sleep time was 9.6 (1.7) (range 0-15) (table I). There were no postoperative bleeding or infective complications.

The need for rescue analgesics during the three postoperative days differed between the groups; this difference was significant ($P < 0.05$) on the first two days after operation, with approximately 50% less consumption in the diclofenac group. The difference was less pronounced on postoperative day 2 ($P < 0.05$) (fig. 1). The average cumulative consumption of paracetamol during the three days after operation was 2945 mg in the diclofenac group and 6120 mg in the placebo group ($P < 0.05$).

After insertion of the first suppository, there was an average increase in VAS pain score of 2 mm in the diclofenac group, but a decrease of 7 mm in the placebo group (fig. 2, table II). Thereafter, there was always a greater decrease in pain score in the active than in the placebo group ($P < 0.01$).

The pain score was dependent also on the time elapsed after the last intake of drug in the diclofenac group, with a significantly greater score ($P < 0.05$) before the morning suppository (10-h medication interval) compared with the other dosing times (6- and 8-h medication intervals, respectively) (fig. 3).

All patients received active medication in a single-blind manner after discharge from hospital (day 3 and onwards). Questioning about efficacy of the suppositories after discharge compared with those given in hospital revealed a tendency towards a greater preference for medication in the follow-up period in the group who received placebo in hospital.

The bleeding time was not different between the groups before or 1 h after operation. On day 3, mean bleeding time in the placebo group (46 s) was significantly ($P < 0.05$) less than the preoperative value (table III).

Mean plasma concentration of diclofenac 1–2 h after suppository administration was 271 (SEM 41) ng ml$^{-1}$; tissue (uvular) concentration was 13 (3) ng ml$^{-1}$. There was a significant positive correlation ($P = 0.006$) between plasma and tissue concentrations (fig. 4), but no correlation between pain scores and plasma or tissue diclofenac concentrations (data not shown).

In the placebo group, nine patients experienced a total of 13 symptoms and in the diclofenac group 11 patients had 14 symptoms. The frequency and nature of these side effects did not differ significantly between the two groups (table IV).

**RESULTS**

We studied 40 patients of mean age 44.5 yr; 19 received diclofenac and 21 placebo. There were no significant differences between the groups in sex, age, weight, duration of operation or peroperative blood loss. Mean apnoea index (SEM) based on estimated sleep time was 9.6 (1.7) (range 0-45) (table I). There were no postoperative bleeding or infective complications.

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**DISCUSSION**

Surgical treatment of snoring and OSAS is now common [12]. UPPP is associated with severe pain in the first week after operation and efficient analgesia is required. Although direct dysfunction or down-regulation of chemosensory mechanisms has not been proven in OSAS patients, hypersensitivity to the respiratory depressant effects of opioids has been proposed [12]. Alternative analgesic agents, for example NSAID, without respiratory depressant effects are therefore beneficial in this group of patients.

The NSAID, diclofenac, was found to provide analgesia in six of seven assessments in the present study. Surprisingly, pain scores 1–2 h after administration of active drug were significantly different from those after placebo at the end of day 1 and on day 2. There may be several explanations for this observation:

(a) The relative change in VAS score after...
of pain development in the postoperative period, with more pronounced pain on days 2 and 3. However, there was no similar trend in the placebo group.

In general, it may be argued that concomitant paracetamol medication may complicate the interpretation of pain scores in a placebo-controlled study. However, this design was necessary for ethical reasons. Moreover, preference for the active medication after discharge from hospital in the placebo group indicates that, in spite of a lower pain score before drug administration in the placebo group on days 2 and 3, additional pain relief was achieved with diclofenac.

The plasma half-life of diclofenac has been estimated to be approximately 90 min [16]. Thus the dose interval used in the present study (6–10 h) corresponds to approximately four to seven half-lives of the drug. Therefore, almost complete washout was allowed between each administration of diclofenac and the pain score before drug intake may be taken as an index of periods with very low plasma concentrations of active drug. Interestingly, the subjectively scored pain was greater after the longer dosing interval in the diclofenac group. However, this seemingly high individual correlation between plasma concentration and analgesic effect is in contrast with large interindividual variation in plasma and tissue concentrations of diclofenac after administration of suppository. A high interindividual variation, reported elsewhere [17,18], may account for the poor correlation between plasma drug concentrations and the therapeutic effects of the NSAID. However, the significant correlation between plasma and tissue concentrations of diclofenac in the present study indicates a high interindividual constancy in distribution to the uvular tissue compartment.

Bleeding complications during and after operation are not uncommon in association with UPPP [12]. Several NSAID, for example aspirin [19-21], ibuprofen [22], naproxen and indomethacin [19, 23], have been reported to increase bleeding time and therefore may be deleterious in this type of operation. The effect on bleeding time may be related to a dual action on the formation of thromboxane A₂ in the platelet and prostacyclin in vascular endothelial cells [24]. In this study, we found no effect of diclofenac on bleeding time. We have no explanation for the significant decrease in bleeding time in the placebo group.

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REFERENCES


