Preemptive Effects of a Combination of Preoperative Diclofenac, Butorphanol, and Lidocaine on Postoperative Pain Management Following Orthognathic Surgery

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The aim of the study was to investigate whether preemptive multimodal analgesia (diclofenac, butorphanol, and lidocaine) was obtained during sagittal split ramus osteotomy (SSRO). Following institutional approval and informed consent, 82 healthy patients (ASA-I) undergoing SSRO were randomly assigned to 1 of 2 groups, the preemptive multimodal analgesia group (group P, $n = 41$) and the control group (group C, $n = 41$). This study was conducted in a double-blind manner. Patients in group P received 50 mg rectal diclofenac sodium, 10 μg/kg intravenous 0.1% butorphanol tartrate, and 1% lidocaine solution containing 10 μg/mL epinephrine for regional anesthesia and for bilateral inferior alveolar nerve blocks before the start of surgery. Postoperative pain intensity at rest (POPI) was assessed on a numerical rating score (NRS) in the postanesthesia care unit (PACU) and on a visual analogue scale (VAS) at the first water intake (FWI) and at 24, 48, and 72 hours after extubation. POPI in the PACU was significantly lower in group P than in group C, whereas there were no significant differences at FWI, 24, 48, and 72 hours after extubation in both groups. Preemptive multimodal analgesia was not observed in this study.

Key words: Preemptive multimodal analgesia; Postoperative pain; Maxillofacial surgery; Orthognathic surgery; Oral surgery.

Recent advances in postoperative pain management have brought about the concept of preemptive analgesia.[1,2] The basis of this concept is that, if certain analgesics are administered before the onset of the surgical stimulus, postoperative pain can be prevented or markedly reduced. To induce preemptive analgesia, the pain hypersensitivity has to be prevented both peripherally and centrally.

A number of studies have been conducted to see whether pain after oral surgery could be prevented in various clinical settings; however, the results were not always satisfactory. Although there have been studies reporting preemptive analgesia upon the removal of the third molar tooth[3–7] and for endodontic therapy[8] with nonsteroidal antiinflammatory drugs (NSAIDs)[3–6,8] or local anesthetics,[7] no one has investigated preemptive analgesia for maxillofacial surgery.

Orthognathic surgery is one of the major maxillofacial procedures that produce strong noxious stimulations. Thus, the authors studied whether preemptive multimodal analgesia (NSAID, kappa opioid receptor agonist, and local anesthetic) could be obtained in subjects undergoing sagittal split ramus osteotomy (SSRO), a representative operation of orthognathic surgery.

METHODS

We studied 82 patients undergoing SSRO for mandibular protrusion or retrusion. All patients were classified

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in status I according to the criteria of the American Society of Anesthesiologists and all gave their written informed consent. This experiment was based on a randomized, double-blind, and controlled trial and was approved by the Ethical Committee, Tokyo Dental College.

Patients were randomly allocated either to a preemptive multimodal analgesia group (group P, $n = 41$) or to a control group (group C, $n = 41$). Subjects in both groups received 10 μg/kg of atropine sulfate and 0.06 mg/kg of midazolam intramuscularly 30 minutes before induction of anesthesia. Lactated Ringer's solution was infused intravenously at a rate of 10 mL/kg/h. Anesthesia was induced with 4 mg/kg of thiopental sodium, given as a single intravenous bolus, and maintained with a mixture of nitrous oxide (3 L/min), oxygen (2 L/min), and isoflurane. Nasotracheal intubation was conducted following intravenous administration of 0.08 mg/kg of vecuronium bromide. Patients were mechanically ventilated with a volume-limited respirator (AV 500, IMI, Saitama, Japan). The isoflurane concentration was adjusted to secure hemodynamic stability during surgery by an anesthetist who did not otherwise participate in this study.

To prevent peripheral sensitization, patients in group P received 50 mg of diclofenac sodium (Voltaren, Novartis Pharma, Basel, Switzerland) rectally immediately after nasotracheal intubation. To prevent central sensitization, 10 μg/kg of 0.1% butorphanol tartrate (Stadol, Bristol, Tokyo, Japan) was administered intravenously at the induction of anesthesia. Our previous study indicated that 10 μg/kg of butorphanol tartrate was able to produce hemodynamic stability during isoflurane anesthesia for oral surgery.[9] In addition, 8 mL of 1% lidocaine solution containing 1 : 100,000 (10 μg/mL) epinephrine (Xylocaine, Astra Japan, Osaka, Japan) was administered for regional anesthesia and for bilateral inferior alveolar nerve blocks 5 minutes before the start of surgery. Patients in group C received 10 μL/kg of physiological saline intravenously at the induction of anesthesia. For hemostasis of the surgical area, 8 mL of a physiological saline containing 1 : 100,000 (10 μg/mL) epinephrine was administered before incision. Patients in group C did not receive drugs, such as opioids, NSAIDs, and local anesthetics, other than nitrous oxide and isoflurane. After surgery, extubation of the trachea was conducted following confirmation of adequate recovery from anesthesia. During surgery, continuous monitoring was conducted for ECG with an electrocardiograph (Polygraph series 360, NEC San-ei, Tokyo, Japan), arterial oxygen saturation with a pulse oximeter (Capnomac Ultima, Datex, Helsinki, Finland), and blood pressure with an oscillometric blood pressure monitor (BP-203i, Nippon Colin, Aichi, Japan) every 5 minutes, and both expiratory carbon dioxide concentrations and end-tidal isoflurane concentrations (ET_{ISO}) with an anesthetic gas monitor (Capnomac ultima, Datex, Helsinki, Finland).

Postoperative pain intensity (POPI) at rest was assessed 1 hour after extubation in the postanesthesia care unit (PACU) using a numerical rating score (NRS) ranging from 0 (no pain) to 10 (worst pain). The POPI was assessed at the first water intake (FWI; 3 hours after extubation) and at 24, 48, and 72 hours after extubation using a visual analogue scale (VAS) from 0 mm (no pain) to 100 mm (worst pain). The patients received an oral or rectal dose of diclofenac sodium, 50 mg, on demand as a postoperative analgesic. Some patients could not take postoperative analgesics orally due to postoperative intermaxillary fixation.

In the author's hospital, diclofenac sodium and other NSAIDs are often administered orally or rectally to reduce pain after oral surgery. When the patient had received the postoperative analgesic before the POPI rating, the score just before medication was recorded as the POPI value. For the assessment of the POPI score at FWI, patients were divided into 2 groups based on whether they received postoperative analgesic supplement before FWI. The period from extubation to the first supplementary postoperative analgesic dosage and the total number of postoperative diclofenac sodium doses administered during the 72 hours after extubation were recorded. In addition, the number of patients who received postoperative analgesic supplement was recorded on the day of surgery and for 3 days after surgery. Only 1 investigator, blinded to the medications given to the patient, assessed POPI in all patients.

For the assessment of intraoperative hemodynamics, ET_{ISO}, systolic blood pressure (SBP), heart rate (HR), and rate-pressure product (RPP = SBP × HR) were recorded during the period from incision to the start of the closing suture, and their mean values, standard deviations (SDs), and coefficients of variation (CVs) were calculated. For patients in group P, the intervals from administration of both diclofenac sodium and butorphanol tartrate to incision, end of surgery, and assessment of NRS were recorded.

Pain scores and the number of postoperative analgesic doses were analyzed using the Mann-Whitney U test. The difference in the number of patients who received postoperative analgesic supplement was analyzed using the chi-square test. The period from extubation to the first supplementary postoperative analgesic administration and the mean values of ET_{ISO}, SBP, HR, and RPP and the CVs of SBP, HR, and RPP were subjected to analysis by Student's t test for independent samples. Statistical significance was assigned for a difference when the P value was less than .05.

Table 1. Demographic Data (Mean ± SD)*

	Group P (n = 41)	*Group C (n = 41)*
Male (*n*)	13	16
Female (*n*)	28	25
Age (years)	20.9 ± 3.7	22.4 ± 4.4
Weight (kg)	58.6 ± 8.9	57.1 ± 8.9
Duration of surgery (minutes)	137.3 ± 44.9	136.0 ± 43.6

* Group P, preemptive multimodal analgesia group; group C, control group.

RESULTS

The 2 groups were similar in sex, age, weight, and duration of surgery (Table 1). There were no significant differences between the 2 groups in POPI scores at FWI (3 hours after extubation) or at 24, 48, and 72 hours after extubation except for those recorded in the PACU (1 hour after extubation) (Figures 1 and 2). There were 33 patients in group P and 34 patients in group C who requested postoperative analgesics. No significant group difference was observed in the period from extubation to the first administration of postoperative analgesics (Figure 3). The total number of postoperative diclofenac sodium administrations was not statistically different between the 2 groups (Table 2). The number of patients who received postoperative analgesic supplement was not statistically different between the 2 groups after surgery (Table 3). The mean values of ET_{ISO}, SBP, HR, and RPP were significantly lower in group P than in group C. The CVs of SBP, HP, and RPP were not significantly different between the 2 groups (Table 4). Table 5 summarizes the intervals from administration of diclofenac sodium and butorphanol tartrate to incision, end of surgery, and NRS assessment in group P.

DISCUSSION

This study was performed to investigate whether preemptive multimodal analgesia could be obtained in patients undergoing SSRO. However, the effects of preemptive multimodal analgesia were not confirmed in SSRO patients with the current protocol. There were no significant differences between the 2 groups either in POPI scores or in the total dosage of postoperative diclofenac sodium.

McQuay[2] reviewed several reports on preemptive analgesia and evaluated their validity on the basis of pre- and postincisional comparison mentioned by Woolf.[1] McQuay, however, accepted the study by Kavanagh et

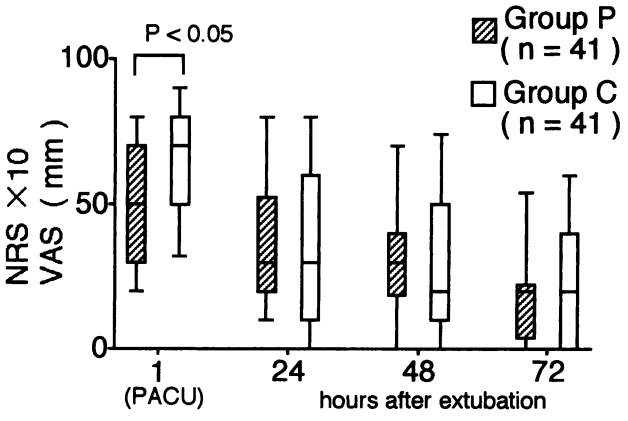

Figure 1. Postoperative pain intensity at rest (POPI). There were no significant differences between the 2 groups in POPI scores at 24, 48, and 72 hours after extubation except for those recorded in the postanesthesia care unit (PACU) (1 hour after extubation). Group P, preemptive multimodal analgesia group; group C, control group; NRS, numerical rating score ranging from 0 (no pain) to 10 (worst pain); VAS, visual analogue scale from 0 mm (no pain) to 100 mm (worst pain). POPI in PACU was assessed using NRS and that at 24, 48, and 72 hours after extubation was assessed using VAS. $P < .05$ between the 2 groups.

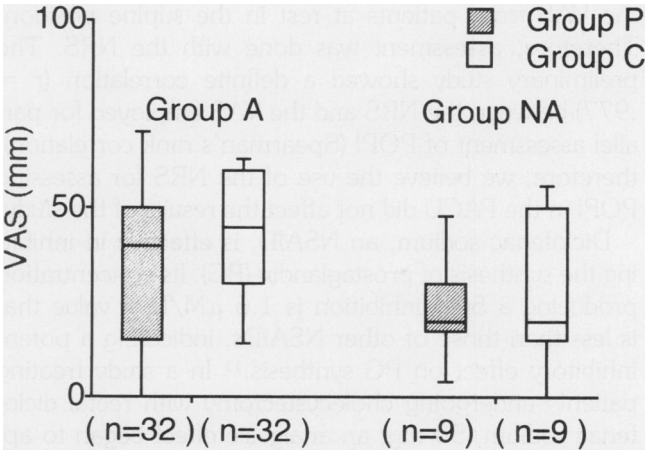

Figure 2. Postoperative pain intensity at rest (POPI) at the first water intake (FWI). There were no significant differences between the 2 groups in POPI scores at FWI (3 hours after extubation). Group P, preemptive multimodal analgesia group; group C, control group; group A, the patient who received postoperative analgesic supplement before FWI; group NA, the patient who did not receive postoperative analgesic supplement before FWI; VAS, visual analogue scale from 0 mm (no pain) to 100 mm (worst pain).

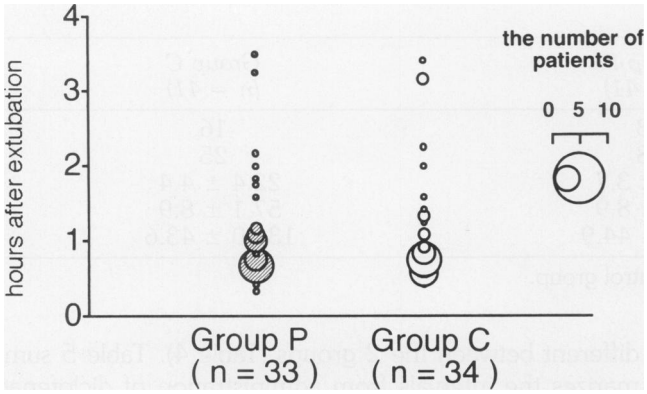

Figure 3. The interval from extubation to the first administration of postoperative analgesics. No significant group difference was observed. 0, the time of extubation; group P, preemptive multimodal analgesia group; group C, control group. There were 33 patients in group P and 34 patients in group C who requested postoperative analgesics.

al,[10] which compared preoperative multimodal analgesia with no preoperative analgesic treatments. The subjects in both groups in the Kavanagh study received morphine on demand postoperatively. The reason why this study was included in McQuay's criteria was that it was the clearest example of a randomized controlled trial using multiple interventions to demonstrate a preemptive effect. The authors believe that this is also applicable to our study.

The assessment of POPI in the PACU was conducted after confirmation of adequate arousal of the patient. However, as our preliminary study (unpublished data) revealed, there was difficulty in obtaining POPI scores on the VAS from patients at rest in the supine position. Therefore, assessment was done with the NRS. The preliminary study showed a definite correlation (r = .977) between the NRS and the VAS employed for parallel assessment of POPI (Spearman's rank correlation); therefore, we believe the use of the NRS for assessing POPI in the PACU did not affect the results of the study.

Diclofenac sodium, an NSAID, is effective in inhibiting the synthesis of prostaglandin (PG). Its concentration producing a 50% inhibition is 1.6 μM/L, a value that is less than those of other NSAIDs, indicating a potent inhibitory effect on PG synthesis.[11] In a study treating patients undergoing cholecystectomy with rectal diclofenac sodium, 50 mg, an analgesic effect began to appear in 34 minutes and lasted until 5 hours after administration.[12] The mean intervals from the administration of diclofenac sodium to incision and to the end of surgery indicate that diclofenac sodium was effective in inhibiting PG synthesis in the present study, with an effect that lasted throughout the procedure.

Odor et al[13] blocked the inferior alveolar nerve with 2 mL of 2% lidocaine solution containing 1 : 80,000 (12.5 μg/mL) epinephrine. The duration of full anesthesia, as assessed by the electric pulp test of molar teeth, was 88 ± 28 minutes (mean ± SD), and complete recovery occurred at a mean of 123 ± 32 minutes. The duration of full anesthesia, as assessed by the pin prick test of soft tissue, was 151 ± 28 minutes, and complete recovery occurred at a mean of 266 ± 44 minutes. Yoshino et al.[14] blocked the inferior alveolar nerve with 2 mL of 1% lidocaine solution containing 1 : 100,000 (10 μg/mL) epinephrine. The duration of anesthesia was 166.2 ± 4.3 minutes. In the present study, surgery was started at least 5 minutes after the induction of regional anesthesia and bilateral inferior alveolar nerve blocks with 8 mL of 1% lidocaine solution containing 1 : 100,000 (10 μg/mL) epinephrine and lasted for a mean of 137.3 ± 44.9 minutes in group P, so that lidocaine would be expected to have provided adequate nerve block during the operation.

Butorphanol, a kappa receptor agonist,[15] appears to exert analgesic effect on pain associated with oral surgery because kappa receptors are known to be present in the spinal trigeminal nucleus.[16] The duration of action after intravenous administration is about 2–4 hours.[17] In the present study, butorphanol tartrate was administered at a dose of 10 μg/kg. The mean interval between butorphanol administration and the end of surgery was 179.1 ± 47.0 minutes (mean ± SD). It appears that the potency and duration of the analgesic effect of butorphanol were adequate during the surgery. Therefore,

Table 2. Total Number of Postoperative Diclofenac Sodium Doses Administered During the 72 Hours After Extubation*

Number of analgesic administrations	*Group P (n = 41)*	*Group C (n = 41)*
0	8	7
1	11	13
2	10	7
3 or more	12	14

* Group P, preemptive multimodal analgesia group; group C, control group.

Table 3. Number of Patients Who Received the Postoperative Analgesic Supplement*

	Group P (n = 41)	*Group C (n = 41)*
Day of surgery	33	34
1 day after surgery	17	15
2 days after surgery	9	13
3 days after surgery	7	3

* Group P, preemptive multimodal analgesia group; group C, control group.

Table 4. Average of Mean Value and Coefficient of Variation (CV) of End-tidal Isoflurane Concentration (ET_{ISO}), Systolic Blood Pressure (SBP), Heart Rate (HR), and Rate Pressure Product (RPP) (Mean ± SD)†

	Group P (n = 41)		*Group C (n = 41)*
Mean value			
ET_{ISO} (%)	1.14 ± 0.33	*	1.61 ± 0.50
SBP (mm Hg)	101.3 ± 9.6	*	110.8 ± 9.2
HR (beats/min)	93.0 ± 14.2	*	109.6 ± 12.8
RPP	9498.6 ± 1941.5	*	12,215.6 ± 1901.2
CV			
SBP (%)	10.0 ± 15.8	NS	8.8 ± 2.5
HR (%)	8.0 ± 3.4	NS	8.0 ± 2.4
RPP (%)	15.4 ± 15.3	NS	14.9 ± 4.0

† Group P, preemptive multimodal analgesia group; group C, control group; NS, not significant.
* $P < .05$ between the 2 groups.

the analgesic effects of diclofenac, lidocaine, and butorphanol should have persisted during SSRO.

Kissin[18] pointed out 3 causes for lack of obvious preemptive analgesia: (1) incomplete effect in the preemptive group: insufficient duration of antinociceptive protection during surgery and during the initial postoperative period (inflammatory phase) and insufficient degree of preventive blockade; (2) partial preemptive effect in the control group: the use of opioids in the control group in induction of anesthesia and during surgery, and (3) surgery with low-intensity noxious stimuli. The mean values of ET_{ISO}, SBP, HR and RPP were significantly lower in group P than in group C. Thus, it seems that adequate antinociceptive effects were obtained in group P patients during surgery. Since the patients in group C did not receive any analgesic before and during surgery, the possibility of a partial preemptive effect can be rejected. In addition, the fact that the mean value of ET_{ISO} was greater in group C than in group P indicates the high-intensity noxious stimulation of SSRO. However, the degree of antinociceptive protection during the initial postoperative period might be insufficient because diclofenac sodium as a postoperative analgesic was only received by patient request. The method of postoperative analgesic administration in the present study possibly caused insufficient duration of antinociceptive protection and insufficient inhibition of the inflammatory pain during the initial postoperative period.

It has been reported that NMDA receptors are involved in central sensitization and that NMDA receptor antagonists blocked the wind-up phenomenon.[19] Clinical studies are underway to reduce postoperative pain through prevention of central sensitization.[20–22] Further studies are needed to investigate the feasibility of inducing preemptive analgesia by administration of NMDA receptor antagonists to patients undergoing SSRO.

In conclusion, preemptive multimodal analgesia was not observed in this study.

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Table 5. Intervals From Administration of Diclofenac Sodium and Butorphanol Tartrate to Incision, End of Surgery, and Numerical Rating Score (NRS) Assessment in Group P (Mean ± SD)

	Butorphanol Tartrate	*Diclofenac Sodium*
Interval from administration to incision (minute)	41.8 ± 8.6	32.4 ± 7.9
Interval from administration to end of surgery (minute)	179.1 ± 47.0	169.8 ± 46.8
Interval from administration to assessment of NRS (minute)	227.2 ± 49.4	217.8 ± 49.3

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