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New method for postoperative pain relief using a combination of noxious and non-noxious stimuli after impacted wisdom tooth extraction

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Abstract: Although in clinical dentistry the major method used for pain relief is oral administration of analgesics, alternative methods are available, such as transcutaneous electrical nerve stimulation (TENS), acupuncture, vibration and conditioned pain modulation (CPM), formerly termed diffuse noxious inhibitory control. The aim of the present study was to investigate the combined effects of non-noxious (TENS) and noxious (CPM) stimuli on postoperative pain after extraction of an impacted wisdom tooth. The study involved 44 patients who were scheduled to undergo impacted wisdom tooth extraction. The patients were randomly allocated into four groups: noxious stimuli, non-noxious stimuli, combined noxious and non-noxious stimuli, and a sham group. On the day after tooth extraction, stimulation procedures for pain relief were performed and changes in the level of perceived pain were scored using a visual analog scale (VAS). The combination of non-noxious and noxious stimuli decreased the VAS scores by 63.7%, indicating a more potent analgesic effect than that in the non-noxious, noxious, and sham groups. This method of analgesia using a combination of non-noxious and noxious stimuli can be applied to patients who are unable to tolerate analgesics, such as those with allergy, hypersensitivity or digestive disorders, and those who are pregnant.

Keywords: conditioned pain modulation; transcutaneous electrical nerve stimulation; impacted wisdom tooth extraction.

Introduction

In clinical dentistry, oral administration of analgesics is frequently used for pain relief (1). However, analgesics may cause a variety of side effects including hypersensitivity, digestive disorders, and hepatorenal disorders. Bronchospasm and anaphylaxis are particularly serious side effects of hypersensitivity (1). When delivered via the oral route, analgesics are absorbed from the gastrointestinal tract, enter the portal venous blood, and thus pass through the liver before entering the systemic circulation for delivery to the receptors leading to metabolism (2) (Corbascio AN et al. Pharmacokinetics and drug interactions, Drug Interactions in Anesthesia, Second Edition, 39-50, Lea & Febiger, Philadelphia, 1986). The first-pass effect through the liver thus greatly reduces the bioavailability of analgesics.

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Table 1 The background of the patients

	Combined	TENS	CPM	Sham
Age (years)	26.2 ± 4.97	25.3 ± 5.48	26.1 ± 3.43	27.5 ± 3.36
Gender (M:F)	6:5	5:6	5:6	5:6

On the other hand, non-noxious stimulation, including electro-acupuncture and transcutaneous electrical nerve stimulation (TENS), can elicit analgesic effects without causing side effects (3,4) and is not subject to the first-pass effect. In addition to oral analgesics, electro-acupuncture (5,6) and TENS (7,8) have also been employed for pain relief because of these advantages.

The phenomenon of "pain inhibiting pain" is a concept referred to collectively as CPM or, formerly, diffuse noxious inhibitory control (DNIC) (9). A series of CPM studies in humans (10-13) have shown that somatosensory evoked potentials (SEP) induced by painful electrical tooth stimulation were reduced by noxious stimulation of the forearm, accompanied by a decrease of tooth pain intensity, as estimated using a visual analog scale (VAS) (10-13). The last of those studies demonstrated reductions in the magnitudes of both SEP amplitudes and VAS values using a combination of non-noxious and noxious stimuli (13).

These results demonstrated that the combined stimuli exerted more potent analgesic effects than either non-noxious or noxious stimuli alone, suggesting that both TENS and CPM activate central mechanisms, including the endogenous opioid and descending pain inhibitory pathways.

Although there have been many independent reports of pain relief with respect to TENS (5,7,8,14,15) and CPM (9,10-13,16-19), few reports (20,21) have described the combined effects of TENS and CPM in humans.

The aim of the present study was to investigate the combined effects of non-noxious and noxious stimuli on postoperative pain after extraction of an impacted wisdom tooth.

Materials and Methods

Patients

Forty-four patients scheduled to undergo impacted wisdom tooth extraction participated, and none of them withdrew during the study period. Approval for the study was obtained from the ethics committee of Tsurumi University (No. 913; 12/9/2011). The patients comprised 21 males and 23 females aged between 20 and 34 years, with a mean age of 26.3 ± 6.36 years (± SD) (Table1). As in the previous study (13), the 44 patients were randomly allocated to four groups, each comprising 11 patients: noxious stimuli (CPM), non-noxious stimuli (TENS), combined noxious and non-noxious stimuli (combined), and a sham group. Chi-squared test revealed no significant inter-group differences in gender ratio.

None of the subjects had any neurological, psychiatric, neuromuscular, endocrine, oral, or maxillofacial disease, and none were being treated concurrently with analgesic drugs including opioids, antidepressants, or cough suppressants. All of the subjects were fully informed of the study procedure and objectives, and provided written consent in accordance with the Declaration of Helsinki. Prior to participation, the subjects were informed that they were free to withdraw from the study at any time, that the study was designed to investigate the perception of pain, and that there was no possibility of tissue injury.

Surgical procedure

All mandibular wisdom tooth extractions were performed by a single specialist between 15:30 and 16:00 at the dental hospital of Tsurumi University. All patients were given an injection of 3.6 mL of 2% lidocaine with 12.5 μg/mL adrenaline (Showa Yakuhin Kako Co., Ltd., Tokyo, Japan; ORA) to the gingiva around the impacted mandibular wisdom tooth by the same specialist oral surgeon. All surgical procedures were performed under local infiltration anesthesia without inferior alveolar nerve block. The mandibular wisdom teeth were classified as IA in 16 cases, class IB in 2 cases, class IIB in 22 cases, and class IIIC in 4 cases (Pell-Gregory classification). After local anesthesia had been achieved, the gingival mucosa and periosteum were incised and the mandibular bone was exposed. The bone was removed to allow access to the tooth root, and the tooth was extracted. During extraction, the tooth was divided into pieces, if necessary. After exodontia, the remaining socket was cleaned to remove any debris.

All patients were treated with prophylactic antibiotics (Astellas Pharma Inc., Tokyo, Japan; Cefdinir 100 mg) 4 and 16 hours after extraction. They were only allowed to take loxoprofen sodium hydrate tablet (Daiichi-Sankyo Co., Ltd., Tokyo, Japan; Loxonin 60 mg each) as an analgesic for severe postoperative pain between 20:00 and 24:00 on the surgical day. After 24:00, analgesic agents

Table 2 The intensity of the electrical stimuli

	Noxious	Non-noxious
Combined (V)	28.8 ± 6.39	13.2 ± 4.92
TENS (V)	NA	12.0 ± 6.00
CPM (V)	25.1 ± 4.13	NA
Sham	NA	NA

NA: Not applicable

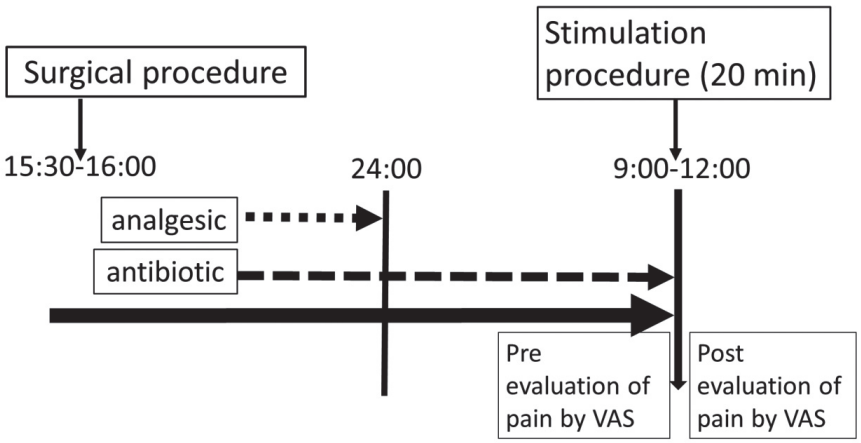

Fig. 1 Study design. A single operator carried out extraction of the mandibular wisdom teeth between 15:30 and 16:00. All patients received prophylactic antibiotics 4 and 16 h after. They were only allowed to take loxoprofen sodium hydrate tablet as an analgesic for severe postoperative pain until 24:00 on the surgical day. The stimulation procedure was performed between 9:00 and 12:00 on the day after extraction.

were prohibited. As a rescue plan if patients felt intolerable pain, they were allowed to take analgesic agents at any time under the condition that if they did so, they would be withdrawn from the study.

Stimulation procedures

The stimulation procedures employed were all carried out by a single dental anesthesiologist using an originally developed device (Ohyou Keisoku Kenkyuusyo, Tokyo, Japan) described previously (13).

According to Svensson et al. (22), conditioning stimulation exerts hypoalgesic effects when applied both contralateral and ipsilateral to a remote site. Here, the ipsilateral median nerve on the forearm was selected as the site for noxious stimulation. Non-noxious stimulation was applied to the buccal region innervated by the trigeminal nerve ipsilateral to the extracted tooth. As the anode, an electrically conductive rubber electrode (diameter 44 mm, area 15.2 mm^2) with a solid gel (Red Dot, 3M Health Care, Tokyo, Japan) was placed on the skin above the median nerve 5 cm from the wrist, and as the cathode a similar electrode was placed on the buccal skin innervated by the trigeminal nerve 5 cm from the anode. A diameter of 44 mm was used to cover the whole area affected by extraction, including the site of swelling. For noxious stimulation, the intensity was determined as 1.2 times the minimum intensity of the stimulus at which a faint pain sensation was used. At this intensity, patients were able to feel a clear pain sensation. In the sham group, electrically conductive rubber electrodes were placed on the forearm and buccal skin, without delivery of an electrical current.

Stimulus intensity

The electrical non-noxious stimulation was applied at an intensity of 13.2 ± 4.92 V (mean ± SE) in the combined group and 12.0 ± 6.00 V (mean ± SE) in the TENS group with a duration of 500 μs at intervals of 20 ms (Table 2). There was no significant difference between these two groups (Student's *t* test).

The electrical noxious simulation was applied at an intensity of 28.8 ± 6.39 V (mean ± SE) in the combined group and 25.1 ± 4.13 V (mean ± SE) in the CPM group with a duration of 1 ms at intervals of 100 ms. To avoid any stimulus expectation, these stimuli were applied randomly at any setting (Table 2). There was no significant difference between these two groups (Student's *t* test).

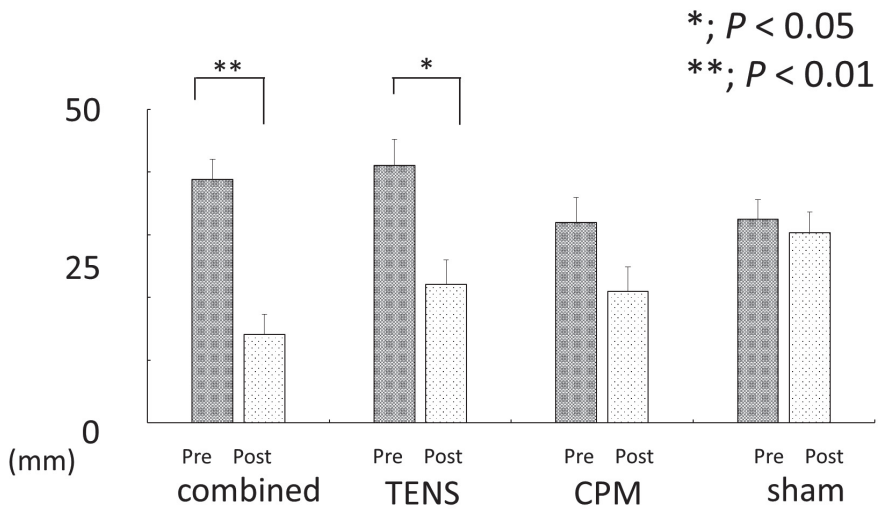

Fig. 2 Changes in VAS scores. The degrees of reduction in the VAS scores in the combined and TENS groups were 63.7% and 46.5%, respectively. There were no significant differences in the pre- and post-stimulation VAS scores between the CPM and sham groups.

The stimulation procedure was performed between 9:00 and 12:00 on the day after extraction (Fig.1). Electrical stimulation was applied to each patient for 20 min in the combined, the non-noxious and the noxious groups. In the sham group, as noted above, although an electrically conductive rubber electrode was placed on the forearm and the buccal skin, the subjects reclined for only 20 min without stimulation.

Postoperative pain intensity in each group was estimated using a VAS before and after the stimulation treatment.

Statistical analysis

The VAS scores were expressed as the mean ± S.E. The Tukey-Kramer test was used to compare the pre- and post-stimulation VAS scores after repeated-measures ANOVA. Differences were considered statistically significant at $P < 0.05$. Statistical analysis was conducted using the SPSS 16.0 software package (SPSS Inc., Tokyo, Japan).

Results

Change in VAS score in the four groups

Tukey-Kramer test revealed no significant differences in the pre-VAS scores among the four groups (Fig. 2). The VAS scores decreased significantly from 38.8 ± 3.29 mm to 14.1 ± 3.22 mm after stimulation in the combined group ($P < 0.01$). The VAS scores in the non-noxious (TENS) group showed a significant decrease from 41.1 ± 4.09 mm to 22.1 ± 3.86 mm after stimulation ($P < 0.05$). The degrees of reduction in the VAS scores in the combined and the non-noxious (TENS) groups were 63.7% and 46.5%, respectively. The difference in the degrees of pain reduction between these groups was significant (Student's t test, $P < 0.05$). The VAS scores in the noxious group were 32.0 ± 3.99 mm for pre-stimulation and 21.0 ± 3.86 mm for post-stimulation. The corresponding VAS scores in the sham group were 32.5 ± 3.07 mm and 30.3 ± 3.37 mm, respectively. There were no significant changes in the pre- and post-stimulation VAS scores between in the noxious (CPM) and the sham groups.

None of the study patients suffered any abnormal or harmful effects. No significant gender rate differences among the four groups (combined, TENS, CPM, and sham) were evident.

Discussion

This study showed that a combination of non-noxious and noxious stimuli decreased the VAS scores after wisdom tooth extraction by 63.7%, exerting an analgesic effect more potent than those in the non-noxious (TENS), noxious (CPM) and sham groups. This combination of non-noxious and noxious stimuli was more effective for nociceptive pain, such as postoperative pain, than non-noxious or noxious stimuli alone.

A previous study had shown that a combination of non-noxious and noxious stimuli had a potent analgesic effect on tooth pain (13). The present findings support this previous observation, and suggest that the potent analgesic effect of combined non-noxious and noxious stimuli is elicited by segmental control and an activated central mechanism, including the endogenous opioid and descending pain inhibitory pathways (23) (Le Bars D et al., Opioids and diffuse noxious inhibitory control

[DNIC] in the rat. Advances in Pain Research and Therapy, 517-539, Raven Press, Ltd., New York, 1995).

Segmental and central control mechanisms elicited by non-noxious and noxious stimulation, respectively, provide additive enhancement of postoperative pain relief. Non-noxious stimulation is commonly used for pain relief as TENS, based on the gate control theory (14). Both high- and low-frequency TENS cause hypoalgesia through release of endogenous opioids in the CNS (8). TENS activates μ opioid receptors at low frequency and δ opioid receptors at high frequency in the spinal cord and rostral ventral medulla (24). In humans, endogenous opioid peptides in cerebrospinal fluid are increased by low- or high-frequency TENS (25,26).

Noxious stimuli can also elicit analgesic effects via activation of a central mechanism, a phenomenon referred to as CPM. This has also been proposed to play a major role in modulation of pain, whereby painful conditioning stimulation in one region inhibits pain in a remote area of the body (16,18). The central involvement of CPM triggered by peripheral Aδ and C fibers emanates from brain structures confined to the caudal-most part of the medulla (10). The neural network of the CPM loop is present in the middle of the brainstem, including the raphe magnus, and mediated by the noradrenergic or serotonergic system (19). CPM is a form of supraspinal descending endogenous analgesia (27,28) that can be antagonized by a low dose of naloxone, an opiate antagonist (29).

Combined non-noxious and noxious stimuli may lead to interaction of endogenous substances with opiate receptor sites, catecholaminergic, serotonergic, and opioid neuronal systems via noxious stimulation (13,19,29).

The intensity of noxious stimulation employed in the present study was fully bearable by patients, the intensity being 1.2-fold that of a faint pain sensation. This intensity of noxious stimulation can be applied clinically.

To date, oral analgesic drugs have been used for postoperative pain relief after surgical removal of impacted wisdom teeth, as this approach is simple and non-invasive (1). However, orally administered analgesics can have potential side effects, including hypersensitivity, digestive disorders, and other issues (2). Analgesia using a combination of non-noxious and noxious stimuli can be an alternative to anti-inflammatory analgesics and narcotics for postoperative pain control after tooth extraction, and is expected to be useful for patients who develop hypersensitivity or digestive disorders in response to analgesics, or for those who are pregnant. The present results may encourage new approaches for management of both acute and chronic pain in the dental, oral, and maxillofacial regions.

Finally, although there were no significant differences in gender ratio between the present four groups (combined, TENS, CPM, and sham), it is well known that clinical and experimental pain studies have yielded consistent evidence of gender differences in pain perception (30). However, some other studies including CPM (30,31) have demonstrated no significant differences in pain perception between genders. In the present study, as there were no significant differences in gender ratios, gender likely had little influence on the results.

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Conflict of interest

The authors declare that there were no competing interests in relation to this study.

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