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A parallel-group comparison study of celecoxib with loxoprofen sodium in third mandibular molar extraction patients

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Abstract. Non-steroidal anti-inflammatory drugs (NSAIDs) are used widely, but they may damage the upper gastrointestinal mucosa owing to their mechanism of action. Selective cyclooxygenase 2 (COX-2) inhibitors are known to have a reduced risk for such damage. In this comparative study, the efficacy and safety of the selective COX-2 inhibitor celecoxib for pain after third mandibular molar extraction were compared with those of loxoprofen sodium. This was a parallel-group comparison study; 107 patients who had undergone third mandibular molar extraction were given celecoxib and 102 were given loxoprofen. The level of pain on a visual analogue scale (VAS) 15 min and 30 min after taking the experimental drug decreased over time, with no significant difference between the two groups. The percentage of patients taking a second dose was 64.5% for celecoxib and 80.4% for loxoprofen. The time to second dose was significantly longer for celecoxib (533.5 min) than for loxoprofen (387.4 min). There was no significant difference in the patients' impression of efficacy between the two groups, with ratings of 'excellent' and 'good' for 77.4% in the loxoprofen group and 74.5% in the celecoxib group. These results demonstrate that celecoxib is of equal clinical value to loxoprofen for acute pain after third mandibular molar extraction.

Key words: celecoxib; loxoprofen sodium; post-exodontic pain; non-steroidal anti-inflammatory drugs; analgesic effect.

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Non-steroidal anti-inflammatory drugs (NSAIDs) are normally used for pain relief after third mandibular molar extraction. The mechanism of action of NSAIDs involves the inhibition of cyclooxygenase (COX) activity, thus suppressing the formation of inflammatory mediators such as prostaglandin E2. COX has two known isozymes, COX-1 and COX-2, and most NSAIDs inhibit both non-selectively. Their inhibition of COX-1 is known to cause a range of side effects, including

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damage to the upper gastrointestinal mucosa, kidney dysfunction, and inhibition of platelet aggregation.[1,2] Gastrointestinal symptoms are a matter of particular concern during long-term use.[3,4]

Celecoxib, a selective COX-2 inhibitor, is used to treat chronic pain from rheumatoid arthritis and osteoarthritis,[5–7] and there are hopes that it may also be useful for acute pain following surgery, trauma, and tooth extraction.[8,9]

Third mandibular molar extraction is the most common oral surgical procedure. The degree of surgical invasiveness of third mandibular molar extraction differs depending on its difficulty, but the use of analgesics is required in almost all cases. A number of different NSAIDs are currently used for post-extraction analgesia, but since most of these are non-selective COX inhibitors, they entail the risk of gastrointestinal damage, including gastrointestinal ulcers, perforation, obstruction, and haemorrhage.[10,11]

In this study, patients who had undergone third mandibular molar extraction were given either loxoprofen sodium, the NSAID most frequently used in Japan for this purpose, or the selective COX-2 inhibitor celecoxib, and their efficacy (analgesic effect during the acute phase) and safety were compared.

Patients and methods

The subjects were patients undergoing third mandibular molar extraction in the department of oral and maxillofacial surgery of the university hospital between October 2012 and July 2013. The patients selected were those requiring third mandibular molar extraction for the first time and who were aged 20–79 years. The study protocol, informed consent form, and patient recruitment documents were approved by the institutional review board or ethics committees. The study was conducted in accordance with the principles of Good Clinical Practice, the Declaration of Helsinki, and local regulatory requirements and laws. All patients provided written informed consent before participating in this study. Treatment was performed on either an inpatient or outpatient basis, and all treatment in this study was covered by Japanese health insurance.

The following were the exclusion criteria: malignant tumour; history of hypersensitivity to the prescribed medication or sulfonamide; aspirin-induced asthma or a history of this condition; gastrointestinal ulcer; serious liver dysfunction; serious kidney dysfunction; serious haematological abnormality; serious cardiac insufficiency; perioperative period for coronary artery bypass surgery; taking aspirin to prevent cardiovascular disease; late pregnancy; use of other anti-inflammatories or analgesics; any other reason warranting exclusion as judged by the attending physician.

Study design

This was a parallel-group comparison study. Subjects were randomly allocated by the envelope method to receive a single dose of either loxoprofen 60 mg (control group) or celecoxib 400 mg (study medication). Pertinent data were recorded, including sex, age, weight, outpatient/inpatient, medical history, and systemic conditions. The patients received local anaesthesia and underwent third mandibular molar extraction because of impaction or pain. Lidocaine plus epinephrine was used as the local anaesthetic in this study. An additional dose of study medication was provided if necessary, but patients who received celecoxib were given a dose of 200 mg on the second and subsequent occasions. Patients were instructed to wait 6 h after taking the first dose before taking the second dose. In principle, patients were only administered one drug, but the administration of antibiotics to prevent infection, as well as of drugs already being taken before the start of the trial to treat systemic conditions, was continued.

Efficacy evaluation—primary end points

To evaluate the improvement in acute pain, patients used a 100-mm visual analogue scale (VAS) to measure pain at the time they first felt pain after third mandibular molar extraction (0 min) and 15 min and 30 min later. They also completed a questionnaire. A ruler prepared for use by the patients was used to measure the VAS. The questionnaire was used to obtain information on the time at which the second dose was taken, in order to evaluate the duration of the analgesic effect.

Efficacy evaluation—secondary end points

As a subjective evaluation of how well the study medication worked, patients were asked to rate it on a four-point scale: 'it worked well' (excellent), 'it worked' (good), 'it worked a little' (fair), or 'it did not work' (poor). Missing values were classified as 'missing'.

Adverse effects were defined as medically undesirable medical events occurring in subjects during the study period, irrespective of whether or not there was any causal relationship. Patients themselves were asked to indicate freely on the questionnaire the type and severity of any symptoms that appeared after extraction and how any adverse effects were treated.

Statistical analysis

For the analysis of both the primary and secondary end points, a *t*-test or χ^2 test was used for comparisons between groups.

Results

Population for analysis

In terms of the composition of the study group, of the total 326 patients enrolled, 160 were randomly allocated to receive loxoprofen and 166 to receive celecoxib. Of these, 109 in the loxoprofen group and 117 in the celecoxib group responded to the post-extraction questionnaire and were included in the safety analysis population. With the exclusion of those patients who provided incomplete answers to the questions in the questionnaire, 102 patients in the loxoprofen group and 107 in the celecoxib group were included in the efficacy analysis population and were the subjects of this study (Fig. 1).

Table 1 shows the baseline characteristics of each patient group. Table 2 shows the level of impaction (Pell–Gregory classification) for the patients in each of the study groups. There was no significant difference between the two groups for any parameter. Ratings on the pain scale when the first dose of the study medication was taken after extraction (0 min) were almost the same, at 60.9 ± 18.9 mm for the loxoprofen group and 60.5 ± 22.6 mm for the celecoxib group. The patient groups were well matched for baseline pain and surgical trauma levels.

Time-specific pain intensity difference

The pain scale showed that pain was relieved in both groups as time passed after taking the study medication (Table 3). VAS scores had decreased significantly at 15 min and 30 min after taking the medication in both groups. The tendency to decrease was almost the same in both groups, and a *t*-test revealed no significant difference in the analgesic efficacy rate between them at 15 min or 30 min (Fig. 2).

Analgesic effect

In the investigation of the proportions of patients who required rescue medication