Long-lasting Mechanical Sensitization Following Third Molar Surgery

Gitte Irene Juhl, MD
PhD Student
Department of Neurology and Danish Pain Research Center
Aarhus University Hospital
Aarhus, Denmark

Peter Svensson, DDS, PhD
Professor
Department of Clinical Oral Physiology
Royal Dental College
University of Aarhus
Aarhus, Denmark

Consultant
Department of Oral and Maxillofacial Surgery
Aarhus University Hospital
Aarhus, Denmark

Sven Erik Norholt
Senior Consultant
Department of Oral and Maxillofacial Surgery
Aarhus University Hospital
Aarhus, Denmark

Troels Staehelin Jensen, MD, Dr Med Sci
Professor
Department of Neurology and Danish Pain Research Center
Aarhus University Hospital
Aarhus, Denmark

Correspondence to:
Dr Gitte Juhl
Danish Pain Research Center
Aarhus University Hospital
Norrebrogade 44
DK- 8000 Aarhus C
Denmark
Fax: +45 8949 3269
E-mail: gij@dadlnet.dk

Aims: *To investigate the degree and duration of neuronal hyperexcitability due to local inflammatory trauma after surgical removal of an impacted mandibular third molar.* ***Methods:*** *A total of 32 healthy men (16 patients, 16 control subjects) underwent quantitative sensory tests (QST) at baseline (preoperatively) and 2, 7, and 30 days following surgical removal of a mandibular third molar. Thermal and mechanical QST was applied to the extraoral and intraoral regions as well as to the dominant forearm.* ***Results:*** *Detection thresholds for thermal and mechanical stimuli did not change over time in patients and control subjects, but pain thresholds (thermal, pressure, electrical) in the control group increased significantly. Patients showed significantly decreased pain pressure thresholds and pressure pain tolerance ($P < .05$ for both) on the operated side and absence of adaptation to the tests for up to 30 days postoperatively.* ***Conclusion:*** *These results indicate that even a minor surgical procedure in the orofacial region may be sufficient to evoke hyperexcitability in an area adjacent to the surgical wound for up to 30 days. The decreased adaptive capacity in the patient group also suggests the involvement of central pain-regulatory mechanisms in response to the surgical trauma.* J OROFAC PAIN 2006;20:59–73

Key words: orofacial, pressure pain, sensitization, third molar

Surgical procedures, even minor ones, carry a risk of chronic pain.[1–4] Neuronal hyperexcitability, peripherally or centrally, has been suggested to be an important factor for the "chronification" of pain.[5–12] Peripheral sensitization after tissue damage is characterized by a changed membrane excitability of the nociceptor in which several mediators, such as potassium ions, hydrogen ions, bradykinin, serotonin, prostaglandins, noradrenaline, neurotrophins, adenosine, and various cytokines are involved.[7,13,14] Central sensitization is the consequence of a cascade of events in the spinal cord or brainstem. Characteristics of the central sensitization are a reduction of the threshold needed to depolarize the neuron, a cellular activity that lasts beyond the activity of the peripheral nociceptor, and a spread of cellular activity to neighboring neurons.[7–12]

Quantitative sensory tests (QST) measure the existence of changed sensitivity in different nerve fibers, illustrated by altered psychophysical thresholds. Thus, QST may be used to assess the clinical correlates of neuronal hyperexcitability peripherally and centrally in experimental as well as clinical pain conditions.[15–22]

Dental injury models, including third molar surgery, are useful in the study of acute pain and the neuronal changes that follow injury.[23] Recently, Huang et al[24] found that surgical removal of third molars represents a significant risk factor for persistent orofacial pain. Presence of neuronal hyperexcitability after a period of acute orofacial pain, including pain after dental surgery, has been studied previously. Hansson et al[25] found increased reaction time to warm stimuli in the painful area 5 to 18 hours after elective surgical removal of an impacted third molar. Eliav and Gracely[26] found decreased detection thresholds to electrical and mechanical intraoral stimulation and reduced pain thresholds to electrical stimulation 2 days after the extraction of a third molar. Ekblom and Hansson,[27] on the other hand, found no change in thermal thresholds in patients with dental disease.

None of these studies have looked at long-term sensation after injury (eg, dental surgery). Since acute pain may be a risk factor for chronic pain, it was decided to study whether and for how long acute pain may influence the existence and development of neuronal hyperexcitability. QST was used to study sensation in the oral and extraoral regions preoperatively and up to 30 days after surgical removal of the mandibular third molar. The aim of the study was to determine whether local inflammatory trauma due to an oral surgical procedure could cause hyperexcitability by applying a battery of intra- and extraoral QST up to 30 days after the operation. Part of the present study has been presented in abstract form.[28]

Materials and Methods

Subjects

The study was conducted according to good clinical practice (GCP) and the Helsinki Declaration and after the approval of the ethics committee (file no. 20020195) of Aarhus County, Denmark and the Danish Data Protection Agency (file no. 2002-44-2182). Before signing the informed consent, all subjects were informed of all study procedures by the investigator.

Sixteen men (mean age, 25 ± 3 years; range, 21 to 29 years) scheduled for elective removal of an impacted mandibular third molar (patients) and 16 age-matched male subjects (mean age, 24 ± 2 years; range, 21 to 30 years) not scheduled for any dental procedure during the study period (controls) participated in the study. All subjects were healthy according to a general physical and oral examination. Oral surgery (standardized surgical technique with elevation of a buccal mucoperiosteal flap, removal of bone distally and buccally, and, if necessary, splitting of the tooth) was performed under local anesthesia (3% Citanest-Octapressin, Astra) without any sedatives before, during, or after surgery by a single experienced oral surgeon (SEN). Acetaminophen/paracetamol (0.5 g Panodil, GlaxoSmithKline) administered orally a maximum of 8 times daily for 1 week was used for postoperative pain control. If additional pain treatment or antibiotics were needed, they were provided by dentists on a 24-hour emergency call.

Experimental Design

QST was performed preoperatively (baseline) and on days 2, 7, and 30 postoperatively. The control group underwent the same tests according to the same time schedule as the patient group. QST was performed to determine the warm, cold, tactile, and electrical detection thresholds (WDT, CDT, TDT, and EDT); the heat, cold, electrical, and pressure pain thresholds (HPT, CPT, EPT, and PPT); and the pressure pain tolerance threshold (PPTT). All intraoral examinations were carried out on the buccal gingiva around the mandibular first molar (supplied by the inferior alveolar nerve). Extraoral examinations were performed on the skin of the lower lip at the termination of the inferior alveolar nerve (its mental nerve branch) and on the volar side of the dominant forearm. Pressure pain and pressure pain tolerance outside the trigeminal-innervated region was performed on the dorsal side of the dominant hand (between the first and second fingers). These extra-trigeminal tests were used as a control. All orofacial QST tests were performed bilaterally. In the patient group the contralateral side was always investigated first, followed by the operated side. In the control group 8 subjects were assigned to have the right side investigated first followed by investigation of the left side; 8 subjects were assigned to have the left side investigated first followed by investigation of the right side. The order of investigation for each subject was kept throughout the study. The same investigator (GIJ) carried out all tests.

QST

Thermal Sensitivity. Testing for WDT, HPT, CDT, and CPT on the face was performed with a 5 × 5-mm water-cooled Peltier probe (Medoc TSA). For thresholds on the hand, a 30 × 30-mm probe was

used. According to a computerized paradigm, the thermal stimulus was increased 1°C/s (baseline, 32°C; maximum, 50.5°C) or decreased 1°C/s (baseline, 32°C; minimum, 8°C for intraoral or extraoral measurements and 0°C for measurement at the forearm) until a sensation of warmth or cold was detected (detection threshold) or pain was experienced (pain threshold). The subjects pushed a stop button when the thresholds were reached. This was repeated 3 times at random intervals (4 to 10 s). The mean value of the 3 determinations was used for further statistical analysis.

Mechanical Sensitivity. A calibrated set of von Frey hair filaments was used to measure TDT at the buccal gingiva around the mandibular first molar and extraorally at the skin of the lower lip and on the hand.[29] The filaments were applied in ascending order to the subject while his eyes were closed. The threshold was defined as the filament that the subject consistently felt (2 out of 3 applications).

PPT and PPTT were also assessed at these intraoral and extraoral sites.[29] At the face the pressure algometer (Somedic) was equipped with a probe 0.5 cm in diameter, and at the hand the Somedic algometer was equipped with a 1-cm-diameter probe.[30] The probes were applied perpendicular to the surface, and a constant pressure (30 kPa/s) was exerted. PPT was defined as the amount of pressure the subject first felt as painful and PPTT as the maximum amount of pressure that the subject could accept. The subjects pushed a stop button whenever the thresholds were reached, at which point the value of the threshold was recorded and displayed. PPT was determined as the mean value of 3 measurements, whereas PPTT was measured only once to avoid longer-lasting changes in sensitivity.

Electrical Sensitivity. The electrical stimulation was delivered to the intraoral and extraoral sites by a constant current device (Aalborg University, Denmark) using a circular anode and cathode probe (0.3/0.7 mm). Each stimulus lasted 0.5 ms.[31] At least 3 series of increasing and decreasing intensities in step of 0.05 to 0.1 mA were used to determine the EDT and EPT in a staircase paradigm.

Assessment of Postoperative Pain

The patients assessed the postoperative pain on a numerical rating scale (NRS),[32] and filled in a diary 3 times daily for 1 week. If pain persisted for a longer period, the patients reported this condition to the investigator. The control subjects reported any presence of pain during the investigation to the investigator.

Statistics

An unpaired *t* test was used for comparison of age between the 2 groups. The baseline data from the orofacial region were compared using 2-way analysis of variance (ANOVA) with the factors group (control/patient) and side (right/left or left/right and contralateral/operated side). The baseline measurements data from the forearm in the 2 groups were compared using the *t* test or Mann-Whitney test. Separate 2-way ANOVAs for the 2 groups were used to test for time effects (baseline, 2, 7, 30 days) and for side-to-side effects (patient group: contralateral side/operated side; control group: right side/left side or left side/right side). Separate 1-way ANOVAs for the 2 groups were used to test for time effects at the forearm (baseline, 2, 7, 30 days). Missing data were not replaced. Student-Newmann-Keuls (SNK) method was used for post-hoc analysis. $P < .05$ was used as the level of significance. Data are presented as mean values ± SEM.

Results

Six of the impacted third molars were located on the right side; 10 were located on the left side. Fifteen of the third molars were in a semi-impacted position (7 of these with a mildly inflamed gingiva).

The duration of the surgical procedure was 12 ± 5 minutes (range, 5 to 29 minutes) and the volume of local anesthetic used was 3.7 ± 0.5 mL (range, 3.6 to 5.4 mL). Seven patients had a maxillary third molar removed as well.

No serious adverse events occurred and no paresthesias were reported during or after the study. During the first postoperative week the following adverse events occurred: long-lasting bleeding (bleeding that existed more than 1 day after the operation) in 4 patients, headache in 3 patients, and extensive edema (lasting 1 week) in 1 patient. Postoperative pain was most intense at the day of surgery except in 1 patient (Fig 1). This patient had prolonged postoperative pain due to extensive edema and experienced neuralgia (shooting unbearable pain) in the trigeminal area on the operated side 1 week postoperatively. Postoperative acetaminophen/paracetamol consumption reflected the pain intensities (NRS scores) experienced in the first postoperative week (Fig 1). No adverse events were reported in the control group, and no dropouts occurred.

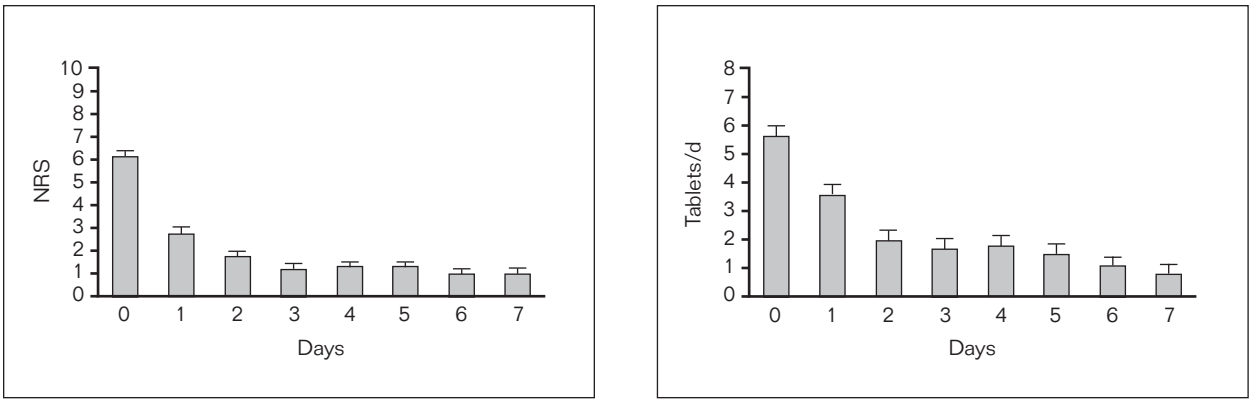

Fig 1 Postoperative pain intensity (mean NRS values) and postoperative pain treatment with acetaminophen/paracetamol (mean values for daily intake of tablets) in the patient group are shown for the day of the operation and the first postoperative week.

Quantitative Sensory Tests

Thermal Sensitivity. At baseline, no significant differences between groups or sides could be detected for intraoral or extraoral CDT (ANOVAs; $F < 0.31$, $P > .58$), WDT (ANOVAs; $F < 3.34$, $P > .07$), CPT (ANOVAs; $F < 2.44$, $P > .12$), and HPT (ANOVAs; $F < 2.77$, $P > .10$). At baseline no significant differences between groups could be detected for forearm CDT (*t* test; $P = .562$), WDT (*t* test; $P = .421$), HPT (*t* test; $P = .424$), or CPT (Mann-Whitney; $P = .050$).

CDT. In the patient group, there was a significant time effect with an increased intraoral CDT at postoperative day 2 compared to days 7 and 30, but not compared to baseline. There were no significant side-to-side effects or interactions between time and side for the intraoral CDT.

In the control group, there were no significant time or side-to-side effects or significant interactions between time and side for the intraoral CDT.

In neither group did time effects or side-to-side effects or significant interactions between time and side influence the extraoral CDT values. CDT at the forearm was not influenced by time effects in the patient or control groups. Table 1 shows the outcome of 1-and 2-way ANOVAs for CDT. Figure 2 shows the absolute values for CDT in the control and patient groups.

WDT. In neither group were any significant time or side-to-side effects observed for intraoral and extraoral WDT. In the patient group there was a significant interaction between time and side for the extraoral WDT on the contralateral side, with a decrease in extraoral WDT at day 30 compared to baseline values.

WDT at the forearm did not demonstrate any significant time effects for the patient or the control groups.

Table 1 shows the outcome of 1- and 2-way ANOVA results for WDT. Figure 3 shows the absolute values for WDT in the control and patient groups.

CPT. The intraoral CPT showed significant time effects in both groups. In the control group intraoral CPT was decreased at days 2, 7, and 30 compared to baseline values, whereas in the patient group intraoral CPT was decreased at day 30 compared to baseline values.

The intraoral CPT showed a significant side-to-side effect and a significant interaction between time and side in the control group; post-hoc analysis demonstrated a significant decrease in intraoral CPT at the left side at days 2, 7, and 30 compared to baseline values. The intraoral CPT in the patient group was not influenced by side effect or significant interaction between time and side.

The extraoral CPT in the control group showed significant time effects with a decrease of extraoral CPT at days 2, 7, and 30 compared to baseline values, without any significant side-to-side effects or interactions between time and side. Extraoral CPTs in the patient group were not influenced by significant interactions between time and side. CPT at the forearm was not influenced by time effects in the patient or control groups. Table 1 shows the outcomes of 1- and 2-way ANOVAs for CPT. Figure 2 shows the absolute values for CPT in the control and patient groups.

HPT. In the control group, no significant time or side-to-side effects were observed in intaoral HPT. However, there was a significant interaction

Table 1 Outcome of 1- and 2-way ANOVA Results for Thermal Sensitivity Tests

	Patients						Controls					
	Time		Side		Time × side		Time		Side		Time × side	
	F	*P*	F	*P*	F	*P*	F	*P*	F	*P*	F	*P*
CDT												
Intraoral	2.94	.044*	0.68	.43	1.32	.28	0.29	.83	0.25	.62	0.12	.95
Extraoral	0.90	.45	0.79	.39	0.66	.58	2.00	.13	0.008	.93	0.03	.99
Forearm(a)	0.99	.95	NA		NA		1.57	.21	NA		NA	
WDT												
Intraoral	1.31	.28	0.05	.82	0.16	.93	1.21	.32	1.13	.31	1.05	.38
Extraoral	1.20	.32	0.003	.96	5.27	.004*	1.47	.24	2.71	.12	0.09	.97
Forearm(a)	0.19	.90	NA		NA		0.09	.97	NA		NA	
CPT												
Intraoral	3.50	.024*	0.001	.99	1.56	.21	5.60	.002*	5.50	.033*	3.74	.017*
Extraoral	2.14	.11	1.36	.26	0.06	.98	4.72	.006*	1.54	.23	1.04	.38
Forearm(a)	0.17	.92	NA		NA		1.12	.32	NA		NA	
HPT												
Intraoral	0.75	.53	2.78	.12	1.55	.22	2.11	.11	0.29	.60	3.85	.016*
Extraoral	0.08	.97	3.02	.10	1.56	.22	8.04	< .001*	0.06	.812	1.24	.31
Forearm(a)	1.12	.35	NA		NA		6.94	< .001*	NA		NA	

(a) indicates 1-way ANOVAs. NA = not applicable.
* P < .05.

between time and side with increases in HPT on the left side at days 2, 7, and 30 compared to baseline values. In the patient group, there were no significant time effects, side-to-side effects, or interactions between time and side.

Significant time effects were observed for extraoral HPT in the control group, with increases in extraoral HPT at days 2, 7, and 30 compared to baseline values. There were no significant time effects in the patient group; there were no significant side-to-side effects in either group. There were no significant interactions between time and side in either group. At the forearm, time effects in the patient group did not influence HPT. In the control group, HPT increased significantly at days 2, 7, and 30 compared to baseline values. Table 1 shows the outcome of 1- and 2-way ANOVA results for HPT. Figure 3 shows the absolute values for HPT in the control and patient groups.

Mechanical Sensitivity. At baseline, no significant differences between the group and side could be detected for intraoral or extraoral TDT (ANOVAs; $F < 1.87$, $P > .178$), intraoral PPT (ANOVAs; $F < 2.58$, $P > .11$), extraoral PPT (ANOVAs; $F < 0.42$, $P > .52$), intraoral PPTT (ANOVAs; $F < 1.07$, $P > .30$), or extraoral PPTT (ANOVAs; $F < 1.43$, $P > .23$). On the forearm, no significant differences between the 2 groups could be detected at baseline for TDT (*t* test; $P = .799$), PPT (*t* test; $P = .081$) or PPTT (*t* test; $P = .068$).

TDT. There were no time effects, side-to-side effects, or significant interactions between time and side for the intraoral or extraoral TDT values in either group. At the forearm, time effects did not influence TDT in either group (Table 2). Absolute values for TDT were not illustrated.

PPT. In the control group, intraoral PPT showed significant time effects, with an increase in PPT at days 2, 7, and 30 compared to baseline values. There were no significant side-to-side effects or interactions between time and side.

In the patient group, the intraoral PPT showed significant time effects, with only an increase in intraoral PPT at postoperative day 30 compared to baseline values. But more importantly, intraoral PPT showed significant side-to-side effect, with a decrease in intraoral PPT on the operated side compared to the contralateral side at days 7 and 30. Furthermore, a significant interaction between time and side was demonstrated, with a decrease in intraoral PPT on the operated side at days 2 and 7 compared to baseline values, whereas intraoral PPT increased on the contralateral side at days 7 and 30 compared to baseline values.

Extraoral PPT showed significant time effects in both groups. In the control group, extraoral PPT increased at days 2, 7, and 30 compared to baseline values, whereas in the patient group the extraoral PPT increased at days 7 and 30 compared to baseline values. No significant side effects or interactions between time and side were demonstrated in either group.

At the forearm, PPT was increased significantly at days 2, 7, and 30 in the control group, but PPT

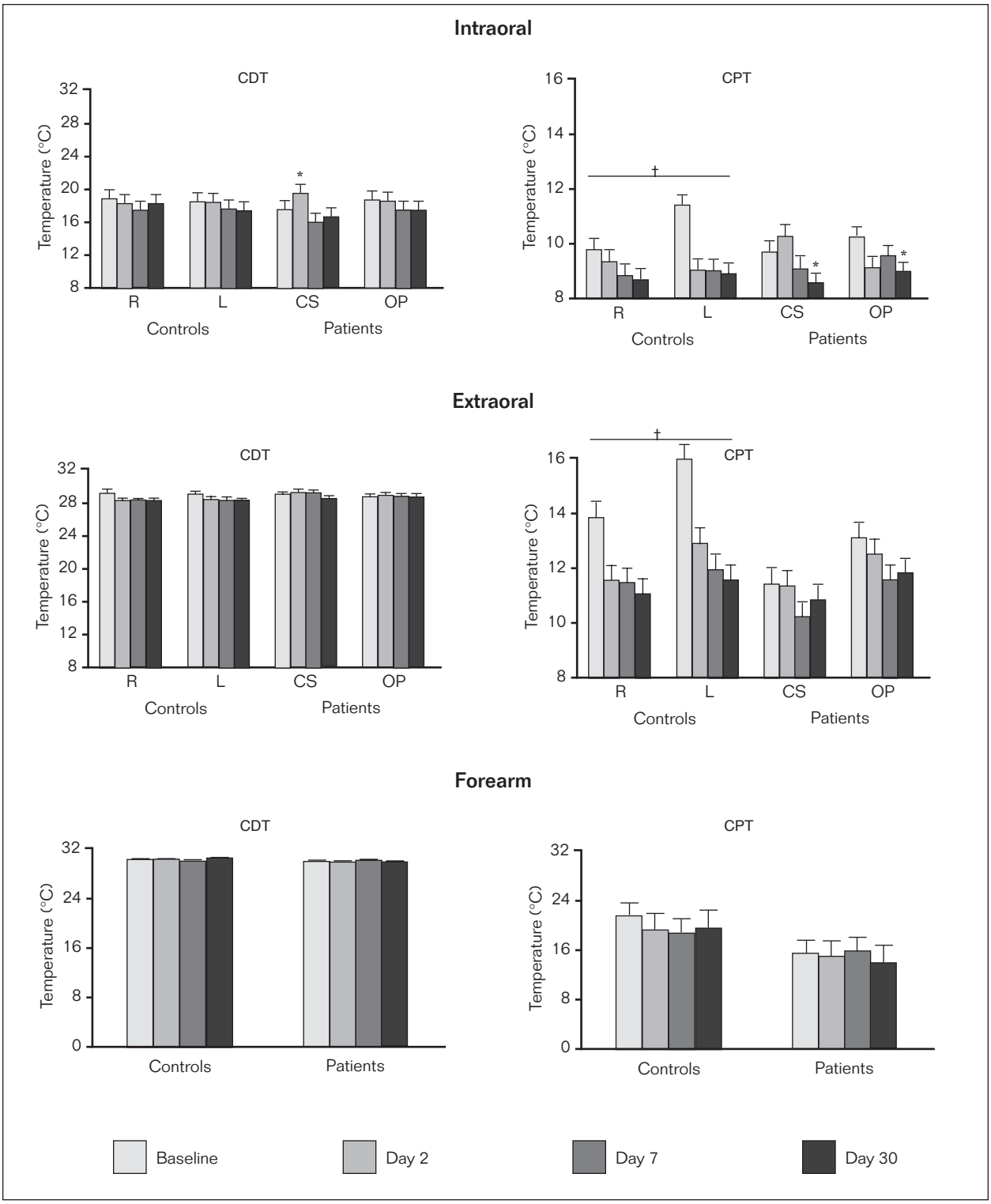

Fig 2 CDT and CPT intraorally, extraorally, and at the forearm for both groups are shown. The measurements are shown in sequential order at baseline and at postoperative days 2, 7, and 30. CS = contralateral side, OP = operated side, R = right, and L = left. *Indicates significant time effect (SNK; $P < .05$) compared to days 7 and 30. † Indicates significant time effect (SNK; $P < .05$) compared to baseline.

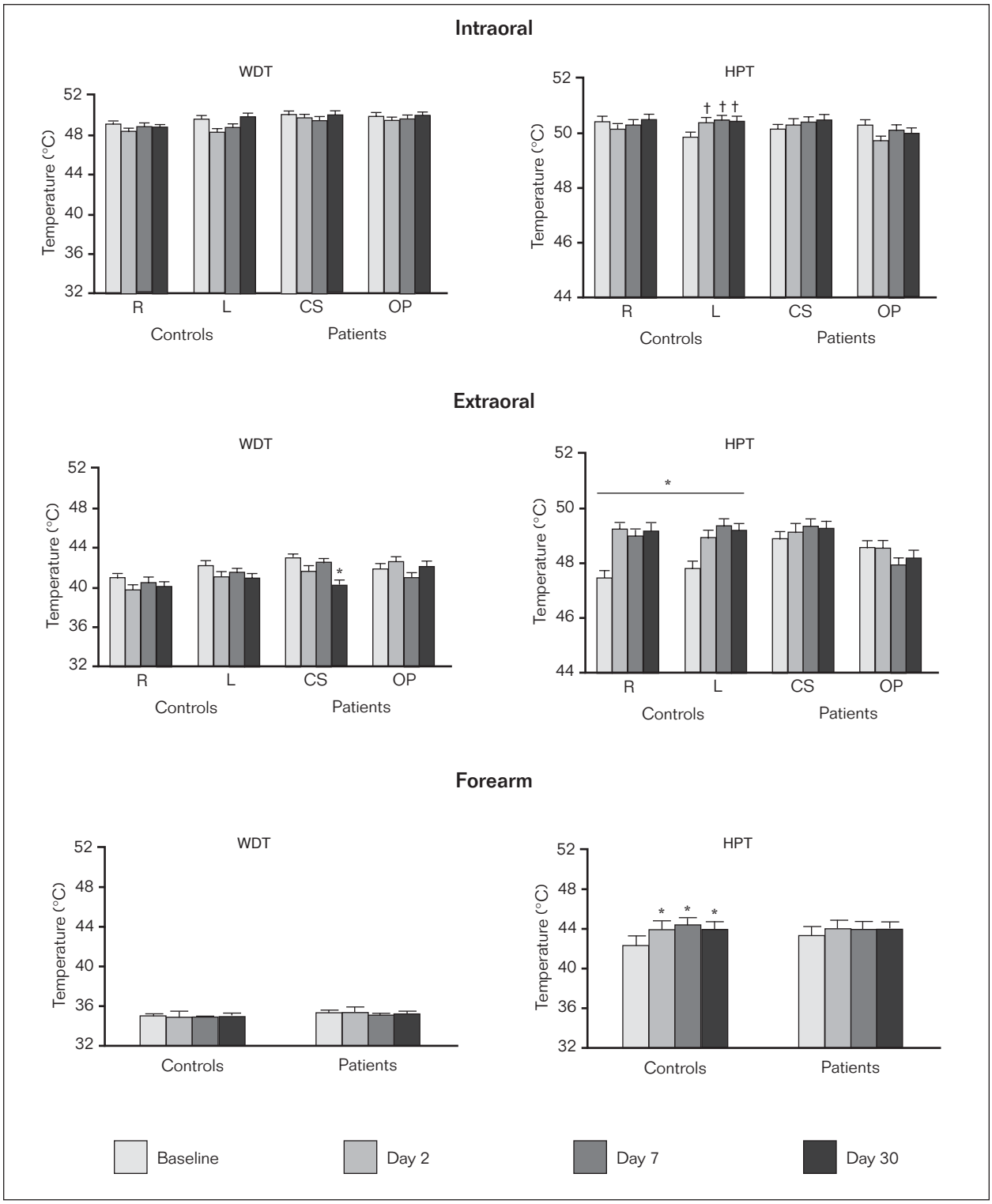

Fig 3 WDT and HPT intraorally, extraorally, and at the forearm for both groups are shown. The measurements are shown in sequential order at baseline and at postoperative days 2, 7, and 30. *Indicates significant time effect in the group (SNK; $P < .05$) compared to baseline. †Indicates significant time effect depending on side ($P < .05$ compared to baseline on the same side).

Table 2 Outcome of 1- and 2-way ANOVA Results for Mechanical Sensitivity Tests

	Patients						Controls					
	Time		Side		Time × side		Time		Side		Time × side	
	F	*P*	F	*P*	F	*P*	F	*P*	F	*P*	F	*P*
TDT												
Intraoral	1.08	.37	0.15	.71	0.83	.48	0.72	.55	0.08	.78	0.83	.40
Extraoral	1.00	.40	1.00	.33	1.00	.40	1.00	.40	1.00	.33	1.00	.40
Forearm(a)	0.80	.50	NA		NA		1.26	.30	NA		NA	
PPT												
Intraoral	8.79	< .001*	4.58	.003*	10.02	< .001*	7.71	< .001*	0.06	.81	0.88	.46
Extraoral	9.73	< .001*	2.45	.14	0.84	.48	10.99	< .001*	0.60	.45	1.64	.19
Forearm(a)	3.99	.014*	NA		NA		8.65	< .001*	NA		NA	
PPTT												
Intraoral	2.47	.08	10.60	.006*	9.74	< .001*	2.88	.046*	0.59	.45	0.78	.51
Extraoral	1.27	.30	8.00	.013*	0.21	.89	4.76	.006*	5.35	.04*	0.97	.42
Forearm(a)	1.78	.17	NA		NA		6.77	< .001*	NA		NA	

(a) indicates 1-way ANOVAs. NA = not applicable.
* $P < .05$.

was only significantly increased at day 30 in the patient group.

Table 2 shows the outcome of 1- and 2-way ANOVA results for PPT. Figure 4 shows the absolute values for PPT in the control and patient groups.

PPTT. In the control group, the intraoral PPTT showed significant time effects, with an increased PPTT at day 30 compared to baseline values. There were no significant side-to-side effects or interactions between time and side. In the patient group, the PPTT showed no significant time effect, but there was a significant side-to-side effect, with a decrease in intraoral PPTT on the operated side compared to the contralateral side at days 2, 7, and 30. Furthermore, a significant interaction between time and side was shown, with a decrease in intraoral PPTT on the operated side at days 2, 7, and 30 compared to baseline values.

In the control group, the extraoral PPTT showed significant time effects, with an increase in PPTT at days 7 and 30. Additionally there was a significant side-to-side effect at day 30, with a decreased PPTT on the left side compared to the right side. There was no significant interaction between time and side. In the patient group, the extraoral PPTT showed no significant time effect; however, there was a significant side-to-side effect at day 7, with a decrease in extraoral PPTT on the operated side compared to the contralateral side. There was no significant interaction between time and side.

At the forearm, PPTT was significantly increased at days 2, 7, and 30 in the control group, whereas PPTT in the patient group was without significant time effects.

Table 2 shows the outcome of 1- and 2-way ANOVA results for PPTT. Figure 4 shows the absolute values for PPTT in the control and patient groups.

Electrical Sensitivity. At baseline no significant differences between groups or sides could be detected for intraoral or extraoral EDT (ANOVAs; $F < 3.04$, $P > .08$) or EPT (ANOVAs; $F < 3.83$, $P > .055$). At baseline no significant differences between the 2 groups could be detected at the forearm for EDT (*t* test; $P = .589$) or EPT (*t* test; $P = .154$).

EDT. Intraoral EDT did not show any significant time effects in either group or side-to-side effects in the control group, whereas in the patient group, there was a significant side effect, with increased detection threshold on the operated side compared to the contralateral side at postoperative day 2. There were no significant interactions between time and side for intraoral EDT in either group. With respect to extraoral EDT, no significant time effects, side-to-side effects, or significant interactions between time and side were observed in either group.

In the patient group EDT at the forearm increased significantly at day 2 compared to day 30 but not compared to baseline values. There was no significant time effect for EDT at the forearm in the control group. Table 3 shows the outcome of 1- and 2-way ANOVA results for EDT. Figure 5 shows the absolute values for EDT in the control and patient groups.

EPT. Intraoral EPTs showed significant time effects, with an increase in EPT at days 7 and 30 compared to baseline in both groups. No significant side-to-side effects or interactions between time and side were observed in either group.

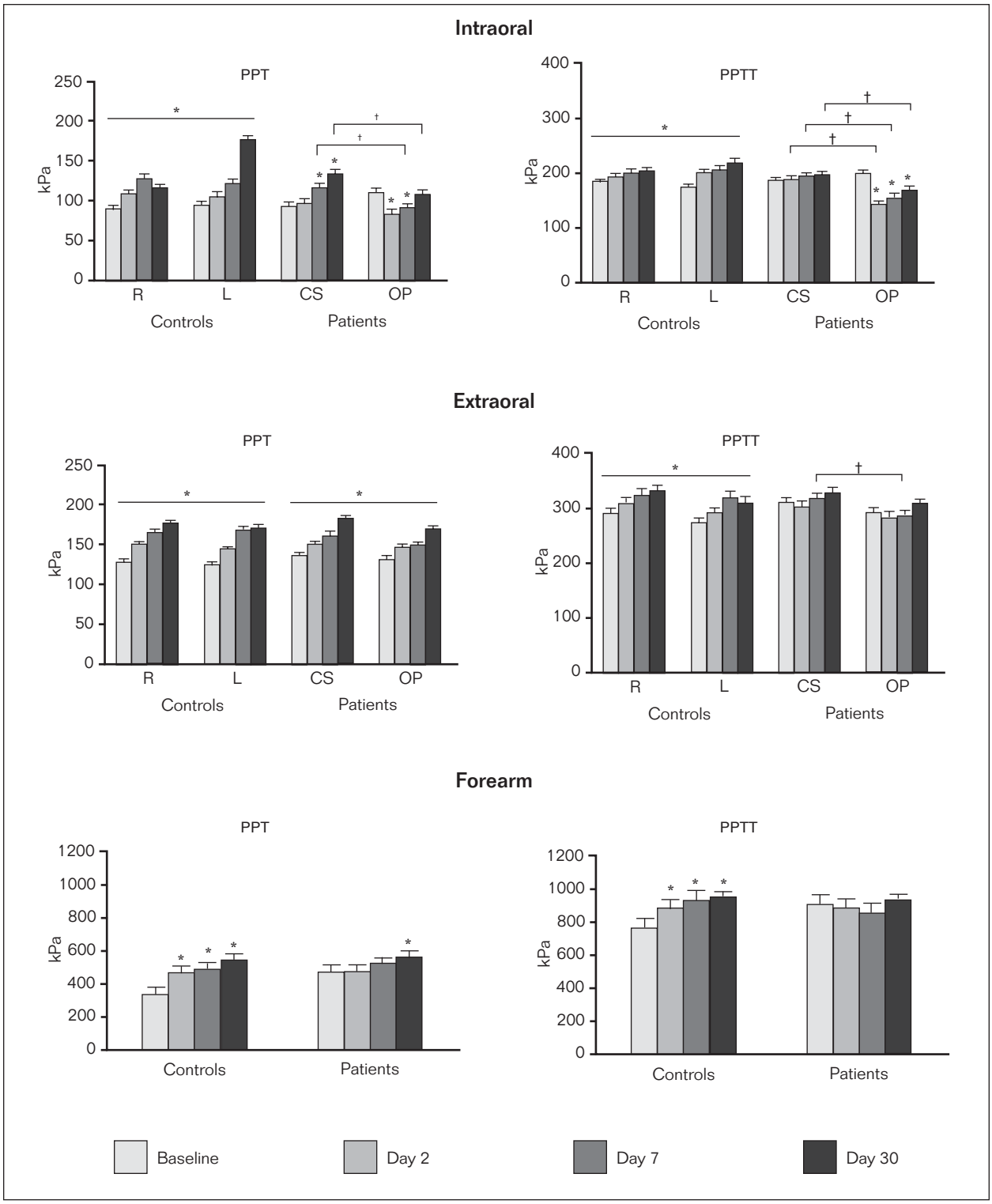

Fig 4 PPT and PPTT intraorally, extraorally, and at the forearm for both groups are shown. The measurements are shown in sequential order at baseline and at postoperative days 2, 7, and 30. *Indicates significant time effect in the group (SNK; $P < .05$) compared to baseline. †Indicates significant side effect in the group (SNK; $P < .05$) compared to opposite side at that time point.

Table 3 Outcome of 1- and 2-way ANOVA Results for Electrical Sensitivity Tests

	Patients						Controls					
	Time		Side		Time × side		Time		Side		Time × side	
	F	*P*	F	*P*	F	*P*	F	*P*	F	*P*	F	*P*
EDT												
Intraoral	1.07	.37	7.95	.014*	1.29	.29	0.48	.70	1.37	.26	0.57	.64
Extraoral	1.17	.34	2.28	.15	0.49	.69	2.32	.09	3.92	.07	1.42	.25
Forearm(a)	3.55	.022*	NA		NA		0.25	.86	NA		NA	
EPT												
Intraoral	4.14	.012*	4.24	.06	2.32	.09	6.67	< .001*	0.10	.79	0.35	.79
Extraoral	1.26	.30	0.05	.81	0.814	.49	4.14	.011*	0.96	.34	0.88	.46
Forearm(a)	2.42	.08	NA		NA		4.13	.011*	NA		NA	

(a) indicates 1-way ANOVAs. NA = not applicable.
* $P < .05$.

Extraoral EPT showed significant time effects in the control group, with increased EPT at days 2, 7, and 30 compared to baseline values. There were no significant side-to-side effects or significant interactions between time and side. In the patient group there were no significant time or side-to-side effects and no significant interactions between time and side.

At the forearm, EPT was significantly increased at day 30 in the control group; EPT in the patient group was without significant time effects.

Table 3 shows the outcome of 1- and 2-way ANOVA results for EPT. Figure 5 shows the absolute values for EPT in the control and patient groups.

Discussion

The main finding in this study of patients undergoing third molar surgery was a significant and long-lasting decrease in intraoral thresholds to mechanical pressure stimuli. In addition, during the 30-day observation period, the control subjects adapted to most tests, and higher pain thresholds resulted. In contrast, this adaptation to test stimuli was absent in the patient group. These findings suggest the presence of peripheral and central hyperexcitability after an injury, even in the absence of spontaneous pain.

Methodological Concerns

The thermal stimulator used for orofacial measurements in the present study was only capable of cooling down to 8°C, which in this setting resulted in a cutoff temperature that sometimes was reached before the subject reached his CPT intraorally. This is in accordance with the findings of Eliav and Gracely.[26] It is recommended for future studies investigating intraoral CPT that the equipment used be able to cool down to 0°C.

Extraoral detection and pain thresholds differed from intraoral thresholds for several modalities. The reason for this is not known, but such differences in thresholds may be due to biophysical differences, eg, in thickness of epithelial layer, conduction properties, or innervation densities.[33]

The tests were performed with the contralateral side stimulated first, followed by the operated side. This design was intended to avoid causing longer and more intense pain on the operated side that might potentially influence the subsequent measurements. This design might nonethless have led to a sequence effect in some of the tests. In some cases, the second measurement being higher than the first was probably due to adaptation as the subject became more familiar with the tests. This sequence effect needs to be considered in future studies.

The natural time course in control subjects over a period of 30 days has, as far as we know, not been described before. Our study demonstrated that the control group showed increased pain thresholds during the test period; such increases were not found in the patient group. These results may indicate that the control subjects adapted to the test, perhaps by becoming more familiar with the test and therefore less anxious. It may be speculated that loss of anxiety reduced descending facilitating pain-control mechanisms altering pain thresholds.[11] In contrast, adaptation was lacking for most of the test in the patients. This feature may be explained by a reduced ability, ie, suppressed adaptation to the test stimuli due to less effective activation of inhibitory mechanisms or enhanced facilitatory mechanisms of descending pain-control systems whenever the patient is stimulated. This issue will be further discussed in the paragraph on the extra-trigeminal findings.

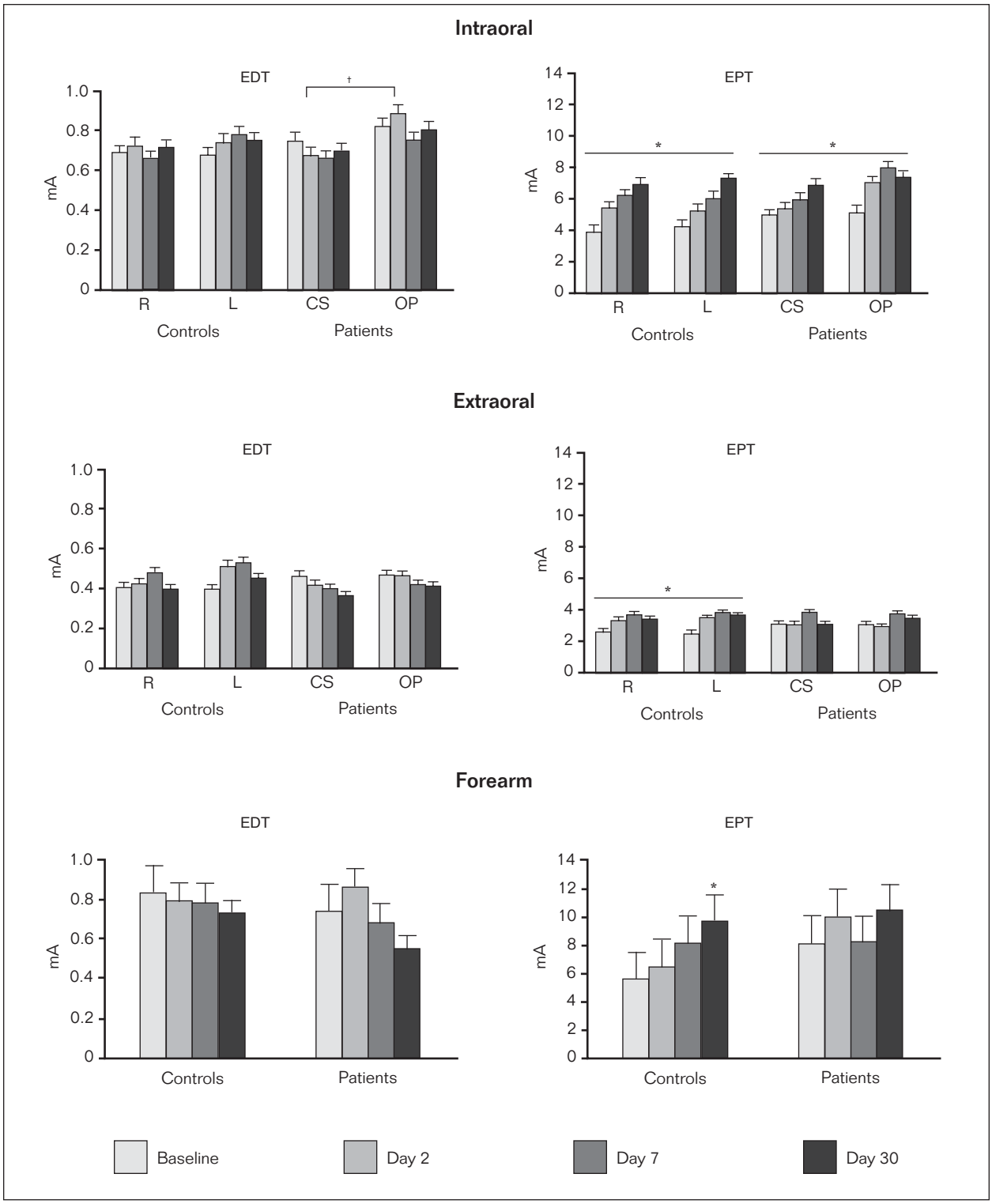

Fig 5 EDT and EPT intraorally, extraorally, and at the forearm for both groups are shown. The measurements are shown in sequential order at baseline and at postoperative days 2, 7, and 30. *Indicates significant time effect in the group (SNK; $P < .05$) compared to baseline. †Indicates significant side effect in the group (SNK; $P < .05$) compared to opposite side at that time point.

Another concern is that pain conditions carry the risk of altering somatosensory sensitivity on the contralateral side.[34] Thus, excluding a control group from an investigation would underestimate the results in the patient group. Therefore, longitudinal studies should preferably include a control group to control for the natural time course and contralateral effects.

Hyperexcitability in the Orofacial Region

Thermal Sensitivity. Thermal stimuli applied to the orofacial region activate small myelinated Aδ and unmyelinated C fibers.[14,18,34] In the present study, thermal detection thresholds were unchanged during the study, which is consistent with normal function of the Aδ fibers and C fibers. These results are in accordance with findings by Hansson et al[25] and Eliav and Gracely.[26] However, cold pain thresholds in the control group became lower (controls subjects endured a lower temperature before pain was experienced) than at the baseline and heat pain thresholds were significantly higher during the observation period compared to the baseline values. During this period, control subjects but not patients became less sensitive to painful cold and heat. Thus, painful stimulation in the orofacial region indicated an increased sensitivity in patients. These findings indirectly support the notion of sensitization of the trigeminal nociceptive system[9–12] in the patients because the observed increase in pain thresholds in the control subjects was lacking in the patients. Such acute sensitization has been demonstrated in patients with musculoskeletal pain disorders.[35]

Mechanical Sensitivity. Overall, the findings of mechanical stimulation, pressure pain, and pressure pain tolerance indicate the existence of oral hyperexcitability on the operated side for at least 1 week after the surgery for pressure pain and for a longer period for pressure pain tolerance. Decreased PPT was expected at day 2 and possibly as well at day 7 in the area adjacent to the surgical wound because of the development of inflammation after the surgical procedure. Thus, the findings at day 2 and day 7 could be explained as consequences of inflammatory processes and hence nociceptor activation and sensitization. Edema (tumor) and erythema (rubor) are 2 symptoms of inflammation and normally would be present for a few days after a trauma. Yet, there was no visible macroscopic edema or erythema present as early as day 2 in the area investigated (except for 1 subject, who did have pronounced edema at day 2). Still, lack of clinical findings of inflammation does not exclude the possibility of ongoing inflammation, as many of the involved processes only are visible microscopically, and the study did not include the investigation of biopsies from the area. However, the advantages of using QST are that these tests may detect functional abnormalities when macroscopic changes are minor or subclinical.[34,36]

PPT and PPTT were significantly reduced during the study even at day 30 on the operated side. This reduction of pain threshold was found at time points when there was no ongoing pain or signs of inflammation. The existence of a reduced PPTT for at least 30 days may be due in part to central sensitization,[9–12] as well as sensitization of peripheral nociceptors on the operated side because direct activation of nociceptors as a consequence of ongoing tissue injury at this late stage is unlikely.[18,37] Langemark et al[38] found reduced pain thresholds in chronic headache patients compared to healthy controls and concluded that this could be the consequence of sensitized nociceptors. Similar observations were made by Svensson et al[39] in chronic jaw-muscle pain patients. In osteoarthritis patients, Kosek and Ordeberg[40] found PPT was lower on the painful side than on the contralateral side before treatment, and that this increased sensitivity to pressure pain was normalized after successful surgery. It was suggested that this increased sensitivity could partly be due to local sensitization. However, as mentioned, central sensitization may also be involved. Kosek and Ordeberg[40] suggested that central sensitization could be 1 explanation for the unilateral decreased pain thresholds in osteoarthritis patients. Sabino et al[41] found in rats that incisor extraction produced changes in substance P receptors down to the level of C7, although Hu[42] explained this finding by bruising of the neck muscles during surgery. Bruising of the neck muscles may also happen in third molar surgery in humans and may explain why central sensitization can be present after third molar surgery. Damage to the inferior alveolar nerve[12] or inflammation of the tooth pulp[10] can also produce prolonged central sensitization in nociceptive neurons of the medullary dorsal horn (MDH) of the trigeminal brainstem nucleus. Furthermore, Imbe et al[9] found that injection of complete Freund's adjuvant (CFA) in the temporomandibular joint of rats resulted in reduced threshold to mechanical stimuli on the CFA-ipsilateral side for at least 14 days. Imbe et al[9] indicated that the changes were a consequence of central sensitization (enlarged receptive fields of MDH nociceptive neurons, increased Fos protein expression in the MDH, and increased MDH preprodynorphin). Hence, the

changes (decreased threshold to mechanical stimuli on the CFA-ipsilateral side at days 1, 3, and 14) paralleled the time course in the present study, although the present study was extended to include measurements 1 month after the surgical procedure. Therefore, the results of the present study are consistent with the findings of Iwata et al[12] and Imbe et al[9] that an orofacial injury involving deep tissues gives rise to a central sensitization that persists for a prolonged period.

Electrical Stimulation. No indications of decreased EDT or EPT were observed in the pres-ent study, which is in contrast to the findings of Eliav and Gracely.[26] Two days after the extraction of a single mandibular third molar in patients, Eliav and Gracely found significant decreased electrical detection and pain threshold on the extraction side compared to the control side. Instead, in the present study, increased intraoral EDT was observed at day 2 on the operated side compared to the contralateral side in the patient group, indicating changes in the intraoral area 2 days after the operation. In the present study the patients underwent a surgical procedure, which resulted in more extensive trauma than the method of third molar extraction used in the study by Eliav and Gracely. This may explain why orofacial sites supplied by Aβ touch fibers of the inferior alveolar nerve developed a transient hypoesthetic period in this study.

In the present study, intraoral EPT increased on both sides in both groups, whereas an increase in extraoral EPT was only seen in the control group. In the patient group, extraoral EPT remained unchanged. This could be a result of trigeminal central sensitization, or it could be due to dysfunction of the descending pain-control system. Therefore, although the results of the present study were not identical to the results of Eliav and Gracely,[26] they may still support the suggestion that an oral trauma causes changes in somatosensory sensitivity indicative of neuronal hyperexcitability.

Extratrigeminal Findings. The overall finding of the tests applied to the extratrigeminal area was an increased pain threshold over time in the control group; this adaptation to the test stimuli was absent in the patient group. These results further support the findings in the trigeminal area. Few studies have applied both trigeminal and extratrigeminal QST after dental surgical procedures. Eliav and Gracely[26] found a tendency toward increased pain thresholds after 1 week at the forearm in control subjects without third molar extraction. However, differences in pain thresholds at the forearm in patients were not investigated.

Adaptation to different kinds of stimulation is a normal physiologic process. This adaptation may be linked to emotions and expectation[43] and explained by indirect activation of the descending pain-control systems.[44,45] The descending pain-control systems originate in part from the rostroventral medulla and comprise both inhibitory and facilitatory mechanisms.[43,45] These mechanisms are under the influence of the amygdala and hypothalamus, which in turn are under the influence of the parabrachial area. This area is a key region implicated in emotional aspects.[43] Subjects' expectation or knowledge of the coming sensory stimulus may therefore indirectly activate the descending pain-control systems and thereby modify the thresholds. In the present study, the controls subjects adapted well to the stimuli, possibly through activation of the inhibitory control mechanisms of the descending pain-control system. In contrast, the operated patients did not adapt to the stimuli, which could be explained by activation of facilitatory mechanisms or suppression of inhibitory mechanisms due to expectation or anxiety of soreness and pain resulting from surgery. However, CPT at the forearm did not change in either group, which might be explained by selective and segmental differences in the descending pain-control systems.[46] Therefore, lack of ability to adapt to the sensory stimulations could be due to a suppressed activation of descending inhibitory mechanisms or enhanced activation of facilitatory mechanisms in the patient group after the surgical procedure.

In conclusion, the present study has documented that even a minor surgical procedure such as third molar surgery can be associated with a state of hyperexcitability in the vicinity of a surgical wound for up to 30 days after surgery. This result suggests that both peripheral and central processes may be involved. Central sensitization of the MDH[9-12] or an imbalance of the descending pain-control systems could explain why patients, unlike control subjects, did not adapt to the sensory stimulations over the study period.

Acknowledgments

The present study was supported by grants from the Danish Pain Research Center, Aarhus University Hospital, Karen Elise Jensens' Foundation, The Lundbeck Found, Denmark, and by grants from the Science Initiative of Aarhus University Hospital, Denmark. The authors have no conflicts of interest.

References

1. Marchettini P, Formaglio F, Barbieri A, Tirloni L, Lacerenza M. Pain syndromes that may develop as a result of treatment interventions. In: Proceedings of the 9th World Congress on Pain. Seattle: IASP Press, 1999:675–688.
2. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology 2000;93:1123–1133.
3. Mikkelsen T, Werner MU, Lassen B, Kehlet H. Pain and sensory dysfunction 6 to 12 months after inguinal herniotomy. Anest Analg 2004;99:146–51.
4. Nikolajsen L, Sørensen HC, Jensen TS, Kehlet H. Chronic pain following Caesarean section. Acta Anaesthesiol Scand 2004;48:111–116.
5. Coderre TJ, Katz J. Peripheral and central hyperexcitability: Differential signs and symptoms in persistent pain. Behav Brain Sci 1997;20:404–419.
6. Koltzenburg M. The changing sensitivity in the life of the nociceptor. Pain 1999;6:93–102.
7. Jensen TS, Gottrup H, Kasch L, Nikolajsen L, Terkelsen AJ, Witting N. Has basic research contributed to chronic pain treatment? Acta Anaesthesiol Scand 2001;45: 1128–1135.
8. Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: Implications for diagnosis and therapy. Life Sci 2004;74:2605–2610.
9. Imbe H, Iwata K, Zhou QQ, Zou S, Dubner R, Ren K. Orofacial deep and cutaneous tissue inflammation and trigeminal neuronal activation. Implications for persistent temporomandibular pain. Cells Tissues Organs 2001; 169:238–247.
10. Sessle BJ. Recent insights into brainstem mechanisms underlying craniofacial pain. J Dent Educ 2002;66: 108–112.
11. Dubner R, Ren K. Brainstem mechanisms of persistent pain following injury. J Orofac Pain 2004;18:299–305.
12. Iwata K, Tsuboi Y, Shima A, et al. Central neuronal changes after nerve injury: Neuroplastic influences of injury and aging. J Orofac Pain 2004;18:293–298.
13. Koltzenburg M. Neural mechanisms of cutaneous nociceptive pain. Clin J Pain 2000;16:131–138.
14. Cadden SW, Orchardson R. The neural mechanisms of oral and facial pain. Dent Update 2001;28:359–367.
15. Kosek E, Ekblom J, Hansson P. Modulation of pressure pain thresholds during and following isometric contraction in patients with fibromyalgia and in healthy controls. Pain 1996;64:415–423.
16. Gottrup H, Andersen J, Arendt-Nielsen L, Jensen TS. Psychophysical examination in patients with postmastectomy pain. Pain 2000;87:275–284.
17. Svensson P, List T, Hector G. Analysis of stimulus-evoked pain in patients with myofascial temporomandibular pain disorders. Pain 2001;92:399–409.
18. Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. Pain 2003;102:1–8.
19. Cruccu G, Anand P, Attal N, et al. EFNS guidelines on neuropathic pain assessment. Eur J Neurol 2004;11:153–162.
20. Eliav E, Gracely RH, Nahlieli O, Benoliel R. Quantitative sensory testing in trigeminal nerve damage assessment. J Orofac Pain 2004;18:339–344.
21. Essick GK. Psychophysical assessment of patients with posttraumatic neuropathic trigeminal pain. J Orofac Pain 2004;18:345–354.
22. Svensson P, Baad-Hansen L, Juhl GI, Thygesen T, Jensen TS. Overview on tools and methods to assess neuropathic trigeminal pain. J Orofac Pain 2004;18:332–338.
23. Byers MR, Närhi MVO. Dental injury models: Experimental tools for understanding neuro-inflammatory interactions and polymodal nociceptor functions. Crit Rev Oral Biol Med 1999;10:4–39.
24. Huang GJ, LeResche L, Critchlow CW, Martin MD, Drangsholt MT. Risk factors for diagnostic subgroups of painful temporomandibular disorders (TMD). J Dent Res 2002;81:284–288.
25. Hansson P, Ekblom A, Lindblom U, Marchettini P. Does acute intraoral pain alter cutaneous sensibility? J Neurol Neurosurg Psychiatry 1988;51:1032–1036.
26. Eliav E, Gracely RH. Sensory changes in the territory of the lingual and inferior alveolar nerves following lower third molar extraction. Pain 1998;77:191–199.
27. Ekblom A, Hansson P. Thermal sensitivity is not changed by acute pain or afferent stimulation. J Neurol Neurosurg Psychiatry 1987;50:1216–1220.
28. Juhl GI, Svensson P, Norholt SE, Jensen TS. Persistent mechanical allodynia and hyperalgesia following oral surgery [abstract]. Presented at the 4th Congress of European Federation of International Association for the Study of Pain Chapters, Prague, Czech Republic, 2–6 Sept 2003.
29. Fruhstorfer H, Gross W, Selbmann O. von Frey hairs: New materials for a new design. Eur J Pain 2001;5:341–342.
30. Norholt SE, Aagaard E, Svensson P, Sindet-Pedersen S. Evaluation of trismus, bite force, and pressure algometry after third molar surgery: A placebo-controlled study of ibuprofen. J Oral Maxillofac Surg 1998;56:420–427.
31. Sang CN, Max MBH, Gracely RH. Stability and reliability of detection thresholds for human A-beta and A-delta sensory afferents determined by cutaneous electrical stimulation. J Pain Symptom Manage 2003;25:64–73.
32. Breivik EK, Bjornsson GA, Skovlund E. A comparison of pain rating scales by sampling from clinical trial data. Clin J Pain 2000;16:22–28.
33. Svensson P. Quantification of Argon Laser-Induced Nociception from Human Oral Mucosa and Facial Skin [thesis]. 1993. [Author: University of Aarhus?]
34. Jääskeläinen SK. Clinical neurophysiology and quantitative sensory testing in the investigation of orofacial pain and sensory function. J Orofac Pain 2004;18:85–107.
35. Graven-Nielsen T, Arendt-Nielsen L. Peripheral and central sensitization in musculoskeletal pain disorders: an experimental approach. Curr Rheumatol Rep 2002;4:313–321.
36. Eliav E, Tal M, Benoliel R. Experimental malignancy in the rat induces early hypersensitivity indicative of neuritis. Pain 2004;110:727–737.
37. Kilo S, Schmelz M, Koltzenburg M, Handwerker HO. Different patterns of hyperalgesia induced by experimental inflammation in human skin. Brain 1994;117:385–396.
38. Langemark M, Jensen K, Jensen TS, Olesen J. Pressure pain thresholds and thermal noci-ceptive thresholds in chronic tension-type headache. Pain 1989;38:203–210.
39. Svensson P, Arendt-Nielsen L, Nielsen H, Larsen JK. Effect of chronic and experimental jaw muscle pain on pain-pressure thresholds and stimulus-response curves. J Orofac Pain 1995;9:347–356.

40. Kosek E, Ordeberg G. Abnormalities of somatosensory perception in patients with painful osteoarthritis normalize following successful treatment. Eur J Pain 2000;4:229–238.
41. Sabino MAC, Honore P, Rogers SD, Mach DB, Luger NM, Mantyh PW. Tooth extraction-induced internalization of the substance P receptor in trigeminal nucleus and spinal cord neurons: Imaging the neurochemistry of dental pain. Pain 2002;95:175–186.
42. Hu JW. Is tooth extraction a good model for dental pain? Pain 2002;99:605–606.
43. Vanegas H, Schaible H. Descending control of persistent pain: Inhibitory or facilitatory? Brain Res Brain Res Rev 2004;46:295–309.
44. Suzuki R, Rygh LJ, Dickenson AH. Bad news from the brain: Descending 5-HT pathways that control spinal pain processing. Trends Pharmacol Sci 2004;25:613–617.
45. Vanegas H. To the descending pain-control system in rats, inflammation-induced primary and secondary hyperalgesia are two different things. Neurosci Lett 2004;361: 225–228.
46. Witting N, Svensson P, Arendt-Nielsen L, Jensen TS. Differential effect of painful heterotopic stimulation on capsaicin-induced pain and allodynia. Brain Res 1998;801:206–210.