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Acute postoperative pain after orthognathic surgery can be predicted by the preoperative evaluation of conditioned pain modulation and pain catastrophizing

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Abstract

Introduction: The incidence and severity of chronic postoperative pain (POP) are major clinical challenges, and presurgical conditioned pain modulation (CPM) and pain catastrophizing scale (PCS) assessments have exhibited predictive values for POP. However, whether CPM and PCS assessments are also predictive of acute POP is unknown.

Objectives: We aimed to investigate the relationship between preoperative CPM and PCS and acute POP severity after orthognathic surgery by assessing preoperative CPM and PCS in 43 patients.

Methods: The pressure pain threshold and tonic painful cold–heat pulse stimulation (applied with a pain intensity score of 70 on a visual analogue scale [VAS 0–100]) were used as the test and conditioning stimuli, respectively. The pain area under the postoperative VAS area under the curve (VASAUC) was estimated. The associations between CPM, PCS, and VASAUC were also analyzed.

Results: No patient experienced chronic POP after 1 month. Negative and positive CPM effects (test stimulus threshold was 0% $>$ and 0% $\leq$ during conditioning stimulation, respectively) were detected in 36 and 7 patients, respectively. For patients with negative CPM effects (CPM responders), multiple regression analysis revealed a prediction formula of log (VASAUC) = ($-0.02 \times$ CPM effect) + ($0.13 \times$ PCS-magnification) + 5.10 (adjusted $R^2 = 0.4578$, $P = 0.00002$, CPM effect; $P = 0.002$, PCS-magnification; $P = 0.0004$), indicating that a weaker CPM and higher PCS scores were associated with more acute POP after surgery.

Conclusion: CPM and PCS can predict acute POP after orthognathic surgery.

Keywords: Acute postoperative pain, Orthognathic surgery, Prediction, Conditioned pain modulation, Pain catastrophizing scale

1. Introduction

For perioperative management, acute postoperative pain (POP) and chronic POP are urgent matters. The International Association for the Study of Pain named 2017 as the "Global Year Against Pain After Surgery,"[9] while 2020 was dedicated to "Prevention of Pain,"[10] indicating their importance.

The pain catastrophizing scale (PCS) is a predictive measure for development of chronic postoperative surgical pain.[38,43] Another suggested predictive factor is endogenous pain modulation, assessed in humans using a proxy called "conditioned pain modulation" (CPM).[38] The incidence and severity of chronic POP after thoracotomy are predicted by an impaired CPM.[48] Moreover, another study including patients after abdominal surgery showed that a smaller preoperative CPM is associated with chronic POP and increased postoperative hyperalgesia.[45] To date, minimal research has focused on CPM and PCS as possible predictors for pain in the acute postoperative period.

We aimed to investigate the relationship between preoperative CPM and PCS and acute POP severity after orthognathic surgery. We hypothesized that CPM and PCS (in combination) could predict acute POP after orthognathic surgery.

2. Methods

2.1. Participants

This study was conducted at the Division of Dental Anesthesiology, Department of Diagnostic and Therapeutic Sciences, Meikai University School of Dentistry. Written informed consent was obtained from all patients before study inclusion. The study was

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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conducted as per the Declaration of Helsinki and the World Medical Association and was approved by the Ethics Committee of Meikai University (A1624). This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (unique ID: UMIN000026719) before conducting the research; preregistration adheres to disclosure requirements of the institutional registry.

The inclusion criteria were (1) patients scheduled for orthognathic surgery, (2) >18 years old, and (3) able to provide informed consent. The exclusion criteria were (1) presence of a psychiatric disease, (2) use of any pain medication 24 hours before the investigation, and (3) unable to provide informed consent. Patients were recruited from April 2017 to May 2019.

2.2. Preoperative evaluation

2.2.1. Assessment of cold and heat pain

Subjective assessments of cold and heat pain thresholds were first performed to shorten the experimental time for the patient by changing the ramp time of cold and heat stimulation to detect the temperature inducing a pain intensity of 70/100 on a visual analogue scale (VAS). Subjective assessments of cold and heat pain were performed in a randomized order with the nondominant forearm using a developed quantitative thermal stimulator device (VICS, Tokyo, Japan).[24–26] The temperature was set at a neutral temperature (32.0°C) and was increased or decreased through computer control ("method of limits") (**Fig. 1**). The baseline temperature was 32°C (neutral temperature) and was applied for 10 seconds to establish heat balance between the probe and skin surface. The temperature was decreased or increased with a ramp time of 2°C/second until the patient felt pain.

After the pain threshold was reached, the ramp time was changed to 0.5°C/second to strictly and carefully detect the temperature inducing a pain intensity of 70/100 on the VAS. When the patient perceived a pain intensity of 70/100 on the VAS, cold and heat temperatures with a pain intensity of 70/100 on the VAS were used for conditioning cold–heat pulse stimulation. The cutoff temperature for cold and heat pain was set at −10 and 47°C, respectively, to avoid inducing thermal injury. If the patient did not feel pain at a VAS score of 70/100 with a temperature between −10 and 47°C, −10 or 47°C was applied for conditioning cold–heat pulse stimulation.

Pain intensity was assessed using a custom-made electronic VAS (0–100 mm), which was sampled and analyzed by a personal computer.[24–26] The left endpoint (0) of the electronic VAS indicated "no pain," and the right endpoint (100) indicated the "worst pain imaginable."

2.2.2. Conditioned pain modulation evaluation

The tonic painful cold–heat pulse stimulation consisted of a sequence of repeated cold and heat stimulation delivered at 20-s intervals (0.025 Hz),[24–26] applied to the nondominant forearm as a conditioning stimulus. Conditioning stimulus was applied for 5 minutes, 2-minute stimulation without the test stimulus and 3-minute stimulation with the test stimulus (**Fig. 1**). The cold and heat temperatures for painful conditioning cold–heat pulse stimulation were temperatures established in the initial test session.

Pressure pain thresholds (PPTs) were applied to the dominant forearm as a test stimulus[23–25,27–29] to assess CPM potency. Pressure pain thresholds were assessed using a custom-made electronic pressure algometer (AIKOH Engineering, Osaka, Japan) with a probe area of 1 cm^2. Pressure pain threshold was defined as the amount of pressure (N) perceived painful by the patient. Pressure was applied at a steadily increasing rate of 3 N/second (30 kPa/second).[2,23–25,27–29]

The patient pressed the stop button when the threshold was reached. PPT measurements were repeated thrice with 1-minute intervals. The mean value of 3 recordings was used for subsequent analysis. Pressure pain threshold was recorded before (baseline) and during the conditioning stimulus. To ensure a constant attention level of the patients throughout the experiment, they were instructed to focus on their PPT.

The CPM effect was calculated as [(PPT at baseline) – (PPT during the conditioning stimulus)]/(PPT at baseline) × 100 (%). This approach resulted in negative CPM scores (CPM effect <0%) for pain inhibition and positive CPM scores (CPM effect ≥0%) for pain facilitation. Thus, a negative CPM score was indicative of effective endogenous pain modulation.

2.2.3. Pain catastrophizing scale evaluation

Participants completed the Japanese version of the PCS questionnaire.[18,19] The pain catastrophizing scale consists of 13 items, and participants were asked to rate the frequency at which they experienced different pain-related thoughts or feelings on a 5-point Likert scale, where 0 represents "not at all" and 4 represents "all the time." Scores of the 3 subscales of the PCS (rumination, helplessness, and magnification) were also calculated in addition to the sum of all items as a total score.

2.2.4. Experimental protocol for the preoperative day

Conditioned pain modulation and PCS evaluations were performed the day before the surgery (**Fig. 1**) at a constant room temperature (25°C). Assessments of cold- and heat-associated pain were conducted in a randomized order in 5-minute intervals. The conditioning stimulation started 10 minutes after the baseline PPT recordings and was completed after PPT reassessment.

2.3. General anesthesia and the surgical procedure

Orthognathic surgeries were performed under general anesthesia with endotracheal intubation using balanced anesthesia with propofol, remifentanil hydrochloride, and rocuronium bromide and regional anesthesia with 1% lidocaine hydrochloride monohydrate containing 1/100,000 adrenaline.

Acetaminophen (1000–2000 mg) was administered 30 minutes before the end of the surgery. For bilateral sagittal split ramus osteotomy and Le Fort type I osteotomy (n = 21), 2000 mg of acetaminophen was administered. For other surgeries (n = 22), 1000 mg was administered.

2.4. Postoperative protocol for pain management and evaluation of surgical pain

For POP management, acetaminophen was administered. On the day after the operation, 1000 to 2000 mg was administered. After postoperative day 1, 3000 mg per day (1000 mg at 8 AM, 12 PM, and 6 PM) was administered. If the pain was not well-controlled, loxoprofen sodium, additional acetaminophen, indomethacin, or other pain medications were administered. In addition, trigeminal nerve block (mandibular, inferior alveolar, maxillary, and mental nerve blocks) or local infiltration anesthesia was administered with levobupivacaine hydrochloride. The dose of analgesics was adjusted and reduced according to the POP level.

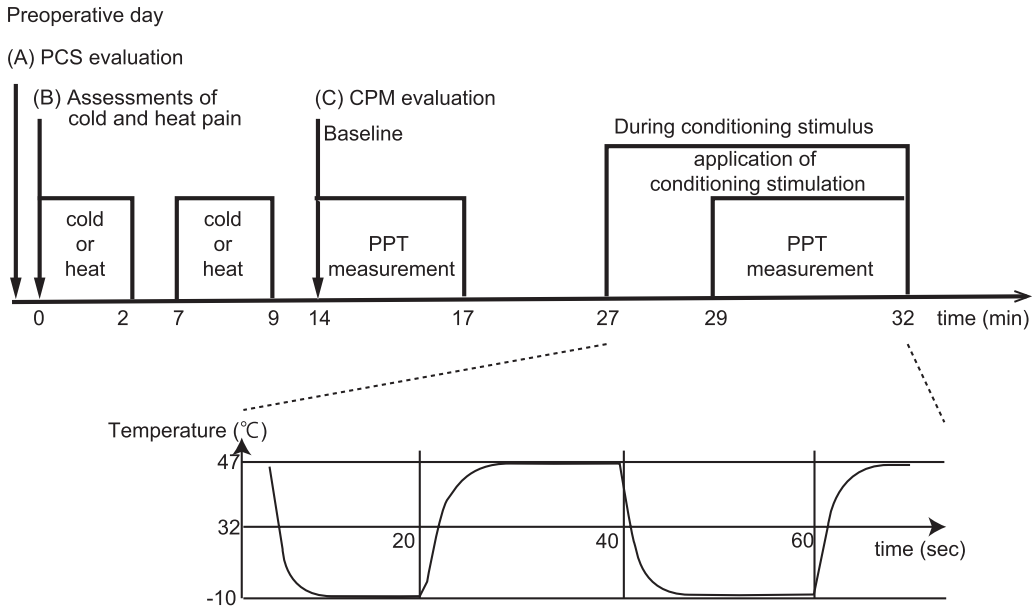

Figure 1. Schematic illustration of the study protocol on the preoperative day. (A) Patients completed the PCS evaluation. (B) Assessments of cold and heat pain were conducted in a randomized order with a quantitative thermal stimulator device at 5-minute intervals. (C) CPM evaluation began 5 minutes after the end of the assessments of cold and heat pain. The tonic painful cold–heat pulse stimulation consisted of a sequence of repeated cold and heat stimulation delivered at 20-second intervals (0.025 Hz) applied as conditioning stimulation. The figure shows an example of the conditioning cold–heat pulse stimulation which consisted of −10 and 47°C. CPM, conditioned pain modulation; PCS, pain catastrophizing scale; PPT, pressure pain threshold.

Postoperative pain intensity was evaluated using a VAS (VAS-POP). On the operative day, VAS-POP assessment was performed immediately after returning to the ward, 1 hour after returning to the ward, and at 9 PM. After postoperative day 1, VAS-POP was assessed at 6 AM, 1 PM, and 7 PM. Furthermore, VAS-POP was evaluated at 8 AM, 12 PM, and 6 PM during acetaminophen administration. Administration of acetaminophen was discontinued if the VAS-POP was less than 30/100 or if the patient did not request an additional prescription. This decision was made during morning rounds.

The period of acetaminophen administration and total administered dose of analgesics were recorded. The postoperative analgesic requirement period was defined as "the final analgesic administration time (day) − the end time of anesthesia (day)."

VAS-POP was evaluated daily until discharge. If VAS-POP did not reach 0/100 at discharge, patients were requested to record it until it reached 0/100. Furthermore, patients were interviewed regarding POP 3 months, 6 months, and 1 year postoperatively. The number of days until VAS-POP reached 0/100 was calculated as "days with pain." Furthermore, VAS-POP area under the curve (VASAUC) (mm × day) was calculated by summing VAS-POP areas. Moreover, in the current study, we defined acute POP as POP until 1 month postoperatively.

2.5. Statistics

The analysis included 43 patients: 36 patients with a CPM effect (responders) and 7 patients without (nonresponders). Data for patient background, temperature, and VAS values for conditioning cold and heat stimulus are shown as medians (interquartile range).

The F-test for homogeneity of variance and the Kolmogorov–Smirnov test were performed before the *t* test. The *t* tests were performed for the PCS-total score, PCS-subscale scores, analgesic requirement period, days with pain, and VASAUC for responders and nonresponders. Statistical significance was set at $P < 0.05$.

Multiple linear regression analysis was used for the analgesic requirement period, days with pain, and VASAUC as outcome variables. For all 43 patients, outcome variables were the analgesic requirement period, days with pain, and VASAUC, and explanatory variables were CPM and PCS. These analyses were repeated for the 36 patients with CPM effect (responders). Multicollinearity between explanatory (independent) variables was assessed using variance inflation factors (VIFs) (reference value of 10) before interpreting the final output. Residuals of the multiple linear regression model were analyzed by graphically plotting the residuals against the predicted values and by plotting normal Q–Q plots. Statistical analyses were performed using the EZR program (Jichi Medical University, Tochigi, Japan).[11]

3. Results

3.1. Patients

Forty-three patients were recruited from the 64 screened patients (**Fig. 2**).

No patients received analgesics 1 day preoperatively. **Table 1** shows patients' demographic data.

Patients without any inhibitory CPM (CPM effect ≥0%) during the conditioning stimulus were defined as "nonresponders." Patients with inhibitory CPM (CPM effect <0%) were defined as "responders." No patient showed 0% CPM effect (**Fig. 3**). Seven patients were nonresponders, and 36 were responders (**Fig. 3**).

3.2. Temperature and visual analogue scale values for conditioning cold and heat stimuli

Results of the conditioning stimulus temperatures are shown in **Table 2**.

The temperatures for cold and heat stimuli with a pain intensity of VAS 70/100 were −2.0°C (−10.0–4.0) and 47.0°C (47.0–47.0), respectively. The VAS values for cold and heat pain were 69.0 (40.5–72.0) and 45.0 (20.5–67.0), respectively, because the heat

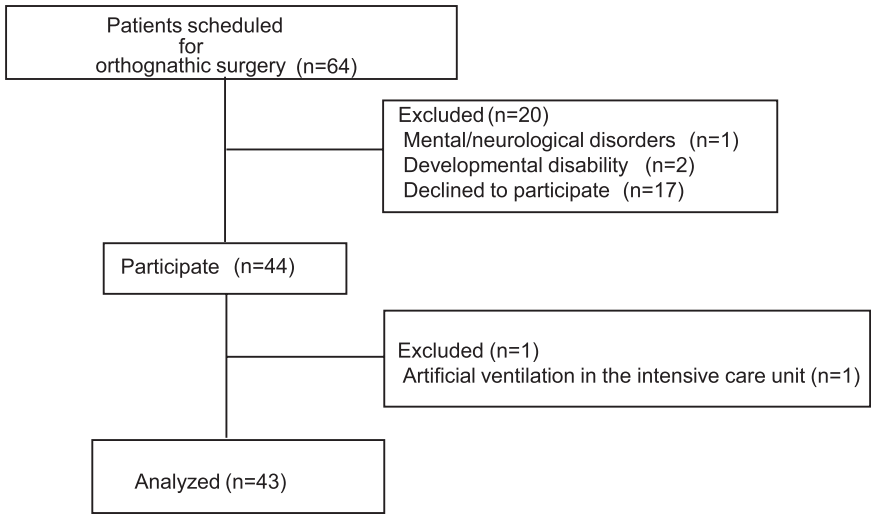

Figure 2. Flow chart of patient selection.

stimulus increment was stopped at 47°C to avoid burns or other injuries.

3.3. Averaged conditioned pain modulation effects and frequency plot of the individual conditioned pain modulation effects

The averaged CPM effects (%) for nonresponders, responders, and all 43 patients were 4.9% (4.5–8.7), −16.3% (−26.1 to −8.5), and −13.1% (−23.3 to −5.5), respectively (**Table 3**). A frequency plot of individual CPM effects is shown in **Figure 3**.

3.4. Pain catastrophizing scale evaluation

Table 3 shows the results of PCS evaluation in nonresponders, responders, and all 43 patients.

3.5. Analgesic requirement period, days with pain, and visual analogue scale area under the curve

Table 4 shows results of the analgesic requirement period, days with pain, and VASAUC in nonresponders, responders, and all 43 patients.

The longest number of days with pain was 20.5 days.

3.6. Postoperative analgesic consumption

3.6.1. Acetaminophen

The administration period for the 7 nonresponders was 8.0 (7.5–9.5) days, and the total dose was 20,000 (17,900–25,500) mg. The administration period for the 36 responders was 8.0 (6.0–9.0) days, and the total dose was 20,500 (17,000–24,000) mg. The administration period for all 43 patients was 8.0 (6.0–9.0) days, and the total dose was 20,000 (17,000–24,000) mg. In 1 nonresponder and 1 responder, the single dose was reduced to 600 mg after POP decreased.

3.6.2. Other analgesics

Among 43 patients, 33 received other analgesics in addition to acetaminophen. Among them, 28 (5 nonresponders and 23 responders) needed administration of loxoprofen sodium hydrate. The single dose was 60 to 120 mg. The administration period for nonresponders, responders, and all patients was 4.0 (3.0–6.0), 3.0 (1.5–5.0), and 3.0 (1.8–5.3) days, respectively.

Intravenous flurbiprofen axetil was administered on the operative day in 3 patients; all were responders. The single dose was 50 to 100 mg, which was only administered once. A single dose of 100-mg celecoxib was administered on the operative day to 1 responder. A single dose of 50-mg indomethacin was administered on the operative day to 9 patients, 1 nonresponder and 8 responders. Pentazocine was administered on the operative day to 1 responder (single dose of 15 mg).

3.6.3. Local anesthesia

Local anesthesia was administered on the operative day for control of POP in 18 patients. Specifically, 0.5% levobupivacaine hydrochloride was administered to 2 nonresponders and 13 responders with an administration dose of 10.0 (9.3–10.0) mL. Moreover, 0.5% bupivacaine hydrochloride hydrate was administered to 1 nonresponder and 2 responders with an administration dose of 6.0 (6.0–8.0) mL.

A mandibular nerve block was administered in 9 patients (all responders): maxillary nerve block in 1 patient (responder), inferior alveolar nerve block in 5 nonresponders and 2 responders, and mental nerve block in 1 nonresponder and 1 responder. Local infiltration anesthesia was administered to 3 responders.

3.7. Statistical analysis

3.7.1. t test

Data showed homogeneity of variance and normal distribution ($P > 0.05$). There were no significant differences between responders and nonresponders in PCS-total, PCS-rumination, PCS-helplessness, and PCS-magnification scores ($P = 0.131$, 0.111, 0.361, and 0.121, respectively). There were no significant differences between responders and nonresponders in the analgesic requirement period, days with pain, and VASAUC ($P = 0.389$, 0.663, and 0.797, respectively).

3.7.2. Normality

For the 43 total patients and 36 patients experiencing the CPM effect (responders), the normal Q–Q plots showed that VASAUC

Table 1

Patient background and operation type.

Patient background	Nonresponders (n = 7)	Responders (n = 36)	Total (n = 43)
Sex (M/F)	0/7	13/23	13/30
Age (y)	31.0 [26.5–40.0]	23.5 [20.0–30.0]	24.0 [21.0–30.0]
Height (cm)	162.0 [160.0–163.0]	164.5 [159.3–171.0]	163.0 [159.0–170.0]
Body weight (kg)	56.0 [54.5–61.0]	57.5 [53.0–64.5]	57.0 [53.0–63.0]
Dominant hand (R/L)	6/1	30/6	36/7
Operation type			
Le Fort type I osteotomy and SSRO	2	19	21
SSRO	4	11	15
SSRO and chin angioplasty	0	2	2
Wassmund method	1	2	3
Surgically assisted rapid palatal expansion	0	1	1
Chin angioplasty	0	1	1

Values are presented as numbers or medians [interquartile ranges]; nonresponders: CPM effect ≧ 0 (%), responders: CPM effect <0 (%).
CPM, conditioned pain modulation; F, female; M, male; L, left; R, right; SSRO, sagittal split ramus osteotomy.

was not normally distributed; thus, a logarithmic translation was required. After logarithmic translation, log (VASAUC) was normally distributed for all patients and responders.

3.7.3. Multiple regression analysis

3.7.3.1. All patients

The prediction model of POP showed that CPM (B [regression coefficient] = −0.01; $P = 0.04$) and PCS-magnification scores (B = 0.10; $P = 0.002$) were significant predictors of log (VASAUC) ($R^2 = 0.3015$) (**Table 5**).

The prediction formula was as follows:

Log (VASAUC) = (−0.01 × CPM effect) + (0.10 × PCS-magnification) + 4.95 (adjusted $R^2 = 0.3015$, $P = 0.0003$, CPM effect; $P = 0.04$, PCS-magnification; $P = 0.002$).

The VIF for CPM effect and PCS-magnification was 1.07 and 1.07, respectively.

3.7.3.2. Responders

The prediction model of POP showed that the CPM (B = −0.02; $P = 0.002$) and PCS-magnification scores (B = 0.13; $P = 0.0004$) were significant predictors of log (VASAUC) ($R^2 = 0.4578$) (**Table 6**).

The prediction formula was as follows:

Log (VASAUC) = (−0.02 × CPM effect) + (0.13 × PCS-magnification) + 5.10 (adjusted $R^2 = 0.4578$, $P = 0.00002$, CPM effect; $P = 0.002$, PCS-magnification; $P = 0.0004$).

The VIF for CPM effect and PCS-magnification was 1.02 and 1.02, respectively.

4. Discussion

To the best of our knowledge, this study is the first to show that preoperative CPM and PCS assessments are predictive of acute POP after orthognathic surgery, ie, weaker CPM and

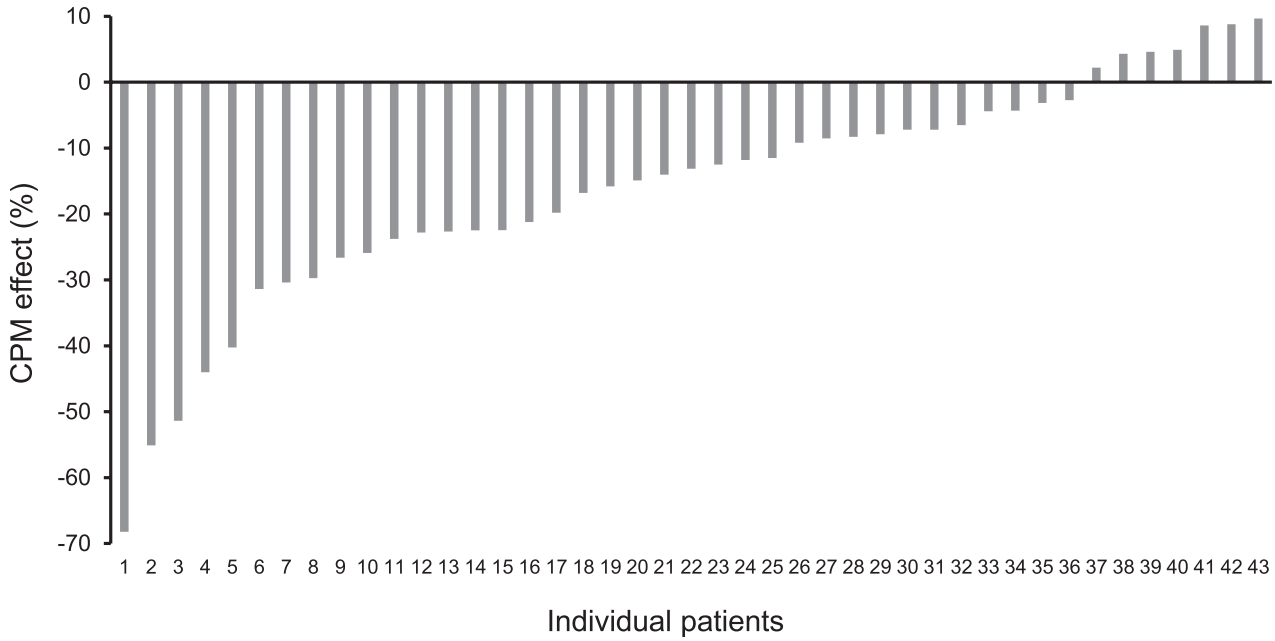

Figure 3. Frequency plot of individual CPM effects for 43 patients. Negative scores (CPM responders) indicate a CPM effect defined by an increased PPT during the conditioning stimulus. CPM, conditioned pain modulation; PPT, pressure pain threshold.

Table 2

Temperature and visual analogue scale (VAS) values for conditioning cold and heat stimulus.

Temperature for cold stimulus (℃)	−2.0 [−10.0 to 4.0]
Temperature for heat stimulus (℃)	47.0 [47.0 to 47.0]
VAS values for cold pain	69.0 [40.5 to 72.0]
VAS values for heat pain	45.0 [20.5 to 67.0]

N = 43; values are presented as medians [interquartile ranges].
CS, conditioning stimulus.

higher PCS scores were associated with more acute POP after surgery.

4.1. Management and prediction of postoperative pain

Management of chronic POP has received increasing attention.[9,20] Preoperative tests such as CPM,[45,48] temporal summation of pain,[31] and PCS[4,12,44] may, to some degree, be used as predictive risk factors for chronic POP in knee osteoarthritis surgery[4,31] and thoracotomy[48] in the spinal region. Although acute POP is shown as a risk factor for chronic POP,[10] little is known about risk factors that can predict acute POP.

Chronic POP is defined as chronic pain developing or increasing in intensity after a surgical procedure and persisting beyond the healing process, ie, at least 3 months postoperatively.[36] However, no consensus is made concerning the duration of acute POP to date. Therefore, acute POP was defined as POP until 1 month postoperatively in the current study.

In this study, the analgesic requirement period, days with pain, and VASAUC were calculated for the evaluation of acute POP. The longest number of days with pain was 20.5 days. The VIF was less than 10, indicating potentially nonharmful collinearity. Thus, CPM and PCS-magnification scores were independent factors for VASAUC, and there was no correlation between CPM and PCS scores. Multiple regression analysis revealed that a weaker CPM effect and higher PCS-total or PCS-subscale scores lead to a longer analgesic requirement period, more days with pain, and higher VASAUC for all patients and responders. Statistical analysis revealed that the analgesic requirement period, days with pain, and VASAUC could be predicted using CPM and PCS-total or PCS-subscale scores as per previous studies focusing on chronic POP.[4,12,44,45,48] Only few studies have focused on predicting acute POP using CPM and/or PCS to date. Strulov et al. assessed the relation between PCS scores and pain after cesarean sections.[39] No significant association between PCS scores and analgesic consumption was observed in the ward; however, PCS correlates with acute post-cesarean section pain. Grosen et al. showed that preoperative CPM and PCS scores were not associated with the development of persistent POP after funnel chest repair, although CPM predicted morphine consumption and PCS scores predicted movement evoked pain intensity in the acute postoperative phase.[8] Yarnitsky et al. reported that efficient CPM predicted a lower risk of chronic postthoracotomy pain, although CPM efficiency was not significant for predicting acute POP intensity.[48] Overall, no unified view has been obtained so far concerning the prediction of acute POP using CPM and/or PCS scores. We demonstrated that acute POP could be predicted using CPM and PCS scores in orthognathic surgery patients. The pain caused by orthognathic surgery is somatic, not visceral. Visceral pain and somatic pain differ in the neurobiological mechanisms that mediate the sensory process.[5] The abovementioned studies include visceral pain in addition to somatic pain. The difference in the surgeries could be a possible reason why acute POP could be predicted using CPM and PCS scores in the current study.

There were no significant differences between responders and nonresponders in PCS-total scores, PCS-subscale scores, analgesic requirement period, days with pain, and VASAUC. To determine whether POP is predicted for nonresponders as well, we performed multiple linear regression analysis for all patients in addition to responders. The adjusted R^2 values were higher, and the *P*-values were smaller for responders than that for all patients. The result implies that although a robust prediction formula was derived for CPM responders, it was also possible to predict acute POP in all patients including CPM nonresponders. Owing to the small numbers of nonresponders, multiple linear regression analysis for nonresponders could not be performed with 2 explanatory variables.

4.2. Conditioned pain modulation evaluation

"Diffuse noxious inhibitory controls" was used to describe CPM in human previously[46] and was first reported by Le Bars et al.[13,14] in 1979 for animals. Diffuse noxious inhibitory control is a phenomenon whereby the activities of convergent neurons in the spinal dorsal horn and trigeminal nucleus are selectively and powerfully inhibited by the application of noxious stimuli in areas distant from their excitatory receptive fields.[13–15] In animal and human studies, it is reported that serotonergic[3] and adrenergic neurons[17,35] are involved in the manifestation of CPM. If CPM reflects specific neurobiological mechanisms underlying endogenous pain modulation, it may be used for evaluation of such mechanisms[22] and possible stratification of patients.

Conditioned pain modulation is generally reduced in patients with chronic pain,[16,28] although they may also have a normal CPM, suggesting that mapping CPM distribution is important to explore the nature of specific groups of patients.[1,28] Hence, such stratification may be important in clinical trials and as this study suggests, for counseling patients.

Table 3

Conditioned pain modulation (CPM) effects and pain catastrophizing scale (PCS).

	Nonresponders (n = 7)	Responders (n = 36)	Total (n = 43)
CPM effects (%)	4.9 [4.5 to 8.7]	−16.3 [−26.1 to −8.5]	−13.1 [−23.3 to −5.5]
PCS-T	28.0 [23.0 to 35.5]	20.5 [14.5 to 29.5]	21.0 [15.5 to 31.5]
PCS-R	16.0 [14.0 to 16.5]	11.0 [9.8 to 15.0]	12.0 [10.0 to 16.0]
PCS-H	7.0 [5.0 to 11.0]	5.5 [2.0 to 10.0]	6.0 [2.5 to 10.0]
PCS-M	6.0 [3.5 to 8.5]	3.0 [1.0 to 5.0]	4.0 [1.0 to 6.0]

Values are presented as medians [interquartile ranges]; nonresponders: CPM effect ≧ 0 (%); responders: CPM effect <0 (%).
PCS-H, pain catastrophizing scale-helplessness; PCS-M, pain catastrophizing scale-magnification; PCS-R, pain catastrophizing scale-rumination; PCS-T, pain catastrophizing scale-total.

Table 4

Analgesic requirement period, days with pain, and visual analogue scale area under the curve (VASAUC).

	Nonresponders (n = 7)	Responders (n = 36)	Total (n = 43)
Analgesic requirement period (d)	8.3 [7.6–9.2]	7.2 [5.7–8.3]	7.3 [5.8–8.7]
Days with pain (d)	12.5 [7.3–12.9]	9.4 [5.9–13.7]	9.6 [5.9–13.3]
VASAUC (mm × d)	243.4 [136.9–279.0]	184.7 [112.3–288.7]	188.0 [107.1–285.7]

Values are presented as medians [interquartile ranges]; nonresponders: CPM effect ≧ 0 (%); responders: CPM effect <0 (%). Days with pain: The following denotes the duration for postoperative pain to reach 0/100 on the VAS. CPM, conditioned pain modulation.

At this stage, it is difficult to compare data across studies because various methodologies for the test stimulus and conditioning stimulus were used[27,33]; thus, developing a gold standard easy-to-use bedside test is important and under development.[1,24–26] The literature shows that the approximate median magnitude of the CPM effect is −25% (ranging from −100% to −3%) (converted values with the definition in Ref. 47).[33] Our previous study showed that PPT was the most reliable method to test CPM[23] among the 13 quantitative sensory testing parameters evaluated.[34] Therefore, the PPT was applied as the test stimulus in this study.

Cold pressor stimulation where the hand is immersed in cold water induced the strongest CPM effect compared with ischemic and mechanical stimuli.[27] Although cold-water immersion of the hand is recommended as conditioning stimulation,[47] preparation of cold water is bothersome in the clinical setting. In addition, the influence of expectation, prediction, and attention for visible input[6] and habituation[49] during cold-water immersion cannot be ruled out. However, expectation and prediction could be eliminated using the probe with the Peltier element because of no visible input for the stimulus modality. Moreover, habituation to the stimulation could be decreased by cold–heat pulse stimulation compared with continuous cold stimulation. In addition, patients were instructed to focus on their PPT to ensure a constant attention level throughout the experiment. Furthermore, there are no reports on inducing the CPM effect with conditioning cold–heat pulse stimulation. Therefore, we developed a new device as a simple bedside tool[24–26] to evaluate the CPM effect with conditioning cold–heat pulse stimulation.[24,25] The cold–heat pulse stimulation consists of 20-second cold and 20-second heat pulse wave (phasic). However, the subjects experience continuous pain during the application of cold–heat pulse stimulation[26]; thus, it can be considered tonic painful pulse stimulation.[26] Although it was demonstrated that the cold–heat pulse stimulation triggered paradoxical sensation,[26] the CPM effect through conditioning cold–heat pulse stimulation was −19.4% (converted value with the definition in Ref. 47) in healthy volunteers[24,25] without a large difference, considering the CPM effect of −25% (ranging from −100% to −3%) (converted values with the definition in Ref. 47) in the above-mentioned literature reviews.[33]

The CPM effect is intensity-dependent.[29] As the conditioning cold–heat pulse stimulation is a new method, cold and heat pain intensity was set at 70/100 on VAS in this study for a strong induction of CPM. However, stimulus-mediated injury can occur.[21] Redness was observed over 48°C in our preliminary data with healthy subjects.[25] Thermal injury should be avoided. Therefore, the cutoff temperature for cold and heat pain was set

Table 5

Multiple linear regression model of factors that explain the analgesic requirement period, days with pain, and visual analogue scale area under the curve (VASAUC) in all patients.

Dependent variable	Predictor	B (estimate)	95% CI	*P*	Adjusted R^2
Analgesic requirement period	CPM	−0.05	−0.10 to −0.01	0.02*	0.1657
	PCS-T	0.06	−0.01 to 0.13	0.09	
	CPM	−0.06	−0.10 to −0.01	0.01*	0.1151
	PCS-R	0.06	−0.1 to 0.21	0.46	
	CPM	−0.06	−0.10 to −0.01	0.01*	0.1697
	PCS-H	0.15	−0.02 to 0.32	0.08	
	CPM	−0.04	−0.09 to −0.001	0.04*	0.2299
	PCS-M	0.31	0.07 to 0.55	0.01*	
Days with pain	CPM	−0.08	−0.16 to 0.004	0.06	0.1234
	PCS-T	0.11	−0.01 to 0.24	0.08	
	CPM	−0.08	−0.16 to 0.001	0.05	0.0703
	PCS-R	0.13	−0.16 to 0.43	0.36	
	CPM	−0.08	−0.16 to −0.003	0.04*	0.1174
	PCS-H	0.27	−0.04 to 0.59	0.09	
	CPM	−0.06	−0.14 to 0.02	0.14	0.1939
	PCS-M	0.60	0.14 to 1.05	0.01*	
Log (VASAUC)	CPM	−0.01	−0.03 to −0.004	0.01*	0.2937
	PCS-T	0.03	0.01 to 0.04	0.003*	
	CPM	−0.02	−0.03 to −0.004	0.01*	0.2069
	PCS-R	0.04	0.003 to 0.09	0.04*	
	CPM	−0.02	−0.03 to −0.005	0.005*	0.2926
	PCS-H	0.07	0.02 to 0.11	0.003*	
	CPM	−0.01	−0.02 to −0.001	0.04*	0.3015
	PCS-M	0.10	0.04 to 0.17	0.002*	

N = 43, *$P < 0.05$. Multiple linear regression with B representing regression coefficients with 95% CI. Days with pain: The following denotes the duration for postoperative pain to reach 0/100 on the VAS.
CI, confidence interval; CPM, conditioned pain moderation; PCS-H, pain catastrophizing scale-helplessness; PCS-M, pain catastrophizing scale-magnification; PCS-R, pain catastrophizing scale-rumination; PCS-T, pain catastrophizing scale-total.

Table 6

Multiple linear regression model of factors that explain the analgesic requirement period, days with pain, and visual analogue scale area under the curve (VASAUC) in responders.

Dependent variable	Predictor	B (estimate)	95% CI	P	Adjusted R^2
Analgesic requirement period	CPM	−0.07	−0.13 to −0.02	0.01*	0.1658
	PCS-T	0.06	−0.02 to 0.14	0.14	
	CPM	−0.07	−0.13 to −0.01	0.02*	0.1157
	PCS-R	0.05	−0.13 to 0.23	0.61	
	CPM	−0.07	−0.13 to −0.02	0.01*	0.1757
	PCS-H	0.16	−0.04 to 0.35	0.11	
	CPM	−0.06	−0.11 to −0.01	0.03*	0.2444
	PCS-M	0.34	0.06 to 0.63	0.02*	
Days with pain	CPM	−0.12	−0.21 to −0.02	0.02*	0.158
	PCS-T	0.12	−0.02 to 0.26	0.09	
	CPM	−0.12	−0.22 to −0.02	0.03*	0.1041
	PCS-R	0.14	−0.17 to 0.46	0.37	
	CPM	−0.12	−0.22 to −0.02	0.02*	0.1569
	PCS-H	0.29	−0.05 to 0.64	0.10	
	CPM	−0.10	−0.19 to −0.001	0.047*	0.2211
	PCS-M	0.61	0.1 to 1.12	0.02	
Log (VASAUC)	CPM	−0.02	−0.04 to −0.01	0.0003*	0.4466
	PCS-T	0.03	0.02 to 0.05	0.0006*	
	CPM	−0.03	−0.04 to −0.01	0.001*	0.2079
	PCS-R	0.05	0.01 to 0.10	0.02*	
	CPM	−0.03	−0.04 to −0.01	0.0002*	0.4512
	PCS-H	0.08	0.04 to 0.13	0.0005*	
	CPM	−0.02	−0.03 to −0.01	0.002*	0.4578
	PCS-M	0.13	0.06 to 0.20	0.0004*	

N = 36, *$P < 0.05$. Multiple linear regression with B representing regression coefficients with 95% CI. Days with pain: The following denotes the duration for postoperative pain to reach 0/100 on the VAS.
CI, confidence interval; CPM, conditioned pain moderation; PCS-H, pain catastrophizing scale-helplessness; PCS-M, pain catastrophizing scale-magnification; PCS-R, pain catastrophizing scale-rumination; PCS-T, pain catastrophizing scale-total.

at −10°C and 47°C, respectively, to avoid inducing thermal injury, although the highest temperature for heat stimulus (47°C) could not induce a pain intensity of 70/100 on a VAS.

Shortening the experimental time is beneficial for performing the experiment with patients. In addition, to avoid habituation to the thermal stimulus, a shorter duration for thermal stimulus is preferable. Therefore, to shorten the total measurement time with different ramp times, subjective assessment of cold and heat pain thresholds was performed first. It was possible to change the ramp time (2°C/second until the patient felt pain and 0.5°C/second thereafter) to detect the temperature strictly and carefully, which resulted in a pain intensity of 70/100 on a VAS.

The limitations of the current study include (1) the contralateral segmental effect caused by the application of test stimulus to the dominant forearm and conditioning stimulus to the nondominant forearm cannot be ruled out as in other previous studies,[47] (2) if the pain intensity of the conditioning heat stimulation did not reach the pain intensity of 70/100 on VAS, it might affect the magnitude of CPM; continuous stimulation might be better to induce more intense pain compared with pulse stimulation, and 3) although the conditioning cold–heat pulse stimulation[24–26] triggers CPM effect,[24,25] the possibility that paradoxical sensation might affect the CPM effect needs to be tested in future studies.

4.3. Pain catastrophizing scale evaluation

In this study, the preoperative PCS could predict acute POP after orthognathic surgery. In particular, PCS-magnification showed the strongest correlation with POP. However, PCS-total, PCS-rumination, and PCS-helplessness are also useful for predicting POP.

The pain catastrophizing scale[19,40,41] represents a cognitive aspect of pain,[19] and its different components, individual interactions, and how catastrophizing can be modeled have recently been reviewed.[32] Catastrophizing is associated with heightened pain intensity in clinical and experimental studies[42] and is a better predictor of disability than disease-related variables or pain.[42] Furthermore, catastrophizing is associated with increased pain behavior, increased use of health care services, longer durations of hospital stay, and increased use of analgesic medication after surgery.[42] Granot and Ferber[7] reported that POP intensity could be predicted by levels of preoperative anxiety and catastrophizing. Another study showed that PCS was a significant predictor of acute POP in the postanesthetic care unit; however, PCS did not predict postoperative analgesic consumption.[30] A meta-analysis suggested that PCS is more strongly linked to acute POP than other psychological factors, such as anxiety (state and trait).[37] Similarly, for chronic POP, a meta-analysis revealed that preoperative catastrophizing and anxiety play important roles in the development of chronic POP,[43] eg, in spine surgery,[44] total knee replacement,[4] and cardiac surgery.[12]

5. Conclusions

Acute POP after orthognathic surgery can be predicted through preoperative evaluation of CPM and PCS.

Disclosures

The authors have no conflicts of interest to declare.

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