A Comparative Study of Oral Analgesics for Postoperative Pain After Minor Oral Surgery

Atsushi Hanzawa, DDS, PhD,* Toshiyuki Handa, DDS, PhD,† Yoshihiko Kohkita, DDS, PhD,† Tatsuya Ichinohe, DDS, PhD,† and Ken-Ichi Fukuda, DDS, PhD*

*Department of Oral Health and Clinical Science, Division of Special Needs Dentistry and Orofacial Pain, Tokyo Dental College, Tokyo, Japan, and †Department of Dental Anesthesiology, Tokyo Dental College, Tokyo, Japan

We compared the effects of preoperative administration of diclofenac sodium, celecoxib, and acetaminophen on postoperative pain in patients undergoing minor oral surgery under general anesthesia. One hundred twenty-eight patients were randomly divided into 4 groups preoperatively treated with diclofenac sodium 50 mg, celecoxib 400 mg, acetaminophen 1000 mg, or placebo. Postoperative pain was managed using intravenous patient-controlled infusion of fentanyl. Assessments included levels of postoperative pain by using visual analog scale (VAS) scores at 4, 5, and 6 hours after administration of the test drug; consumption of fentanyl up to each time point; and time to first requirement for fentanyl. Our study demonstrated that, for diclofenac sodium and celecoxib in comparison with placebo, there were significantly lower VAS scores at 4, 5, and 6 hours after oral administration of the study drug; a longer period of time to first requirement for fentanyl after surgery; and less consumption of postoperative fentanyl. A similar analgesic effect versus placebo was noted for acetaminophen but only at the 5- and 6-hour time points. In contrast, no significant differences in VAS scores at 4 hours after administration or time to first requirement for fentanyl were observed between acetaminophen and placebo. Furthermore, no significant differences in measurements were observed between the study drugs at any time point. These findings suggest that oral administration of celecoxib 400 mg is suitable for controlling postoperative pain, and as effective as diclofenac sodium 50 mg. Acetaminophen 1000 mg also exerts analgesic effect with slower onset for postoperative pain.

Key Words: Oral analgesics; Postoperative pain; Minor oral surgery; NSAIDs; Acetaminophen; Celecoxib.

Minor oral surgical procedures, such as dissection and detachment of the gingival mucosa and periosteum or removal of bone tissue, are relatively invasive, with a high incidence of postoperative pain, the level of which is frequently high.^{1–3} Postoperative pain may be caused by postsurgical inflammation secondary to invasive stimulation, and it markedly affects patient recovery and satisfaction.^{4–6} Therefore, postoperative pain relief is important and drugs having not only a strong analgesic effect but also anti-inflammatory effects are desirable.

Preparations recommended for use in postoperative analgesia include opioid analgesics, nonselective non-

steroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase (COX)-2 inhibitors, and acetaminophen.⁷ In the field of oral surgery, nonselective NSAIDs have been frequently used for postoperative pain relief.⁸ However, there is concern about gastrointestinal dysfunction and suppression of platelet function with the administration of nonselective NSAIDs because of inhibition of prostaglandin and thromboxane synthesis by COX-1.^{9,10} In addition, the utility of opioids is limited because of adverse effects including nausea, vomiting, and drowsiness. In addition, in some countries, for example the United States, there is a great concern over opioid misuse. Therefore, oral analgesics that are effective and have a better safety profile are necessary.

In this study, we sought drugs with appropriate analgesic effects and a low incidence of side effects. We preoperatively administered diclofenac sodium, celecoxib, or acetaminophen, each of which has a different mechanism of action, to patients undergoing minor oral surgery under general anesthesia and compared their levels and duration of postoperative pain.

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Address correspondence to Dr Atsushi Hanzawa, Department of Oral Health and Clinical Science, Division of Special Needs Dentistry and Orofacial Pain, Tokyo Dental College, 2-9-18, Misakicho Chiyoda-ku, Tokyo 101-0061, Japan; hanzawaatsushi@tdc.ac.jp.

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METHODS

Subjects

This study was approved by the Ethics Committee of Tokyo Dental College (approval number 592) and registered in a clinical trials database (UMIN000019431), and written informed consent was obtained from all study participants. The subjects were patients aged 20–65 years with an American Society of Anesthesiologists physical status classification of 1 or 2 and scheduled for extraction of any type of impacted third molars or removal of plates and screws under general anesthesia in an operating room at Tokyo Dental College, Suidobashi Hospital, between January and December 2015, inclusive. Participants were excluded if they had a history of asthma, acute or chronic kidney injury, a history of drug abuse, and/or chronic pain or allergy to any medications used in the study. Pregnant women were also excluded.

Analgesic and Anesthetic Protocols

The subjects were randomly divided using a double-blind method into the following 4 groups: group D, treatment with a nonselective NSAID, diclofenac sodium 50 mg; group C, treatment with a selective COX-2 inhibitor, celecoxib 400 mg; group A, treatment with an antipyretic analgesic with central analgesic effects, acetaminophen 1000 mg; and group P, treatment with a placebo. Each study drug was orally administered with a small amount of water immediately before the patient entered the operating room. In the operating room, electrocardiographic, automatic blood pressure monitoring, and pulse oximetry devices, as well as monitoring equipment for bispectral index and muscle relaxation, were applied, and an intravenous line was established in the left cephalic vein. For induction of anesthesia, remifentanyl was administered by continuous infusion at 0.25 $\mu\text{g}/\text{kg}/\text{min}$ and propofol was administered via target-controlled infusion for a predicted blood level of 3.5 $\mu\text{g}/\text{mL}$. When the patient did not respond to calling of his or her name and loss of the eyelash reflex was confirmed, an endotracheal tube was inserted nasally after intravenous injection of 0.6 mg/kg rocuronium bromide. Anesthesia was maintained with 0.125–0.5 $\mu\text{g}/\text{kg}/\text{min}$ remifentanyl and a propofol blood level of 3.5–5.0 $\mu\text{g}/\text{mL}$ by target-controlled infusion, while paying attention to changes in bispectral index and hemodynamics. Before the surgical procedure commenced, 2% lidocaine (containing 12.5 $\mu\text{g}/\text{mL}$ epinephrine) was administered utilizing only infiltration anesthesia around the operative field. After completion

of the surgical procedure, sugammadex 2 mg/kg was administered. We confirmed that the patient had sufficiently emerged from anesthesia before extubation and transfer to a recovery room. No analgesics were administered at completion of the surgical procedure, and postoperative pain management by intravenous patient-controlled analgesia (IV-PCA) was started at that time. For IV-PCA, 5 mg/2 mL droperidol and 28 mL of saline were added to 1 mg/20 mL fentanyl to prepare a total volume of 50 mL. Fentanyl was administered using an infusion pump (CADD-Legacy PCA pump; Smiths Medical, Ashford, UK) set at 20 μg per fentanyl dose and a lockout time of 10 minutes. In the event of uncontrollable pain, even with IV-PCA, diclofenac sodium 50 mg was available for use as rescue medicine in suppository form.

Patient Assessments

Levels of postoperative pain in patients were assessed by visual analog scale (VAS) scores at 4, 5, and 6 hours after administration of the study drug, consumption of fentanyl up to each time point, and time to first requirement for fentanyl. For VAS measurements, each patient was asked to rate his or her pain on a 100-mm horizontal scale, where the left end (0 mm) was no pain, the right end (100 mm) was the most intolerable pain imaginable, and the length was used as the pain score. When symptoms of side effects such as nausea occurred after the surgical procedure, the types and frequencies were recorded.

Statistical Analysis

All of the data are expressed as the mean $\pm$ SD or median (range). The study data were analyzed using Statistical Package for the Social Sciences version 19.0 software (SPSS, Chicago, Ill). For statistical comparison among groups, gender differences were analyzed using an $m \times n \chi^2$ test and pain scores were analyzed using the Kruskal-Wallis H test and the Mann-Whitney U test with Bonferroni correction. Non-repeated-measures analysis of variance and the Student-Newman-Keuls test were used for analysis of patient background, consumption of fentanyl, and time to first request. A p value of $<.05$ was considered to be statistically significant. The calculated number of subjects was 128 using G*Power version 3.1.92, where the effect size was 0.3 (which is a medium effect size by the conventional Cohen definition), the alpha error was 0.05, and the power was 0.8.¹¹

Table 1. Patient Demographic Data*

	Group P (n = 32)	Group D (n = 32)	Group C (n = 32)	Group A (n = 32)
Age, y	35.7 ± 11.6	36.8 ± 11.6	36.7 ± 11.5	33.2 ± 10.6
Height, cm	163.3 ± 8.3	164.3 ± 7.7	164.4 ± 7.2	165.5 ± 7.9
Weight, kg	58.5 ± 10.4	61.6 ± 15.5	58.0 ± 10.8	60.1 ± 9.2
Gender, male/female	13/18	15/16	14/17	16/17
Local anesthetic, mL	7.4 ± 2.1	6.7 ± 1.7	6.7 ± 2.0	7.3 ± 2.4
Duration of surgery, min	81.0 ± 53.1	86.2 ± 47.8	82.6 ± 32.3	86.6 ± 53.5
Duration of anesthesia, min	130.2 ± 54.3	122.6 ± 63.8	136.6 ± 37.7	118.4 ± 46.5
Type of surgery				
Extraction of the impacted third molars	17	22	21	21
Removal of plates and screws	15	10	11	11

* Data are expressed as number of patients or mean ± SD. There were no statistically significant differences between the groups.

RESULTS

There were 128 study participants (after exclusion of 8 patients who had a fever on the day of surgery and 6 patients who underwent a long surgery) from 142 patients who consented to participate after receiving a full explanation of the study protocol.

No significant differences in gender, age, height, weight, amount of local anesthetic, operative time, or anesthesia time were observed between the 4 groups (Table 1).

The VAS scores were significantly lower at 4 hours after administration in groups D and C, and at 5 and 6 hours after administration in groups D, C, and A, compared with those in group P. No significant difference in VAS scores was observed at any time point among groups D, C, and A (Figure 1).

Consumption of fentanyl after surgery was significantly lower in groups D, C, and A than in group P at 4, 5, and 6 hours after administration. No significant

difference in consumption of fentanyl was observed at any time point among groups D, C, and A (Figure 2).

The time to first requirement for fentanyl was significantly longer in groups D and C than in group P (Table 2).

No incidence of uncontrollable pain or gastrointestinal dysfunction such as nausea or vomiting after surgery was observed in any of the patients.

DISCUSSION

This study demonstrated that when diclofenac sodium 50 mg, celecoxib 400 mg, or acetaminophen 1000 mg was orally administered preoperatively in patients who underwent minor oral surgery under infiltration local anesthesia with propofol/remifentanyl general anesthesia, participants exhibited a decrease in postoperative IV-PCA consumption of fentanyl for all of the 3 test drugs up to 6 hours postoperatively. However, the analgesic efficacy of acetaminophen might have been insufficient in the early 4-hour postanalgesic time period after the procedure; a level of analgesic efficacy similar

Figure 1. Box plots for visual analog scale (VAS) scores at 4, 5, and 6 hours after administration of study drug. Data are expressed as medians, percentiles, and ranges. * $p < .05$ compared with the placebo group; ** $p < .01$ compared with the placebo group by Kruskal-Wallis H test and Mann-Whitney U test with Bonferroni correction.

Figure 2. Consumption of fentanyl up to 4, 5, and 6 hours after administration of study drug. Data are expressed as mean ± SD. * $p < .05$ compared with the placebo group; ** $p < .01$ compared with the placebo group by non-repeated-measures analysis of variance and Student-Newman-Keuls test.

Table 2. Time to First Requirement for Fentanyl†

	<i>Group P</i>	<i>Group D</i>	<i>Group C</i>	<i>Group A</i>
Time, min	177.6 ± 46.3	215.1 ± 55.9*	240.6 ± 49.0**	203.7 ± 74.1

† Data are expressed as mean ± SD.

* $p < .05$ compared with the placebo group.

** $p < .01$ compared with the placebo group.

to that of celecoxib and diclofenac sodium was obtained in the later stages.

Diclofenac sodium inhibits both COX-1 and COX-2, whereas celecoxib selectively inhibits COX-2. NSAIDs, including diclofenac sodium, are known to have adverse effects such as gastrointestinal dysfunction, suppression of renal function, and suppression of platelet function by inhibiting COX-1.^{12,13} In addition, long-term administration may increase the incidence of side effects.^{9,14,15} However, diclofenac sodium, which has analgesic and anti-inflammatory effects for postoperative pain in minor oral surgery, is widely used.^{16,17} Because diclofenac sodium 50 mg is reported to exert an analgesic effect similar to that of ibuprofen 600 mg,¹⁸ we orally administered diclofenac sodium 50 mg preoperatively in this study. Regarding side effects, there were no complaints about gastrointestinal dysfunction by the patients or about difficult perioperative hemostasis by the operators. However, only a single dose was used in this study because of fentanyl PCA use postoperatively, in contrast with long-term administration, which causes an increase in the incidence of adverse events.^{9,14,15}

Celecoxib was developed with the aim of reducing the occurrence of gastrointestinal dysfunction.¹⁹ It was shown to exhibit an analgesic effect similar to that of ibuprofen in a study by Cheung et al,²⁰ and is reported to cause gastrointestinal dysfunction and suppression of platelet function less frequently.²⁰ In addition, use of a high dose does not increase the incidence of gastrointestinal dysfunction.²¹ Furthermore, some studies suggest that celecoxib is not associated with an increased risk of cardiovascular events in comparison with nonselective NSAIDs.²² Thus, celecoxib is expected to be useful as a preemptive analgesic for acute pain after oral surgery. Because a dose of 400 mg is recommended as optimal based on the expected level of pain after oral surgery,²⁰ we used this dose in our study. The results showed that celecoxib significantly reduced pain when compared with placebo and that its analgesic efficacy was similar to that of diclofenac sodium 50 mg. As the beta half-life of celecoxib (8 ± 3.5 hours) is longer than that of diclofenac sodium (1.2 hours) and acetaminophen (2.91 ± 0.38 hours), celecoxib is excellent for longer action,²⁰ and in this study resulted in prompt and sufficient analgesic effect for pain, including acute pain with reactive inflammation. Celecoxib has been used for

chronic diseases including osteoarthritis, rheumatoid arthritis, and low back pain in the field of rheumatology, but is being used increasingly for the treatment of acute pain. Recart et al²³ reported that when celecoxib 200 or 400 mg was administered to patients who underwent minor otolaryngologic surgery under general anesthesia with desflurane/remifentanyl, the requirement for fentanyl after surgery was decreased in comparison with placebo. Some studies of oral combination therapy of celecoxib 400 mg and an opioid in orthopedic surgery have reported that pain was significantly suppressed when celecoxib was combined with an IV-PCA infusion of morphine for management of postoperative pain after knee replacement arthroplasty.²⁴ Further, the concomitant use of celecoxib and an opioid significantly decreased the consumption of opioid in arthroscopic meniscus surgery.²⁵ In this study, oral administration of 400 mg celecoxib significantly decreased consumption of fentanyl in IV-PCA, which supports these previous reports.

Acetaminophen is an extremely weak inhibitor of COX in the periphery²⁶ and has been shown to act mainly in the central nervous system.²⁷ Thus, acetaminophen has negligible peripheral anti-inflammatory effects, but is effective for mild to moderate pain. It has reduced side effects compared with NSAIDs, so is relatively safe to administer assuming maximum dosing guidelines are followed.²⁸ In addition, acetaminophen is known to be somewhat effective for postoperative pain when a sufficient dose is administered.²⁹ Therefore, we considered that acetaminophen 1000 mg might effectively relieve postoperative pain in minor oral surgery. However, the study results suggest that the analgesic efficacy of acetaminophen 1000 mg may not be adequate for pain relief at a relatively early stage after surgery. It may be that factors derived from surgical invasion, such as reactive inflammation, are important factors in postoperative acute pain in oral surgery. The prostaglandin concentration associated with acute tissue damage is known to reach maximum levels after 1 hour,³⁰ whereas the analgesic effect of acetaminophen on peripheral inflammation is limited. Presumably, there were similar conditions in group P, where postoperative pain was managed with fentanyl alone. Fentanyl exerts its analgesic effect by acting on opioid receptors in the central nervous system without any anti-inflammatory

effects.³¹ There were significantly higher VAS scores in the fentanyl-only group (group P, the placebo group) compared with the other groups.

In this study, in which we studied patients who underwent minor surgery under infiltration local anesthesia with propofol/remifentanyl general anesthesia and orally administered acetaminophen 1000 mg, diclofenac sodium 50 mg, or celecoxib 400 mg immediately before surgery. We obtained VAS scores ≤ 50 mm, which generally indicates the ability to perform normal daily activity,³² at all the time points studied. In addition, the requirements for fentanyl were lower than placebo. Thus, our results suggest that these study drugs exerted a variable postoperative analgesic effect when administered preoperatively. One review in orthopedic surgery showed that postoperative analgesia is superior with concomitant preoperative use of a nonselective NSAID or selective COX-2 inhibitor with acetaminophen based on reduced postoperative opioid use.³³ Although we did not use a concomitant traditional NSAID or selective COX-2 inhibitor with acetaminophen in this study, multimodal postoperative pain management via combination therapy with analgesics from different classes should be considered for surgical procedures in which the incidence of postoperative pain is expected to be severe.

Because the surgical cases in this study were not identical and the surgery was conducted under total intravenous anesthesia in all cases, our results cannot be easily compared with previously reported results, which is a weakness of this study.

CONCLUSION

Preoperative oral administration of celecoxib 400 mg and diclofenac sodium 50 mg exerted a significant postoperative analgesic effect for minor oral surgical procedures performed under general anesthesia with infiltration local anesthesia. Acetaminophen 1000 mg also exerted a significant analgesic effect but with slower onset for relief of postoperative pain.

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