Diversity of Opioid Requirements for Postoperative Pain Control Following Oral Surgery—Is It Affected by Polymorphism of the μ -Opioid Receptor?

Ken-ichi Fukuda, DDS, PhD,* Masakazu Hayashida, MD, PhD,† Kazutaka Ikeda, PhD,‡ Yoshihiko Koukita, DDS, PhD,* Tatsuya Ichinohe, DDS, PhD,§ and Yuzuru Kaneko, DDS, PhD§

*Division of Dental Anesthesiology, Department of Oral Health and Clinical Science, Tokyo Dental College, Suidoubashi Hospital, Tokyo, Japan, †Department of Anesthesiology, Saitama Medical University International Medical Center, Saitama, Japan, ‡Division of Psychobiology, Tokyo Institute of Psychiatry, Tokyo, Japan, and §Department of Dental Anesthesiology, Tokyo Dental College, Chiba, Japan

We experience individual differences in pain and sensitivity to analgesics clinically. Genetic factors are known to influence individual difference. Polymorphisms in the human *OPRM1* gene, which encodes the μ -opioid receptors, may be associated with the clinical effects of opioid analgesics. The purpose of this study was to determine whether any of the 5 common single-nucleotide polymorphisms (SNPs) of the *OPRM1* gene could affect the antinociceptive effect of fentanyl. Fentanyl was less effective in subjects with the G allele of the *OPRM1* A118G SNP than in those with the A allele, and subjects with the G allele required more fentanyl for adequate postoperative pain control than those with the A allele. In the future, identifying SNPs might give us information to modulate the analgesic dosage of opioid individually for better pain control. Factors underlying individual differences in sensitivity to pain other than genetic factors may include environmental and psychological factors. We therefore examined the effects of preoperative anxiety on the analgesic efficacy of fentanyl in patients undergoing sagittal split mandibular osteotomy (SSMO). From among the patients enrolled in the study, 60 patients (male/female: 18/42, age: 24.6 ± 6.7 years) who gave informed consent were examined for correlations between preoperative trait/state anxiety, as measured by the state-trait anxiety inventory (STAI) on the day before surgery, and postoperative consumption of patient-controlled analgesia (PCA) fentanyl and visual analog scale (VAS) assessment by patients. Levels of trait and state anxieties measured by the STAI were correlated with neither the consumption of PCA fentanyl nor postoperative VAS assessment. These findings suggest that psychological factors are unlikely to affect postoperative pain or the use of analgesics.

Key Words: Polymorphism; μ -Opioid receptor; Postoperative pain; Patient-controlled analgesia; Preoperative anxiety.

Individual differences in sensitivity to pain and to analgesics are known to vary among patients in daily clinical practice. The amount of analgesics, such as

opioids, used for postoperative pain control, even following the same surgery, also varies substantially among patients. Factors possibly underlying these individual differences include environmental, psychological, and genetic factors. We conducted a study involving patients undergoing oral surgery to identify genetic and psychological factors responsible for the diversity of opioid requirements by examining, respec-

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Address correspondence to Dr Ken-ichi Fukuda, 2-9-18, Misaki-cho, Chiyoda-ku, Tokyo, Japan, 101-0063; kfukuda@tdc.ac.jp.

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Figure 1. Changes in operative time for sagittal split mandibular osteotomy and volume of intraoperative bleeding are shown.

tively, the effect of polymorphisms in the μ -opioid receptor gene and that of preoperative anxiety on postoperative pain (fentanyl requirement). This report describes the background and current progress of our study.

BACKGROUND

Selection and Setting of Target Surgery

Individual differences in sensitivity to pain are preferably examined in healthy subjects. If sensitivity to analgesics for postoperative pain control is to be examined, pathological condition, degree of surgical invasiveness, surgical site, surgical procedure, and the surgeon's level of skill should to the extent possible be consistent across subjects. The target surgery we selected was sagittal split mandibular osteotomy (SSMO), a procedure in orthognathic surgery. Almost all patients undergoing SSMO are young and healthy people aged 10–30 years. Patients undergoing this surgery have an asymmetric facial appearance. Because patients have no inflammation or injury, the pathological condition of patients undergoing SSMO should be almost the same as those of patients undergoing tumor resection, although some morphological differences may exist between the 2 patient populations. The degree of surgical invasiveness, surgical site, and surgical procedure are highly consistent across cases. At Tokyo Dental College, a total of 300–400 cases of SSMO (total from 3 hospitals in Chiba, Ichikawa, and Suidobashi) are performed annually using nearly the same procedure. Figure 1 shows the changes in operative time for SSMO and volume of intraoperative bleeding at the hos-

Figure 2. Frequency of need for postoperative analgesics following sagittal split mandibular osteotomy (SSMO) compared with that following oral soft tissue surgery.

pitals over the past 15 years. Both have decreased annually overall but have remained constant over the past few years. Although increased use of propofol for maintenance of general anesthesia may have contributed to the decrease in bleeding volume,¹ the decrease in operative time is probably attributable to the surgical procedure used in our hospitals. Hypotensive anesthesia, which used to be essential for SSMO, is currently required in almost no patients. In addition, the present study involved only patients for whom SSMO was performed by 1 of 3 experienced surgeons. As described above, the target surgery was selected so that intraoperative factors affecting postoperative pain would be as consistent as possible across patients.

Range of Postoperative Pain Following SSMO

A certain level of pain is required for comparison of postoperative pain. Figure 2 shows a comparison of the level of postoperative pain following SSMO and that following oral soft tissue surgery (in terms of frequency of requirement for postoperative diclofenac). SSMO involves osteotomy, and thus causes somewhat more pain than other oral surgery procedures. Levels of postoperative pain following SSMO have been measured by various indicators, as follows: 0–100 mm on visual analog scaler (VAS) at 3 hours postoperatively,² 0–400 mg diclofenac requirement in the first 72 hours postoperatively,² 0–92 mg consumption of morphine by patient-controlled analgesia (PCA) in the first 72 hours postoperatively,³ and 0–640 μ g consumption of fentanyl in the first 24 hours post-

Figure 3. Measurement of latency to pain perception before (PPLpre) and after (PPLpost) administration of fentanyl. (A patient's hand was immersed in ice-cold water so that more than half of the area of the dorsum of the hand was under-water.)

operatively (from a study listed below). These findings indicate substantial variation and diversity as well as apparent individual differences in both the level of postoperative pain and the consumption of analgesics used to control postoperative pain.

STUDY 1

Genetic Factors Underlying Individual Differences in Sensitivity to Pain

Genetic factors are responsible in part for individual differences in sensitivity to pain. Whereas 99.9% of the human genome sequence is shared among all individuals, the remaining 0.1%, ie, polymorphisms, contributes to individual differences. Single-nucleotide polymorphisms (SNPs) account for the largest number of polymorphisms. An SNP involves the alteration of a single nucleotide base; for example, adenine may be replaced by guanine, or thymine may be replaced by cytosine. These SNPs are one type of individual difference. About 3–6 million base pairs are thought to differ from person to person. Provided below are the results of our study on the relationship between polymorphisms and individual differences in sensitivity to pain following SSMO.

Methods

We examined the effects of 5 SNPs representative of 4 linkage disequilibrium blocks of the human μ -opioid

Figure 4. Intraoperative and postoperative procedures.

receptor gene (A118G, IVS2 + G691, IVS3 + G5953A, IVS3 + A8449G, and TAA + A2109) on the analgesic efficacy of fentanyl in patients undergoing SSMO. Performance of the study was approved by the Ethics Committee of Tokyo Dental College. We enrolled 108 patients scheduled to undergo SSMO at Tokyo Dental College Suidobashi Hospital who provided written informed consent to participate in the study.

After being taken into the operating room, each patient was instructed to immerse his or her finger into ice-cold water, and the amount of time until the patient felt cold stress–induced pain (latency to pain perception) was measured before (PPLpre) and 3 minutes after (PPLpost) the intravenous administration of fentanyl at 2 µg/kg (Figure 3). The PPLpre value was regarded as an index of sensitivity to cold stress–induced pain. With the cutoff value of latency to pain perception (maximum effect) set to 150 seconds,

Table 1. Patient Background and Surgical Data†

Age	25.7 ± 6.7 (18 to 47)
Male/female	40/68
Body weight (kg)	58.2 ± 10.3 (42 to 97)
PPLpre (s)	17.2 ± 1.8 (3 to 130)*
PPLpost (s)	41.8 ± 4.0 (4 to 150)*
%MPE	20.7 ± 2.7 (–19 to 100)*
Anesthesia time (min)	167 ± 23 (101 to 243)
Operative time (min)	106 ± 19 (70 to 177)
Total dose of propofol (mg/kg)	27.0 ± 3.7 (17 to 38)
Total fentanyl dose (µg/kg)	3.31 ± 1.82 (0 to 10.3)
Total PCA fentanyl dose (µg/kg)	3.16 ± 2.67 (0 to 13.8)
VAS at 3 h postoperatively (mm)	31.2 ± 23.5 (0 to 90)
VAS at 24 h postoperatively (mm)	27.4 ± 18.7 (0 to 73)

† Data are expressed as mean ± SD. PPLpre indicates latency to pain perception before administration of fentanyl; PPLpost, latency to pain perception after administration of fentanyl; %MPE, analgesic efficacy of fentanyl; PCA, patient-controlled analgesia; VAS, visual analog scale.

* $P < .05$.

Table 2. Frequencies of 5 single-nucleotide polymorphisms (SNPs)*

A118G	AA: 31 (28.7%)	AG: 54 (50.0%)	GG: 23 (21.3%)
IVS2+G691C	GG: 7 (6.5%)	GC: 34 (31.5%)	CC: 67 (62.0%)
IVS3+G5953A	GG: 87 (80.6%)	GA: 18 (16.7%)	AA: 3 (2.8%)
IVS3+A8449G	AA: 86 (79.6%)	AG: 17 (15.7%)	GG: 5 (4.6%)
TAA+A2109G	AA: 92 (85.2%)	AG: 14 (13.0%)	GG: 2 (1.9%)

* SNP indicates single-nucleotide polymorphism.

%MPE = $(\text{PPLpost} - \text{PPLpre}) / (150 - \text{PPLpre}) \times 100$ was calculated and used as an index of the analgesic effect of fentanyl. SSMO was performed under general anesthesia with nitrous oxide at 2 L/min, oxygen at 1 L/min, propofol (3.5 $\mu\text{g/mL}$, by target-controlled infusion), and fentanyl (290–1020 μg). Ten milliliters of whole blood samples for DNA extraction was collected from each patient during surgery. After surgery, postoperative pain was controlled by PCA with intravenous fentanyl. A PCA pump was filled with 2 mg/20 mL fentanyl, 5 mg/2 mL droperidol, and 28 mL saline. The consumption of fentanyl within the first 24 hours postoperatively and the levels of spontaneous pain as measured by VAS at 3 and 24 hours postoperatively were recorded (Figure 4). Data were examined by analysis of variance.

Results

Patient background data and surgical data are summarized in Table 1 and the frequencies of the 5 SNPs in Table 2. PPLpre was significantly correlated with A118G ($P = .0032$); patients with the G allele exhibited significant shortening of PPLpre. This finding indicates the involvement of A118G in individual differences in sensitivity to pain. %MPE was also significantly correlated with A118G ($P = .0109$); those with a G allele exhibited a significantly lower %MPE than

Figure 5. Relationships between analgesic efficacy of fentanyl (%MPE) and A118G genotypes.

those without it (Figure 5). Consumption of PCA fentanyl within the first 24 hours postoperatively was also significantly correlated with A118G ($P = .0695$). When patients were divided into 3 genotype groups, a significant difference was found by *t* test between those with AA and those with GG ($P = .0398$); the fentanyl requirement by those with GG was almost double that by those with AA (Figure 6). These findings indicate that A118G reduces the analgesic effect of fentanyl and increases postoperative fentanyl requirement.

STUDY 2

Psychological Factors Underlying Individual Differences in Sensitivity to Pain

Factors underlying individual differences in sensitivity to pain other than genetic factors may include environmental and psychological factors. Healthy patients who have never experienced surgery under general anesthesia and are scheduled to undergo SSMO may experience preoperative anxiety and wonder how painful it will be to have the bone of their face cut. We therefore examined the effects of preoperative anxiety on the analgesic efficacy of fentanyl in patients undergoing SSMO.

Figure 6. Relationships between postoperative consumption of fentanyl (patient-controlled analgesia [PCA]) and A118G genotypes.

Figure 7. Relationship between postoperative consumption of fentanyl (patient-controlled analgesia [PCA]) and preoperative anxiety level (state-trait anxiety inventory [STAI]).

Methods

From among the patients enrolled in the study, 60 patients (male/female: 18/42, age: 24.6 ± 6.7 years) who gave informed consent were examined for correlations between preoperative trait/state anxiety, as measured by the state-trait anxiety inventory (STAI) on the day before surgery, and postoperative consumption of PCA fentanyl and VAS assessment by patients. Patients were grouped based on levels of trait and state anxiety according to the Japanese version of the STAI assessment and grading criteria. Postoperative data were then compared among preoperative anxiety groups by the Kruskal-Wallis test.

Results

Patients were grouped by levels of trait and state anxieties measured by the STAI as follows: 9 patients in group II, 20 in group III, 15 in group IV, and 16 in group V by trait anxiety level, and 4 patients in group II, 19 in group III, 20 in group IV, and 17 in group V by state anxiety level. Levels of trait and state anxieties measured by the STAI were correlated with neither the consumption of PCA fentanyl nor postoperative VAS assessment (Figures 7 and 8).

These findings suggest that psychological factors are unlikely to affect postoperative pain or the use of analgesics.

DISCUSSION AND CONCLUSION

We examined whether genetic and psychological factors are involved in individual differences in sensitivity to pain and the use of analgesics. The present study involved healthy patients undergoing oral surgery in which the effects of intraoperative factors such as surgical invasiveness were minimized, and demonstrated

Figure 8. Relationship between visual analog scale (VAS) at 24 hours postoperatively and preoperative anxiety level (state-trait anxiety inventory [STAI]).

that A118G, an SNP of the human μ -opioid receptor gene, is responsible for individual differences in the analgesic efficacy of fentanyl. Although A118G has been shown to be related to the amount of morphine required for pain control,⁴ the present study revealed that it also affects the analgesic efficacy of fentanyl. Fentanyl requirement for pain control may thus be predicted by determining this polymorphic A118G genotype. Many other SNPs have been identified in the human μ -opioid receptor gene as well. More case studies will be needed for the realization of “tailor-made pain control” in the future.

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REFERENCES

1. Ahn HJ, Chung SK, Dhong HJ, et al. Comparison of surgical conditions during propofol or sevoflurane anesthesia for endoscopic sinus surgery. *Br J Anaesth*. 2008;100:50–54.
2. Nagatsuka C, Ichinohe T, Kaneko Y. Preemptive effects of a combination of preoperative diclofenac, butorphanol, and lidocaine on postoperative pain management following orthognathic surgery. *Anesth Prog*. 2000;47:119–124.
3. Handa T, Fukuda K, Hayashida M, Koukita Y, Ichinohe T, Kaneko Y. Effects of intravenous adenosine 5'-triphosphate on intraoperative hemodynamics and postoperative pain in patients undergoing major orofacial surgery: a double-blind placebo-controlled study. *J Anesth*. 2009;23:315–322.
4. Rekvag TT, Klepstad P, Baar C. The Val158Met polymorphisms of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. *Pain*. 2005;116:73–78.