The cyclooxygenase-2 inhibitor celecoxib and alveolar osteitis

Abstract
Purpose of the study: The purpose of this study was to report our clinical experience, in a pilot study, of the use of the selective cyclooxygenase-2 (COX-2) inhibitor celecoxib, pre-emptively, to control pain in patients after surgical extraction of a mandibular molar tooth.

Patient and methods: This randomised, double-blind, placebo-controlled, prospective clinical trial was conducted over an eight-month period. Participants were randomly allocated to receive a standard oral dose of 200mg celecoxib, 400mg ibuprofen, or a placebo containing lactose, pre-emptively, one hour before surgery. Each patient was prescribed amoxicillin 500mg three times per day postoperatively for seven days. The participants were given standardised participant information sheets, and written informed consent was subsequently obtained from the participants prior to the commencement of the study.

Results: The results showed that 13% of the patients who had ibuprofen had severe pain two to three days postoperatively. This was diagnosed as alveolar osteitis, which is in line with the universally accepted outcome for the surgical extraction of mandibular molar teeth. Statistical analysis (Chi-square test) confirmed that the ibuprofen group had a significantly higher alveolar osteitis incidence than the celecoxib group (p≤0.05) and the placebo group (p≤0.05).

Conclusion: This is the first reported study to demonstrate that the use of celecoxib resulted in a significant decrease in the occurrence of alveolar osteitis.

Key words: Celecoxib, cyclooxygenase-2, COX-2 inhibitor, NSAIDs, ibuprofen, alveolar osteitis.

Introduction
The cyclooxygenase-2 (COX-2) inhibitors widen the spectrum of pharmacological management of pain and inflammation for many patient groups. Prior to the introduction of COX-2 inhibitors, patients were exposed to harmful side-effects associated with the long-term use of non-selective non-steroidal anti-inflammatory drugs (NSAIDs), such as gastric ulcer bleeding and perforations, or the risk of addiction with the long-term use of narcotics. COX-2 inhibitors offer greater safety in conjunction with comparable efficacy, compared to simpler NSAIDs, in managing pain, including acute dental pain. COX-2 inhibitors are the medication of choice for use in patients with gastric disease for both prophylactic or post-treatment analgesic pain management. Until recently, COX-2 inhibitors were gaining more popularity for pain relief in general. In fields such as oral surgery, there has been an increase in the prescribing of COX-2 inhibitors. The use of the traditional NSAID
ibuprofen, had been challenged by these ‘promising’ COX-2 inhibitors. However, in the last few years interest in the cardiovascular effects of the relatively selective COX-2 inhibitors has been intense. In October 2004, rofecoxib was withdrawn from world markets after a randomised placebo-controlled trial found that doses of 25mg/d increased rates of cardiovascular events in patients with colorectal polyps. The results were confirmed by several large pharmacological epidemiological studies. Celecoxib continues to be widely used, despite meta-analyses of randomised controlled trials showing an increased risk of myocardial infarction. The differences between rofecoxib and celecoxib appear important from both a clinical and regulatory standpoint. Based on the randomised data, celecoxib appears to be unsafe in doses of 400mg or more. However, at doses of 200mg or less there is no convincing evidence of an increased risk of cardiovascular events with celecoxib, which remains on international markets. These results seem to point to different dose–effect gradients in the vascular compartment across the ranges of doses of celecoxib and rofecoxib that were used in clinical practice.

Despite the abundance of research concerning the effectiveness of many analgesics, including their pre-emptive analgesic effectiveness, there is little information regarding the pre-emptive analgesic effectiveness of celecoxib at the lower dose of 200mg. Furthermore, review of the literature does not allow a judgment about whether any claimed advantages of celecoxib outweigh the elevated cardiovascular risk seen with high doses.

The purpose of this study was to report our clinical experience, in a pilot study, on the use of the selective COX-2 inhibitor celecoxib, pre-emptively, to control pain in patients after surgical extraction of a mandibular molar tooth. This report documents the remarkable decrease in the occurrence of alveolar osteitis when celecoxib was used one hour pre-emptively. Alveolar osteitis (also known as dry socket) is a disruption to the healing of the alveolar bone following extraction of the tooth. Alveolar osteitis occurs when the blood clot at the site of a tooth extraction is disrupted prematurely. This leaves the alveolar bone unprotected and exposed to the oral environment. This is often extremely unpleasant for the patient, as symptoms include extreme pain (sometimes worse than the toothache that indicated the extraction), a foul taste, bad breath, and swelling in the infected area. There may also be lymph node involvement.

Patients and methods

This randomised, double-blind, placebo-controlled, prospective clinical trial was conducted at Euro-Oral Hammastunnikekeskus in Helsinki, Finland, over an eight-month period. Participants were randomly allocated to receive a standard oral dose of 200mg celecoxib, 400mg ibuprofen, or a placebo containing lactose, pre-emptively, one hour before surgery. The doses were selected based on the product labelling and other currently available product information. Each patient was given a prescription for 1,000mg of paracetamol as a rescue medication in case the study medication did not provide sufficient pain relief. Each patient was prescribed amoxicillin 500mg three times per day postoperatively for seven days. Patients were not prescribed any postoperative analgesia apart from paracetamol as a rescue medication.

Eligibility and exclusion criteria

Patients (n=464) who were healthy and classified as status I according to the American Society of Anesthesiologists physical classification were eligible for participation in the study. These patients were 229 men and 227 women who were scheduled to undergo surgical removal of a mandibular molar. The surgery was performed under local anaesthesia, with 2% lignocaine containing 1:80,000 epinephrine, by the same surgeon. Surgery time and the amount of anaesthetic used were recorded to gauge the degree of surgical difficulty. From six hours before surgery, patients were not allowed to take any medication that could affect the analgesic response. Patients were excluded if they had any conditions that contraindicated the use of NSAIDs or COX-2 inhibitors, were pregnant or nursing, had psychological or psychiatric conditions, were taking psychotropic medications, or had active ulcers or gastro-intestinal bleeding, liver dysfunction, inflammatory intestinal disease, or decreased kidney function. The participants were given standardised participant information sheets, and written informed consent was subsequently obtained from the participants prior to the commencement of the study. The institutional review board approved the protocol and the informed consent document.

For the analysis of differences in frequencies of postoperative complications, including alveolar osteitis, in various patient groups, the Chi-square test was applied, defining p<0.05 to be a significant difference. Statistical analysis was performed using the software SigmaStat 3.0 (SPSS Inc., USA).

Results

Of the 464 participants, eight (1.7%) did not complete the trial because they failed to present at the postoperative review. A total of 229 men and 227 women participated in the study, with a mean age of 38.9 ± 7.7 years. There were 72 men and 75 women in the celecoxib group, 80 men and 82 women in the ibuprofen group, and 77 men and 70 women in the placebo group. The mean weights for the celecoxib, ibuprofen and placebo groups were 77 ± 10, 74 ± 14, and 70 ± 16kg, respectively. There were no significant differences in age or weight between the groups. The mean duration of surgery was 30.9 ± 21.6 minutes and did not vary significantly between the groups. The mean volume of local anaesthetic administered was 5.1ml, and this volume did not differ significantly between the groups.

Safety profile

No persistent or unexpected adverse events were reported. The most common adverse events were nausea (occurring in 22%, 13.3% and 18.1% of placebo, celecoxib and ibuprofen patients, respectively), headache (13.1%, 10.2% and 9.7%), and vomiting (10.3%, 3.3% and 4.1%). Vomiting occurred more frequently in placebo patients.
than in celecoxib patients \((p<0.05)\). None of the other between-group differences in nausea or headache were statistically significant \((p>0.05)\).

A total of 13\% of the patients who took ibuprofen had severe pain two to three days postoperatively. This was diagnosed as alveolar osteitis, which is in line with the universally accepted outcome for the surgical extraction of mandibular molar teeth. Alveolar osteitis occurred more frequently in placebo patients \((21.1\%)\). None of the celecoxib patients developed alveolar osteitis postoperatively. The ibuprofen group had a significantly higher alveolar osteitis incidence than the celecoxib group \((p \leq 0.05)\) and the placebo group \((p \leq 0.05)\).

The use of the celecoxib resulted in a significant decrease in the occurrence of alveolar osteitis \((Table 1)\).

**Discussion**

The selective COX-2 inhibitors have been found to exert significant opioid-sparing effects after dental, gynaecologic, orthopaedic, and other non-cardiac surgical procedures, apparently without causing serious adverse effects. Recently, studies of the long-term administration of COX-2 inhibitors have aroused concern regarding their potential to increase the risk of thromboembolic events after vascular surgery. Alveolar osteitis is beyond the scope of this study. We understand that the reason for dry socket happening could be a multi-factorial one, including the surgical management of the flap at the time of the surgery and postoperatively. However, the same surgeon operated on the patients and the same medical regimen was used for all patients postoperatively. Also, systematic review of the medication prescribed to the patients over the past two years revealed that the use of a COX-2 inhibitor drug was the only variant that could possibly have resulted in the decreased incidence of dry socket. COX-2 inhibitors not only lack the antiplatelet effects of aspirin; by inhibiting the production of prostacyclin, they also disable one of the primary defences of the endothelium against platelet aggregation, hypertension and atherosclerosis. COX-2 inhibitors also promote an imbalance in favour of vasoconstriction. These biologic actions suggest that COX-2 inhibitors might increase the risk of clot formation. While this might have a harmful effect in patients undergoing vascular surgery, it might have a beneficial effect in stabilising the blood clot in the alveolar socket following dental extraction. Stabilising the blood clot would ultimately decrease the incidence of infection and alveolar osteitis postoperatively. Based on the randomised data, celecoxib appears to be unsafe in doses of 400mg or more. However, at doses of 200mg or less there is no convincing evidence of an increased risk of cardiovascular events with celecoxib, which remains on international markets. Higher and lower doses of celecoxib have been evaluated in the treatment of dental pain. However, higher doses have not been reported to provide significant additional analgesic effects, and lower doses were less effective than NSAIDs. In studies of acute pain, celecoxib 200mg has been shown to provide analgesic effects significantly greater than those with placebo and comparable to those with aspirin 650mg, with a slight improvement in effect when the dose was increased to 400mg. Similarly, ibuprofen 400mg provided maximum efficacy in patients with acute pain, with no additional clinical efficacy demonstrated at higher doses. Overall, doses selected for the present study reflect the maximum single dose for the relief of acute pain postoperatively. The use of small doses of celecoxib 200mg pre-emptively shows promising results in reducing
pain and alveolar osteitis in patients undergoing surgical dental extractions.

Conclusion
This is the first reported study to demonstrate that the use of celecoxib resulted in a significant decrease in the occurrence of alveolar osteitis.

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References