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Evaluation of piroxicam-β-cyclodextrin as a preemptive analgesic in functional endoscopic sinus surgery

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Abstract

The preemptive analgesic efficacy and adverse effects of preoperatively administered piroxicam-β-cyclodextrin for post-endoscopic sinus surgery pain was determined in a prospective, double-blind, randomized, clinical study. Seventy-five American Society of Anesthesiologists status I-II patients, aged 18-65 years, were divided into three groups with similar demographic characteristics: group 1 received 20 mg piroxicam-β-cyclodextrin, group 2 received 40 mg piroxicam-β-cyclodextrin and group 3 received placebo orally before induction of general anesthesia. A blinded observer recorded the incidence and severity of pain at admission to the post-anesthesia care unit (PACU), at 15, 30, and 45 min in the PACU, and 1, 2, 4, 6, and 24 h postoperatively. All patients received patient-controlled morphine analgesia during the postoperative period and consumption was recorded for 24 h. During the PACU period, mean visual analogue scale values were significantly lower in groups 1 and 2 compared to group 3 ($P < 0.05$). During the postoperative period, morphine consumption was 3.03 ± 2.54, 2.7 ± 2.8, and 5.56 ± 3.12 mg for each group, respectively ($P < 0.05$). As a side effect, bleeding was observed in groups 1 and 3, nausea and vomiting in all groups, and edema only in group 3. However, no significant differences were detected in any of the parameters analyzed, which also included epigastric pain, constipation/diarrhea and headache. Similar hematological test results were obtained for all groups. Preemptive administration of piroxicam-β-cyclodextrin effectively reduced analgesic consumption, and 40 mg of the drug was more effective than 20 mg piroxicam-β-cyclodextrin without side effects during the postoperative period.

Key words: Analgesia; Piroxicam-β-cyclodextrin; Preemptive analgesia; Endoscopic sinus surgery

Introduction

Functional endoscopic sinus surgery (FESS) is a standard procedure for the treatment of chronic sinusitis. This procedure is assumed to be more comfortable and less painful for patients. Nonetheless, it is associated with mild to moderate postoperative pain, which is related to both surgical and nasal packing (1).

When the expected postoperative pain ranges from mild to moderate, routine analgesic treatment is usually based on non-opioid analgesics with rescue opioids (2). However, there is no consensus concerning the optimal analgesic regimen after endoscopic nasal surgery and an opioid-oriented treatment is still often used (3).

Non-steroidal anti-inflammatory drugs (NSAIDs) have a well-documented effect on acute postoperative pain (4). NSAIDs may be given preemptively or at the end of surgery (5). In adults, some studies report significantly better analgesia with NSAIDs administered before surgery (6,7).

Piroxicam, a non-selective inhibitor of cyclooxygenase, belongs to a large group of NSAIDs and analgesic drug. Piroxicam is well absorbed within 30 min after oral administration. It is very effective for the treatment of pain of different characteristics and of inflammatory processes at a recommended dose regimen of 20 mg once a day or 10 mg twice a day (8). Moreover, piroxicam at 40 mg/day has been shown to be very effective in the treatment of acute pain (9). Piroxicam-β-cyclodextrin (PBCD) is the first NSAID in which the active substance is complexed within the cyclic oligosaccharide, cyclodextrin (10). Since piroxicam is immediately bioavailable in this formulation, the onset of action is similar to that of a parenteral drug. The absorption rate of PBCD (5/h) was faster than that of piroxicam (1.41/h). Pain relief was found to increase with drug concentration in a hypothetical effect compartment. PBCD demonstrated an advantage with an onset of pain relief being obtained

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1 h earlier than with piroxicam alone (10).

The aim of the present prospective study was to compare the efficacy and adverse effects of 20 or 40 mg PBCD preoperatively administered for the treatment of postoperative pain to adult patients following endoscopic sinus surgery.

Patients and Methods

The study was approved by the local Ethics Committee (Ref. No. 207) and patients gave written informed consent to participate. Seventy-five patients of both genders aged 18-65 years meeting physical status I or II of the American Society of Anesthesiologists (ASA) and undergoing endoscopic sinus surgery were allocated to receive PBCD (Cycladol®, Abdi Ibrahim, Turkey): 20 mg PBCD (group 1, N = 25), 40 mg PBCD (group 2, N = 25) or placebo with a vitamin complex (group 3, N = 25). The randomization list was prepared using a computer-generated sequence of random numbers immediately before induction of anesthesia.

Patients who were unable to cooperate, who had a history of gastric bleeding, impaired liver and/or renal function, a history of drug or alcohol abuse, chronic pain requiring major analgesics, sedatives, or corticosteroids, or who had a known allergy to NSAIDs or other drugs used in the study were excluded. The type of surgery, anesthetic induction and management were standardized. After application of routine noninvasive monitors, such as ECG, NIBP, SpO_2 (Datex-Ohmeda-GE), an intravenous (*iv*) cannula (18G Mediflon-Eastern Medikit Ltd., India) was inserted.

No premedication or prophylactic antiemetic drugs were given. All patients received anesthesia with 2-2.5 mg/kg propofol and 1 µg/kg remifentanyl. Muscle relaxation with 0.1 mg/kg vecuronium was given to facilitate tracheal intubation and mechanical ventilation. Standard monitoring was used, including electrocardiography (Lead II), heart rate, noninvasive arterial blood pressure, and pulse oximetry. The attending anesthesiologist managing intraoperative anesthesia was blinded to patient grouping. Anesthesia was maintained with 1.5-2% sevoflurane, remifentanyl infusion and 65% nitrous oxide in oxygen. The same surgeon performed all the surgical procedures using a standard surgical technique.

At the end of surgery, all anesthetics were discontinued, the patients were extubated after recovery of adequate spontaneous ventilation, and transferred to the post-anesthesia care unit (PACU).

An independent blinded observer recorded the degree of pain at PACU admission and at 15, 30, and 45 min in the PACU, and then at 1, 2, 4, 6, and 24 h after PACU in the ear, nose and throat (ENT) surgery department. In the PACU, all patients received morphine via an *iv* patient-controlled analgesia (PCA) pump (Pain Management Provider; Abbott, USA) with the following initial parameters: 1.0 mg/mL prepared; basal rate, 0; bolus, 1.0 mg per time; lockout period, 5 min. PCA continued during the 24 h after surgery. The degree of pain was measured using a 10-cm visual analogue scale (VAS, where "0" is no pain and "10" the worst imaginable pain). In case of inadequate pain relief (VAS ≥4 cm), rescue *iv* analgesia was given with 1 mg bolus of morphine injected at 5-min intervals until adequate pain relief was achieved, and morphine consumption during the 24 h after surgery was recorded. Total morphine consumption and demand/delivery ratio per patient during the 24-h period were recorded in all groups and compared. Demand/delivery ratio was defined as the number of analgesic requests made by the patients and the number of those requests, which resulted in successful deliveries.

Hematological tests (prothrombin time (PT) and active partial thromboplastin time (aPTT), were evaluated during the preoperative and postoperative periods. Nausea/vomiting and other adverse effects (epigastric pain, edema, headache, bleeding, and sleep disorders) were also assessed during the 24-h postoperative period.

Statistical analysis

Demographic data, duration of anesthesia and duration of surgery of the groups were compared by the Student *t*-test. Total additional analgesic consumption and pain scores (VAS) were analyzed by the Mann-Whitney U-test. Nominal data (ASA, gender, the need for "rescue" analgesics, and incidence of side effects) were compared between groups using the chi-square or the Fisher exact test. Data are reported as means ± SD, median values (25%-75%), and numbers (N). A P value of <0.05 was considered to be significant.

Results

The study involved 75 patients, with 25 patients in each treatment and placebo group. No patient was excluded from the study for any reason, and the drug was well tolerated. No differences in demographic parameters were observed between the three groups (Table 1).

Morphine consumption and demand for supplementary analgesia in the preemptive groups were significantly lower than that in the control group ($P < 0.05$), i.e., 3.03 ± 2.54 mg in group 1 and 2.7 ± 2.8 mg in group 2 *vs* 5.56 ± 3.12 mg in group 3 ($P < 0.05$). The bolus/demand ratio (%) for group 2 (43.1 ± 25.7%) was significantly lower than that for group 1 (62.9 ± 19.2%) and group 3 (78.1 ± 23.5%) during the 24-h PCA period ($P < 0.05$; Table 2).

Table 3 shows the incidence of side effects and the hematological tests for the three groups. Side effects were not related to the need for doses of morphine, and bleeding was controlled simply by changing nasal cavity packing without the need for surgical intervention. Sixteen percent of the patients in group 3 bled in the ENT surgery department period compared with 8% of the patients in group 1. Eight percent of the patients in group 3 had edema compared

with 0% in groups 1 and 2. Twenty percent of the patients in group 3 had nausea and vomiting compared with 16% of the patients in group 1 and in group 2. Nevertheless, the differences between groups for incidence of side effects and hematological parameters, such as PT and aPTT, were not statistically significant (Table 3).

Figure 1 shows mean VAS changes during the postoperative period in the three groups. During the PACU period, VAS values were 1 in groups 1 and 2, and 6 in group 3 only in the first 45 min of the PACU period ($P < 0.05$). After the PACU period, VAS values were lower in groups 1 and 2 than in group 3 without significant differences during the 24-h recovery period (Figure 1).

Discussion

No reports were identified in the literature in PubMed, from 1990 to 2009, on the use of PBCD for postoperative analgesia after endoscopic sinus surgery, although it has been shown to be effective in reducing pain in other situations (11-18). NSAIDs are gaining popularity in the management of pain associated with ambulatory surgery. PBCD was regarded as an effective analgesic at doses of 20 and 40 mg/day. Preemptive administration of PBCD effectively reduced morphine consumption, and especially the 40-mg dose was found to be more effective than the 20-mg dose and than the treatment administered to the control group during the postoperative period (11-18).

Surgical trauma generates powerful nociceptive impulses by the procedure itself and by the action of proteolytic and inflammatory agents that are released following tissue injury. This release of inflammatory mediators may result in pain for several hours.

The analgesic action of NSAIDs has been explained on the basis of their inhibition of the enzymes that synthesize prostaglandins. However, it is clear that NSAIDs exert their analgesic effect not only through peripheral inhibition of prostaglandin synthesis but also through a variety of other peripheral and central mechanisms. It is now known that there are two structurally distinct forms of the cyclooxygenase enzyme (COX-1 and COX-2). COX-1 is a constitutive member of normal cells and COX-2 is induced in inflammatory cells. Inhibition of COX-2 activity represents

Table 1. Demographic data of the patients included in the study.

	Group 1 (20 mg PBCD)	Group 2 (40 mg PBCD)	Group 3 (placebo)
Age (years)	33.9 ± 14.0	39.5 ± 14.6	34.9 ± 15.8
Gender (male/female)	16/9	17/8	18/7
Weight (kg)	67.6 ± 13.0	72.4 ± 9.3	71.2 ± 16.2
ASA I/II	20/5	21/4	23/2
Surgery duration (min)	142.2 ± 84.5	136.8 ± 60.6	159.6 ± 113.2
Anesthesia time (min)	156.6 ± 84.5	154.4 ± 62.3	179.6 ± 123.8
PACU period (min)	34.2 ± 6.6	35.2 ± 7.7	33.0 ± 3.1

Data are reported as means ± SD or number for 25 patients in each group. PBCD = piroxicam-β-cyclodextrin; ASA I/II = physical status I or II of the American Society of Anesthesiologists; PACU = post-anesthesia care unit.

Table 2. Patient control analgesia characteristics.

	Group 1 (20 mg PBCD)	Group 2 (40 mg PBCD)	Group 3 (placebo)
Analgesic consumption (mg)	3.03 ± 2.54	2.7 ± 2.8	5.56 ± 3.12*
PCA ratio (%demand/delivery)	62.9 ± 19.2	43.1 ± 25.7#	78.1 ± 23.5

Data are reported as means ± SD for 25 patients in each group. PBCD = piroxicam-β-cyclodextrin; PCA ratio = patient control analgesia ratio (number of analgesic requests that resulted in successful deliveries). *$P < 0.05$, compared to groups 1 and 2. #$P < 0.05$ compared to groups 1 and 3 (Mann-Whitney U-test).

Table 3. Summary of adverse effects and hematological tests in all groups.

	Group 1 (20 mg PBCD)	Group 2 (40 mg PBCD)	Group 3 (placebo)
Epigastric pain	-	-	-
Nausea/vomiting	4 (16)	4 (16)	5 (20)
Edema	-	-	2 (8)
Constipation/diarrhea	-	-	-
Headache	-	-	-
Bleeding	2 (8)	-	4 (16)
Sleep problems	-	-	-
PT (s)			
Preoperative	12.6 ± 0.96	12.66 ± 1.31	12.75 ± 1.16
Postoperative	13.33 ± 1.46	13.57 ± 1.46	14.45 ± 3.4
aPTT (s)			
Preoperative	28.03 ± 2.3	27.53 ± 3.05	29.35 ± 4.22
Postoperative	27.18 ± 2.53	27.12 ± 2.87	29.66 ± 4.37

Data are reported as means ± SD or number with percent in parentheses for 25 patients in each group. PBCD = piroxicam-β-cyclodextrin; PT = prothrombin time; aPTT = activated partial tromboplastin time.

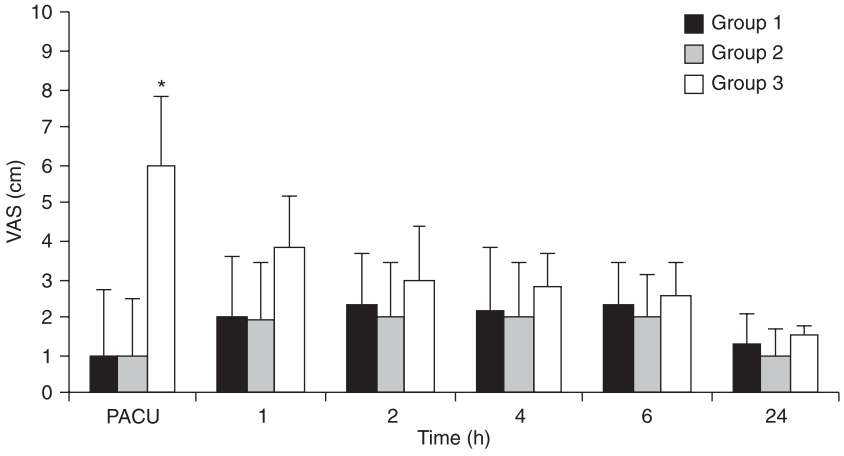

Figure 1. Intensity of postoperative pain determined by the visual analogue scale (VAS, "0" is no pain and "10" the worst imaginable pain). Data are reported as means ± SD for 25 patients in each group. Post-anesthesia care unit (PACU) period included 15, 30 and 45 min after the operation in the operating theatre; 1, 2, 4, 6, and 24 h were in the ENT surgery department. *P < 0.05 compared to groups 1 and 2 according to VAS scores (Mann-Whitney U-test).

the most likely mechanism of action of NSAID-mediated analgesia, while the ratio of inhibition of COX-1 to COX-2 by NSAIDs should determine the likelihood of adverse effects. There is increasing evidence that NSAIDs have a central mechanism of action that augments the peripheral mechanism. This effect may be the result of interference with the formation of prostaglandins within the central nervous system (19).

Moreover, laboratory and clinical studies (20,21) have provided evidence that inhibition of COX-2 up-regulation at the spinal level is a key factor for preoperative NSAID efficacy. Piroxicam is a nonselective COX inhibitor. Therefore, the analgesic effect of NSAIDs might also depend on a central effect. Recent investigations have shown preemptive analgesia by NSAIDs to be effective (6,7,22). In preemptive analgesia, selection of the drug and dose is very important.

Piroxicam, a potent NSAID, has low solubility in water and a long absorption time, reaching a maximum concentration within about 2 h (23). Free, non-complexed piroxicam has a longer half-life (30 to 60 h) in healthy individuals than most of the other currently available NSAIDs, and requires administration only once daily. Piroxicam can be complexed with β-cyclodextrin, an inert cyclic oligosaccharide molecule, which is a non-reducing macro-ring formed by 7α-1, 4-glycosidic-linked glucose units. The resulting complex, PBCD, considerably increases the water solubility as well as the rate of dissociation of poorly soluble piroxicam, leading to a higher rate of gastrointestinal absorption than piroxicam. The absorption rate of PBCD has been demonstrated to be considerably faster than that of free piroxicam (24). Hence, peak blood concentrations of the drug are more rapidly achieved, and the analgesic peak also sets in earlier. Clinically, this results in an earlier onset of analgesia compared with *im* administration, generally within 30 min *vs* 2 to 4 h when compared to the standard formulation (25). Paolaggi and Lefrançois (26) suggested that the clinical advantages of PBCD were clearly demonstrated in an acute back pain model. Oral PBCD provided a rapid onset of analgesia and, more importantly, this rapid-onset effect was coupled with a longer duration of activity.

Although FESS is now among the most common head and neck surgical procedures, there have been very few studies of the subsequent levels of pain. However, information on the severity and duration of the pain that a patient can expect to experience after FESS is of great importance. It can enable better patient counseling, allowing patients to be more prepared for the postoperative experience and possibly improving the outcome. In fact, the severity of expected pain may be the deciding factor for many patients on whether to proceed with FESS or to suffer their existing pain due to nasal or sinus disease.

Pain after nasal and sinus surgery is usually maximal in the first 24 h. During this time, patients usually take narcotic analgesics for symptomatic relief. Morphine is the most widely used drug to control postoperative pain. Although morphine is effective, it is also associated with frequent adverse effects such as sedation, nausea, vomiting, urinary retention, pruritus, and respiratory depression. For this reason, commonly used protocols of postoperative analgesia are based on a multipharmacologic approach, which includes non-opioid analgesics in order to achieve a morphine-sparing effect with a concomitant reduction in morphine-related adverse effects. NSAIDs and, more recently, selective or non-selective COX-2 inhibitors are among the most commonly used non-opioid analgesics for such a purpose (27). The present study was based on the hypothesis that oral PBCD as preemptive analgesia would reduce the severity of a patient's pain in the first 24 h after FESS and thereby diminish the amount of narcotics consumed. Furthermore, we believed that by interrupting the pain early, the patient's overall pain perception/anxiety state would be diminished and that improved pain control in the first 6 postoperative hours would have a carryover effect on the ensuing period.

In comparative trials, PBCD acted more rapidly and provided greater pain relief than piroxicam (26) or etodolac (28). Patients treated with PBCD required a shorter treat-

ment period for the pain to disappear in comparison with patients treated with other NSAID, supporting the hypothesis that pain may be self-limiting provided that the initial acute painful phase is rapidly and effectively treated (29). A meta-analysis demonstrated that a single oral dose of piroxicam (20-40 mg) had a similar efficacy as intramuscular morphine (10 mg) in patients with moderate to severe postoperative pain (30).

The analgesic effects of rofecoxib and hydrocodone/acetaminophen have been evaluated in FESS. Previous studies have demonstrated decreased postoperative narcotic requirement in patients undergoing ambulatory surgery who were treated with NSAIDs preoperatively (5,30). Cepeda et al. (31) reported a significant reduction in morphine consumption and opioid-related side effects in the early postoperative period by adding *iv* ketorolac to an opioid-based analgesia. Similarly, Turan et al. (5) reported that preoperative oral administration of rofecoxib provided a significant analgesic benefit and reduced the need for rescue opioids in patients undergoing nasal septal and sinus surgery. Our results are consistent with these reports. In our study, significantly decreased narcotic requirements were shown in endoscopic sinus surgery patients treated preoperatively with oral PBCD. We found a single dose of 40 mg PBCD to be effective for 24 h, and this was safe and comfortable when compared with 20 mg and placebo.

Reported adverse effects associated with the preoperative use of NSAIDs include headache, nausea, vomiting, dizziness, bleeding, and gastric pain. In our study, most of the participants reported no adverse effects. The anticipated gastrointestinal and neurologic adverse effects were not seen in the study groups. No adverse problems were encountered with the preoperative administration of 40 mg PBCD.

Endoscopic sinus surgery is associated with moderate pain right after surgery that can be prevented by using NSAIDs. Oral preemptive analgesia with 40 mg PBCD is a simple procedure, which decreases postoperative pain and the need for analgesic rescue medication after functional endoscopic sinus surgery.

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