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Quantitative Sensory Testing and Human Surgery

Effects of Analgesic Management on Postoperative Neuroplasticity

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Background: **Altered central nervous system sensory processing (neuroplasticity) is a basic mechanism underlying postoperative pain that can be made visible using quantitative sensory testing. Using quantitative sensory testing, the authors investigated how perioperative analgesia affects postoperative neuroplasticity and how this relates to clinical pain measures.**

Methods: **Patients undergoing back surgery received placebo, fentanyl, or ketorolac (n = 15 per group) before isoflurane–nitrous oxide anesthesia. Preoperatively to 5 days postoperatively, we measured thresholds to electrical skin stimulation at the incision site, arm, and leg; pain scores; and morphine patient-controlled analgesia consumption.**

Results: **Decreased pain thresholds *versus* preoperatively were seen 5 days postoperatively, with decreases greater for ketorolac (−63%; $P = 0.00005$ *vs.* preoperatively) than placebo (−45%; $P = 0.008$ *vs.* preoperatively) but nonsignificant for fentanyl (−36%; $P = 0.9$ *vs.* preoperatively). Mainly nonnociceptive thresholds were increased up to 24 h postoperatively. Postoperative clinical pain measures were similar across drug groups. Postoperative pain tolerance threshold changes did not correlate with preoperative clinical pain measures but were inversely related to preoperative thresholds for placebo and ketorolac but not fentanyl.**

Conclusions: **Without analgesia, neuroplasticity after surgery was inhibitory the first 24 h and followed at 5 days by excitation. Fentanyl efficiently preempted this hyperalgesia, but hyperalgesia was greater with ketorolac than with placebo. Clinical pain measures neither reflected the different effects of ketorolac and fentanyl on postoperative neuroplasticity nor permitted prediction of postoperative neuroplasticity. The information obtained by perioperative quantitative sensory testing is separate from and additional to that from clinical pain measures and may enable more mechanism-based approaches to surgical analgesia management in the future.**

PERIOPERATIVE pain management—like other areas of pain management—is still very much symptom based. Further improvement in perioperative pain management is likely to be dependent on the development of more mechanism-based approaches.[1] This shift will be made possible by the development of diagnostic methods permitting insight into the mechanisms underlying pain and nociception. One such basic mechanism is the alteration of peripheral and central nervous system function.[2,3] These alterations, which can be excitatory or inhibitory and are termed *neuroplasticity*, are now considered to play an important role in all areas of pain, both chronic and acute.[3–5] Neuroplasticity may be a significant factor in determining acute—and perhaps chronic—pain outcomes after surgery.[3–5]

Quantitative sensory testing (QST) quantifies nervous system input–response relations, allowing detection and quantification of nociceptive neuroplasticity. QST can thus provide insight into nociceptive mechanisms, with the potential to provide the diagnostics necessary for mechanism-based approaches to perioperative nociception and pain management. In an earlier study,[6] we demonstrated that QST based on electric transcutaneous stimulation is feasible for the demonstration of neuroplasticity in the perioperative clinical context.

Animal studies show postnociceptive neuroplasticity to be complex, varying according to time, being both inhibitory and excitatory, and affecting spinal as well as supraspinal structures.[3–5,7] Extrapolation from animal data to the human clinical context is difficult, as demonstrated by the preemptive analgesia debate, making the collection of actual human data necessary.[8–12] However, human QST data regarding the postoperative course and nature of central neuroplasticity and its relation to clinical measures of pain (*e.g.*, pain scores, analgesia use) continue to be sparse. Furthermore, the effects of analgesic management on postoperative central neuroplasticity remain largely unstudied.

The current clinical study is based on and expands earlier research by our group.[6] Its main goals are to investigate the effect of perioperative analgesic management by opioids or nonsteroidal antiinflammatory drugs on postoperative neuroplasticity using QST and, thus, to determine the feasibility of a more mechanism-based approach to perioperative nociception management. A further goal is to study the relations between QST and clinical pain measures in the perioperative context.

Materials and Methods

Using a prospective, randomized, placebo-controlled, double-blinded design and after institutional review board approval (Geneva University Hospital, Geneva, Switzerland), we studied 45 patients with American Society of Anesthesiologists physical status I and II who were scheduled to undergo elective surgery for intervertebral disc herniation. Randomization was by computer-

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generated randomization table and sealed, sequentially numbered envelopes specifying the treatment to be given. The surgical procedure (fenestration, removal of disc fragments) was standardized and the same for all patients. Patients were recruited the afternoon before surgery and gave written informed consent. At this time, a detailed history and physical examination were performed, and instruction was given on threshold testing and patient-controlled analgesia (PCA) use. Regarding PCA, patients were told to titrate themselves to acceptable pain intensity levels of approximately 3, corresponding to a numerical rating scale (NRS; 0 = no pain, 10 = maximum imaginable pain).

Patients

To recruit a homogeneous group in whom pain—as opposed to neurologic deficit—was the main symptom, patients conformed to the following criteria: (1) significant lower back pain with impairment of everyday activities over the past month (pain NRS score greater than 5 for more than three quarters of the time for at least 1 month, accompanied by typical sciatic pain radiating into the leg), and (2) significant and typical findings on physical examination (local lower back pain or tenderness, muscle stiffness or spasm, reduced mobility; positive Lasegue sign on at least one side). An additional indication for surgery was identifiable anatomical intervertebral disc abnormality on neuroimaging. Exclusion criteria included significant focal neurologic motor deficit, peripheral neuropathy, and diseases predisposing to peripheral neuropathy, such as diabetes mellitus or major alcohol abuse. Bed rest and a standard antiinflammatory scheme of 3 × 100 mg oral diclofenac daily were started in all patients 3 days before surgery.

Preoperative Testing

Patients received no premedication on the morning of surgery. On entering the operating theater, they were assigned to one of the three treatment groups (n = 15 per group) *via* sealed envelope. A nurse who was not further involved in the study (to assure blinding) opened the envelope and prepared a blinded infusion for subsequent use. The blinded short infusion consisted of 100 ml NaCl, 0.9% (placebo group), 3 μg/kg fentanyl in 100 ml NaCl, 0.9% (fentanyl group), or 30 mg ketorolac in 100 ml NaCl, 0.9% (ketorolac group). Before insertion of intravenous access, patients were asked about the presence of acute low back and leg pain (*i.e.*, sciatica) and to rate the intensity of each using the NRS. Next, taking care not to stimulate major nerves directly, an observer who was blinded to the patient's pain status performed quantitative sensory testing. QST consisted of determining thresholds to transcutaneous constant current electric stimulation (Digistim; Biometer A/S, Copenhagen, Denmark), using tetanic stimulation at 100 Hz (0.2-ms square wave pulses, ramping rate ~0.1 mA/s) applied *via* self-adhesive electrodes 3 cm apart. Thresholds for sensation, pain detection, and pain tolerance (electric current just felt, just becoming painful, and just becoming intolerably painful, respectively) were determined at standardized back, leg, and arm sites on the predominantly painful (sciatica) side. These measures can be expected to reflect Aβ-, Aδ-, and C-fiber sensory inputs, respectively.[13] Measurements at the back (site of surgical incision: T10 dermatome, ipsilateral and contralateral to the painful side) were performed 10 cm lateral to the planned incision so as to include only secondary hyperalgesia reflecting central neuroplasticity. The leg site (affected by sciatica) was at the anterior mid-thigh level (L3 dermatome), and the arm site (distant from site of surgery) was at the anterior mid-humeral level (C5 dermatome). Thresholds were quantified consecutively in a run in an identical fashion, with the average of three runs separated by 5 min being used for analysis. If two threshold values differed by more than 20% between runs, testing was repeated until stable. All QST testing was performed by two persons (O. W. S., C. S.), and the study was completed within a year.

Anesthesia

Venous access was established, and the blinded short infusion was given. Ten minutes later, anesthesia was induced with 5 mg/kg thiopental followed by 0.1 mg/kg vecuronium. After tracheal intubation, isoflurane (initially 1.5%, then modified according to hemodynamic reactions to incision and surgery) and nitrous oxide in oxygen (fraction of inspired oxygen [F_{IO_2}] = 0.4) were used to maintain anesthesia as necessary. No other drugs were used for anesthesia, which always lasted less than 1 h in total. Morphine PCA was started in the postanesthesia care unit and continued until 24 h postoperatively (loading bolus: 60 μg/kg; demand bolus: 25 μg/kg; lockout time: 8 min). For the period of morphine PCA, patients did not receive any other analgesics. A background infusion of 15 $\mu g \cdot kg^{-1} \cdot h^{-1}$ morphine was used during the first 2-h stay in the postanesthesia care unit. This was discontinued on transfer to the ward, and the lockout interval increased to 15 min. After 24 h, analgesia was continued to day 5 by oral diclofenac at 3 × 100 mg only.

Postoperative Measures

At 1, 2, 4, 6, and 24 h and 5 days after extubation, thresholds and pain NRS scores in the leg and back were obtained as described in the Preoperative Testing section, together with observer sedation rating scores (5 = wide awake, 1 = unable to be roused) and cumulative morphine consumption (not day 5).

Statistical Analysis

Statistical analysis was performed using the software package Statistica for Windows (release 4.5; Statsoft Inc., Tulsa, OK). Based on previous threshold results,[6,14] the

Table 1. Patient Characteristics

Drug Group	Age, yr	Weight, kg	Height, cm	Gender, M/F
Placebo	53.5 (24–64)	75 (67–82)	172 (163.5–176.5)	9:4
Fentanyl	37 (27–62)	75 (64–82.5)	177 (163–180)	12:3
Ketorolac	47.5 (21–59)	70 (58–77.5)	170 (164–173)	10:3

Demographic data of patient groups. Ages are shown as medians (ranges in parentheses), weights and heights as shown medians (interquartile ranges in parentheses). The M/F ratio is given as absolute numbers. There are no significant differences between the groups.
M/F = male/female.

current study was predicted to have the ability to identify pain tolerance threshold changes of 20% for a group size of n = 12 (α = 5%, β = 20%; two-tailed testing). Patient group demographic data were compared using Kruskal-Wallis analysis of variance (ANOVA). Baseline sensation, pain detection, and pain tolerance thresholds were compared using two-way ANOVA (factors: drug group, measurement site) with *post hoc* Tukey honest significant difference testing. The hypothesis of a significant relation between preoperative leg or back pain (NRS) and preoperative pain tolerance thresholds was tested using Spearman rank order correlations.

Postoperative changes in group sensation, pain detection, and pain tolerance thresholds were analyzed using repeated-measures three-way ANOVA (factors: drug group, measurement site, time) and *post hoc* Tukey testing. Differences in morphine consumption for drug group were tested using two-way repeated-measures ANOVA (factors: drug group, time) and Tukey testing. Pain NRS and observer sedation scores were compared using Kruskal-Wallis ANOVA, with Bonferroni-corrected *post hoc* Mann–Whitney U testing as necessary. We used Spearman rank order correlation analysis to test the following hypotheses:

1. Does preoperative pain predict postoperative pain (days 1 and 5), PCA morphine consumption (day 1), or changes in pain tolerance thresholds (days 1 and 5)?
2. Do preoperative pain tolerance thresholds predict postoperative pain tolerance threshold changes (days 1 and 5), pain (days 1 and 5), or PCA morphine consumption (day 1)?

For statistical analysis, significance was assumed for $P < 0.05$. For Spearman correlations, $R > 0.4$ was considered to be relevant, and multiple comparison corrected statistical significance was set at $P < 0.0005$ for preoperative *vs.* postoperative correlations and $P < 0.01$ for preoperative baseline correlations.

Results

Patient Characteristics and Baseline Values

Two placebo and two ketorolac group patients had incomplete pain data and were excluded from analysis. Patient characteristics (table 1) were similar in the three drug groups. Baseline pain tolerance thresholds did not differ according to drug group or threshold site, with similar results for pain detection thresholds, except that baseline values in the ketorolac group were just significantly higher than in the placebo group ($P = 0.049$; table 2). Postoperative analysis was therefore performed on *changes* in thresholds. Sensation thresholds at baseline were significantly higher in the leg dermatome than at other sites ($P < 0.002$), and there was no difference between drug groups (table 2). Preoperative baseline pain scores in the leg and back were similar in the three drug groups (table 3). Spearman testing revealed no relevant and significant correlations between preopera-

Table 2. Preoperative Threshold Values (Baseline)

	Arm	Back (Contralateral)	Back (Ipsilateral)	Leg
Fentanyl group	—	—	—	—
Sensation	1.0 (0.9)	1.1 (0.8)	1.2 (0.8)	1.4 (1.1)†
Pain detection	4.9 (3.2)	5.4 (3.1)	6.1 (3.1)	4.8 (2.8)
Pain tolerance	9.3 (3.9)	9.0 (3.1)	9.5 (3.4)	8.3 (4.3)
Placebo group	—	—	—	—
Sensation	0.8 (0.7)	0.8 (0.5)	0.9 (0.5)	1.9 (2.1)†
Pain detection	5.3 (3.5)	5.0 (3.7)	4.7 (3.4)	5.7 (5.2)
Pain tolerance	9.7 (4.2)	9.6 (5.1)	9.3 (4.7)	8.6 (6.0)
Ketorolac group	—	—	—	—
Sensation	0.9 (0.7)	1.3 (1.1)	1.4 (1.3)	1.9 (1.4)†
Pain detection	6.9 (6.2)*	7.9 (6.8)*	7.8 (6.8)*	6.3 (5.1)*
Pain tolerance	11.4 (7.0)	10.7 (8.5)	11.6 (6.9)	9.0 (6.1)

Preoperative thresholds (mA) in the three drug groups. Values are shown as means (SD in parentheses). Back sites are contralateral or ipsilateral to the side with the most pain.

* Significant *versus* placebo group. † Significant *versus* other sites.

Table 3. Clinical Pain Measures

Time	Preoperative	1 Hour	2 Hours	4 Hours	6 Hours	24 Hours	5 Days
Leg pain/sciatica*	—	—	—	—	—	—	—
Fentanyl	1 (0–3)	2 (1–4)	0 (0–2)	0 (0–2)	0 (0–4)	0 (0–2)	2 (0–4)
Placebo	0 (0–6)	2 (0–4)	2 (0–4)	1 (0–5)	0 (0–2)	1 (0–2)	0 (0–2)
Ketorolac	0 (0–4)	0 (0–3)	0 (0–3)	0 (0–2)	0 (0–3)	0 (0–2)	0 (0–3)
Back/wound pain*	—	—	—	—	—	—	—
Fentanyl	0 (0–4)	4 (2–6)	3 (2–5)	3 (2–5)	3 (0–4)	1 (0–3)	1 (0–2)
Placebo	0 (0–2)	5 (3–6)	3 (2–4)	4 (2–5)	2.5 (1–3)	2 (1–4)	1 (1–1)
Ketorolac	0 (0–2)	4 (3–6)	3 (2–4)	2 (1–3)	1 (1–4)	1 (0–3)	3 (0–3)
Morphine use†	—	—	—	—	—	—	—
Fentanyl	—	6.4 (6.4)	10.3 (7.9)	16.8 (14.9)	20.9 (21.0)	42.0 (31.1)	—
Placebo	—	6.2 (5.1)	9.7 (9.0)	15.2 (15.3)	18.4 (18.1)	33.5 (33.3)	—
Ketorolac	—	6.8 (6.1)	11.4 (8.7)	16.9 (16.2)	32.0 (23.5)	40.5 (37.9)	—

Time course of pain NRS in back and leg, and postoperative cumulative morphine PCA consumption (mg). NRS values are medians and interquartile ranges, morphine PCA values are means and standard deviations. There are no statistically significant differences present between the drug groups.

* NRS of pain: minimum = 0; maximum = 10. † Cumulative PCA consumption (mg).

NRS = numerical rating scale; PCA = patient-controlled analgesia.

tive pain tolerance thresholds and preoperative leg or back pain NRS scores.

Postoperative Course of Sensation Thresholds

The course of postoperative sensation thresholds was significantly affected by time ($P < 0.000001$) and the interaction time × drug group ($P < 0.0006$; fig. 1). There was no longer a significant effect of threshold measurement site, either alone or in combination with other factors; thus, further analysis was performed on data pooling results from all sites. Sensation thresholds for placebo and fentanyl patients were significantly increased compared to preoperative baseline from 1 to 24 h postoperatively (4 h: +133%, +160%; $P = 0.0002$, $P = 0.00009$ *vs.* preoperatively, respectively). In the ketorolac group, significant threshold increase was present from 1 to 4 h postoperatively (4 h: +107%; $P = 0.00005$ *vs.* preoperatively). At 6 h postoperatively, values in the fentanyl group were significantly higher than for ketorolac ($P < 0.001$).

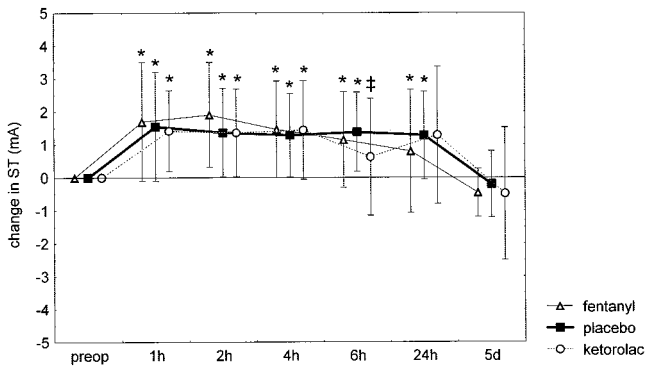

Fig. 1. Change in sensation thresholds postoperatively (mean, SD) in patients receiving placebo, fentanyl, or ketorolac preoperatively. X-axis: *change* in sensation thresholds in milliamperes; Y-axis: time points postoperatively. *$P < 0.05$ *versus* preoperative baseline; ‡$P < 0.05$ *versus* fentanyl group.

Postoperative Course of Pain Detection Thresholds

Drug group ($P = 0.02$), time ($P < 0.000001$), and the interaction drug group × time ($P = 0.004$) all significantly affected postoperative change in pain detection thresholds (fig. 2). Site of threshold measure, individually or in interaction with other factors, had no significant effect, and results from all sites were therefore pooled for analysis. The decrease in pain detection threshold at 5 days was significant only in the ketorolac group (−68%; $P = 0.00005$ *vs.* preoperatively). Ketorolac values at 5 days were significantly lower than in the placebo ($P = 0.04$) and fentanyl ($P = 0.002$) groups.

Postoperative Course of Pain Tolerance Thresholds

Pain tolerance threshold changes were also significantly affected by time ($P < 0.000001$) and the interaction drug group × time ($P = 0.005$; fig. 3). Threshold measurement sites had no significant effect, alone or in interaction, and data from all sites were thus pooled as before. Day 5 thresholds were significantly lowered in the placebo (−45%; $P = 0.008$ *vs.* preoperatively) and ketorolac (−63%; $P = 0.00005$ *vs.* preoperatively) groups. Fentanyl group thresholds were significantly increased 4 h postoperatively (+63%; $P = 0.04$ *vs.* preoperatively). At 5 days postoperatively, thresholds in the ketorolac group were significantly lower than in the fentanyl group (−63% *vs.* −36%; $P = 0.04$).

Postoperative Course of Clinical Pain Measures

Postoperative back and leg pain NRS scores and morphine PCA consumption were similar between drug groups throughout (table 3). Observer sedation scores did not differ at any time according to drug group, showed median scores (range) of 4 (2–5) and 4 (3–5) at 1 and 2 h postoperatively, and had returned to preoperative baseline values of 5 by 4 h postoperatively.

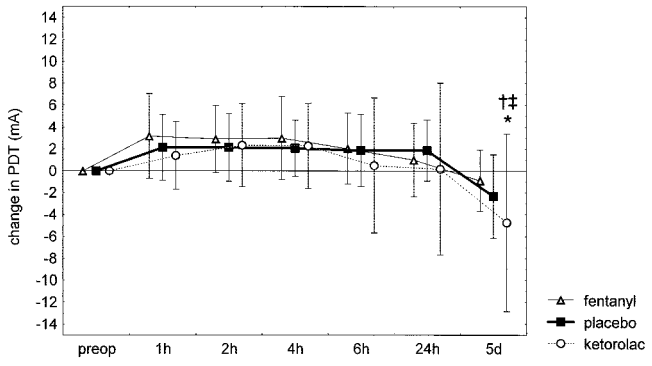

Fig. 2. Change in pain detection thresholds postoperatively (mean, SD) in patients receiving placebo, fentanyl, or ketorolac preoperatively. X-axis: *change* in pain detection thresholds in milliamperes; Y-axis: time points postoperatively. **P* < 0.05 *versus* preoperative baseline; †*P* < 0.05 *versus* placebo group; ‡*P* < 0.05 *versus* fentanyl group.

Correlations between Preoperative and Postoperative Factors

Patients with lower preoperative pain tolerance thresholds showed smaller decreases in thresholds on postoperative days 1 and 5 in the placebo and ketorolac but not fentanyl groups (fig. 4). Preoperative pain tolerance thresholds did not predict postoperative clinical pain measures (*i.e.*, pain, analgesia use), and preoperative clinical pain measures did not predict postoperative changes in pain tolerance thresholds.

We found significant correlations between preoperative pain and postoperative clinical pain measures. These were different in the different drug groups. For placebo patients, preoperative back pain was negatively correlated with day 5 leg pain (R = −0.58, *P* = 0.0001). For fentanyl, preoperative leg pain negatively related to leg pain at 5 days postoperatively (R = −0.62, *P* = 0.0004), and preoperative back pain correlated negatively with day 5 back pain (R = −0.63, *P* = 0.0004). In the ketorolac group, however, preoperative leg pain related *positively* to back pain at 5 days postoperatively (R = 0.78, *P* = 0.00001), and preoperative back pain correlated *positively* with both day 5 back pain (R = 0.78, *P* = 0.00001) and 24-h cumulative morphine consumption (R = 0.54, *P* = 0.00005).

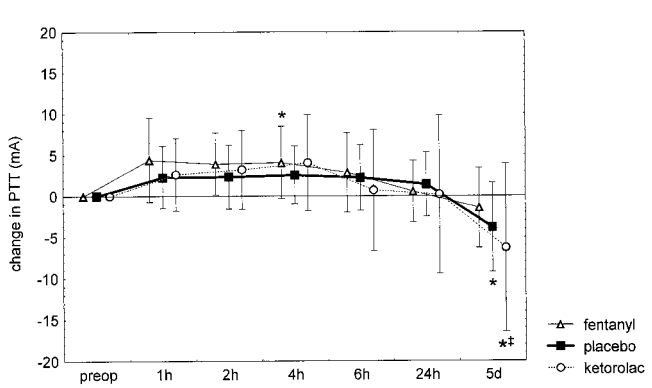

Fig. 3. Change in pain tolerance thresholds postoperatively (mean, SD) in patients receiving placebo, fentanyl, or ketorolac preoperatively. X-axis: *change* in pain tolerance thresholds in milliamperes; Y-axis: time points postoperatively. **P* < 0.05 *versus* preoperative baseline; ‡*P* < 0.05 *versus* fentanyl group.

Discussion

This study shows that perioperative analgesic management can positively influence potentially undesirable excitatory neuroplasticity after surgery. These positive effects, which apply to fentanyl but not ketorolac analgesic supplementation, are not reflected in clinical measures of pain symptoms, such as pain scores or analgesic consumption, but are made visible by QST. If future improvements in perioperative pain and nociception management are dependent on a shift from symptom-based to mechanism-based approaches, then perioperative QST has the potential for providing a necessary new diagnostic tool to achieve this shift through the insight into pain and nociception mechanisms that it provides.

Early Postoperative Neuroplasticity: Inhibition

During the first 24 h after surgery, the predominant neuroplastic response is inhibition, more manifest for nonnociceptive (sensation thresholds) than nociceptive processing (pain thresholds). Inhibition affecting mainly sensation thresholds is not explained by the accompanying morphine analgesia as this should have its greatest effect on pain tolerance thresholds.[15,16] The inhibition is thus likely to reflect the body's own inhibitory response to surgical stress and pain. One candidate mechanism is descending noxious inhibitory controls, which inhibit wide-dynamic-range sensory neurons in the spinal posterior horn and therefore also affect nonnociceptive sensory inputs.[17–19]

Later Postoperative Neuroplasticity: Excitation

A consistent and highly significant reduction of pain thresholds (*e.g.*, hyperalgesia) is visible on postoperative day 5—suppressed by fentanyl supplementation but increased with ketorolac compared to placebo. For the placebo and ketorolac groups (but not fentanyl), higher preoperative pain thresholds go with greater postoperative pain threshold reductions. The increased postoperative pain sensitivity very likely expresses central excitation as seen after nociception in experimental animal models (particularly if nonintact)[3,4,8,11,12] in which noxious input has been shown to sensitize spinal and supraspinal neuronal as well as macroglial structures.[20–22]

Postoperatively, the increased pain sensitivity is equally visible at all threshold measurement sites, suggesting a supraspinal (or at least highly multisegmental) origin. Preoperatively, however, thresholds in the leg were increased compared to the other sites. Two possible rationales for the lack of difference between the various threshold measurement sites after surgery can be

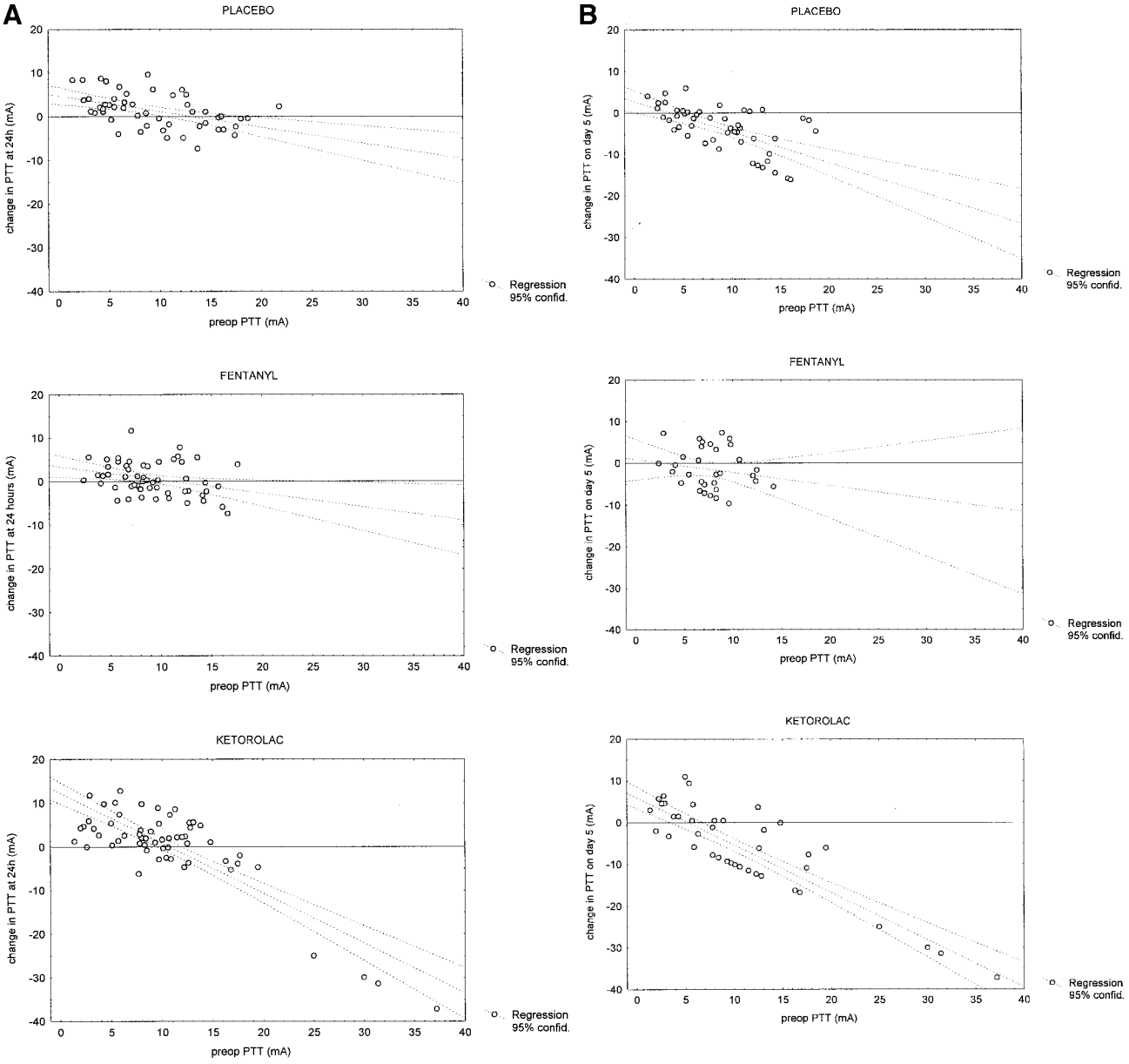

Fig. 4. Correlations between preoperative pain tolerance thresholds (PTTs) and postoperative decreases in PTTs 24 h (*A*) and 5 days (*B*) postoperatively for the three drug groups (preoperative placebo, fentanyl, or ketorolac supplementation). Linear regression lines and their 95% confidence intervals are shown. Spearman correlations were significant and negative for the ketorolac (24 h: R = −0.50, *P* = 0.00006; 5 days: R = −0.76, *P* = 0.0000001) and placebo (24 h: R = −0.49, *P* = 0.0001; 5 days: R = −0.63, *P* = 0.000001) but not fentanyl (24 h: R = −0.31, *P* = 0.017; 5 days: R = −0.14, *P* = 0.41) groups.

offered: Postoperative neuroplasticity extending beyond the segments of surgery (*i.e.*, supraspinal neuroplasticity) is more important than (*i.e.*, dominant to) segmental (spinal) neuroplasticity,[11] and/or the threshold differences between the sites are smaller than the study power permits us to detect (*i.e.*, 30%; *cf.* Discussion, Study Design).

A number of explanations are possible—alone or in combination—for the manifestation of increased pain sensitivity after 24 h postoperatively. First, it may well be that postoperative morphine analgesia as used in this study is incapable of suppressing established nociceptive generalized central sensitization, as demonstrated in the animal literature,[3,5,8] and that morphine merely prevents its manifestation. The differences in pain sensitivity appearing on ending morphine application after 24 h would hence reflect differences in the efficacy of inhibiting prior nociceptive input due to surgery. Then, fentanyl given before surgery would inhibit nociceptive central sensitization better than ketorolac or morphine given afterward, with particularly the latter suggestion being well supported in the experimental pain literature.[3–5,8] Second, the falling thresholds by 24 h would further suggest that descending noxious inhibitory con-

trols and/or other endogenous inhibitory mechanisms are waning, perhaps because of decreasing acute nociceptive inputs from the surgical wound—a phenomenon also described in the animal literature.[23] A further possible explanation could be the tolerance (during infusion) and rebound hyperalgesia (after infusion) described with longer-duration opioid infusion, albeit mainly for higher doses of potent opioids such as fentanyl, alfentanil, or remifentanil.[24–26] All of our three study groups still showed at least a trend to hyperalgesia at 5 days postoperatively. However, for most of the first 24 postoperative hours, morphine was only given by bolus—not as continuous infusion. It might thus be possible that we are in addition seeing an interaction of central nociceptive sensitization with hyperalgesia due to cessation of morphine PCA at 24 h, but this is highly speculative. Unfortunately, we did not obtain threshold measures closer to the end of morphine PCA (*e.g.*, at 48 h postoperatively), so the resolution of this question awaits further research.

Postoperative Neuroplasticity and Fentanyl

The current study documents highly efficient inhibition of postoperative excitatory neuroplasticity by the opioid fentanyl started preoperatively. Of note is the fact that only in fentanyl-supplemented patients was there no significant inverse correlation between preoperative pain thresholds and postoperative threshold changes. When opioids are started only postoperatively (placebo group, postoperative PCA morphine), increased pain sensitivity becomes manifest once they are stopped. These results suggest—in keeping with animal model evidence—that opioids inhibit nociceptive excitatory neuroplasticity much more effectively when used before as opposed to after nociception.[4,5,7,12] Attempts over the last decade to demonstrate such effectiveness of preemptive opioid analgesia for human surgery using clinical pain measures have been unconvincing.[5,9,10,12] The results of the current study confirm the positive effect of analgesic preemption on postoperative neuroplasticity in humans and explain why studies using clinical pain end points were relatively unsuccessful in showing its effectiveness: Clinical pain measures and neuroplasticity measures (QST) do not substitute for each other.

Postoperative Neuroplasticity and Ketorolac

The lack of inhibitory effect of the nonsteroidal antiinflammatory drug ketorolac on postoperative central excitatory neuroplasticity in this study is surprising and not easy to explain. This result does, however, support the utility of QST for nociceptive neuroplasticity in uncovering differences in the mechanisms of analgesia not reflected by clinical pain symptoms. Recent research has demonstrated a major role for *central* cyclooxygenase (COX)-2 isoenzyme induction in the genesis of central sensitization after nociceptive inflammation, with combined central and peripheral COX-2 inhibition being particularly synergistic in reducing the excitatory consequences of nociceptive input.[20,21] It has been suggested that ketorolac penetrates poorly into the central nervous system, and this may be one reason for its disappointing effects.[27] Another reason may be that ketorolac inhibits the COX-1 isoenzyme more than the COX-2 isoenzyme.[28] A further factor could be the impairment of stress- or nociception-induced endogenous analgesia mechanisms described with prostaglandin synthesis inhibiting drugs, which would go with the tendency toward lesser early inhibitory neuroplasticity in our ketorolac patients.[29,30] A better understanding of this phenomenon awaits further research with more classic COX-2 inhibiting drugs.

Neuroplasticity versus *Clinical Pain Measures*

We were unable to demonstrate a significant relation between thresholds and clinical pain measures in this study. Better relations might have emerged with regard to dynamic pain measures such as pain on movement, which we did not measure, although this remains to be definitively proven.[31] While inability to demonstrate threshold *versus* clinical pain relations could partly be because of design constraints (further discussed below, in Study Design), it is not entirely unexpected if recent advances in our understanding of the processing of nociception and pain are taken into account.[32] The conscious pain experience is the result of a long chain of *serial* processing rising up through the central nervous system, making the initial nociceptive event but one of many contributing factors to the multifactorial pain experience (*cf.* IASP definition of pain).[32] In contrast, alterations in nervous system processing (neuroplasticity) with nociception already occur at the lowest levels of central nervous processing, with spinal dorsal horn neurons having direct, *parallel* access to higher centers further controlling central neuroplasticity, arousal, and stress responses.[32] Thus, nociceptive neuroplasticity may not only potentially provide insight into mechanisms underlying surgical pain and nociception, but may also give us access to the nociceptive load resulting from surgery. We would therefore suggest that measures of neuroplasticity and pain provide different but complementary information about nociception and its modulation and that one cannot be used as a surrogate for the other.

Comparison with Other Studies

The current study results agree with earlier reports demonstrating either increases in pain sensitivity to mechanical or electrical stimulation[7,33] or generalized inhibition to electrical stimulation[34–36] after human surgery. Subsequent detailed studies document the presence of segmental excitation, abolished by analgesic supplementation (opioid agonists, *N*-methyl-D-aspartate antagonists), and early postoperative inhibition, increased by

analgesic supplementation.[6,14] A recent study[37] of back patients before surgery showed different kinds of preoperative pain to be associated with either increased or decreased thresholds to electric skin stimulation. In the current study, we were unable to formally demonstrate a significant relation between preoperative pain and preoperative thresholds, perhaps because of small group numbers as compared to the study cited. However, we did demonstrate postoperative pain threshold changes to be *larger* in patients with *higher* preoperative thresholds.

Study Design

The study results might have been influenced by the sensory testing paradigm, considerations of statistical power, and drug effects. We chose electrical stimulation for its long history of validated use, reproducibility, and easy clinical application.[38,39] Potential criticisms include the mixed nerve fiber response it can produce (dependent on stimulus characteristics) and its nonphysiologic nature. However, both these characteristics may be advantageous for our purposes: Surgical nociception affects multiple nerve populations, too; and electrical stimulation, perhaps less dependent on cutaneous nociceptors, could be more directly sensitive to central excitatory and inhibitory neuroplasticity than other more physiologic stimuli.[12,38,39] To minimize variability, patients underwent several test runs and were carefully instructed about the sensory testing paradigm before inclusion. Sensitization by electrical stimulation was curtailed by spacing testing and stopping on reaching the pain tolerance threshold, and the effect of reaction time minimized by slow ramping (0.1 mA/s). *Post hoc* power testing shows that sample size was adequate to detect clinically relevant differences of at least one third for thresholds and morphine use.

We did not collect isoflurane concentrations intraoperatively and cannot therefore exclude that there may have been group differences in the amount of isoflurane used intraoperatively. However, the impact of isoflurane on central sensitization is small compared to that of opioids and may be attenuated by nitrous oxide supplementation.[40] Nevertheless, the results of the current study should be taken to apply for the whole anesthesia package—isoflurane, nitrous oxide, and analgesic supplement together—and not for the analgesic supplement alone. Isoflurane or nitrous oxide hangover is unlikely to have affected postoperative results, as subanesthetic isoflurane concentrations have no effect on pain detection thresholds,[41] and the effects of nitrous oxide on the same continue for approximately 30 min after discontinuation.[42] Opioids (*e.g.*, morphine, fentanyl) have no or minor direct effects on sensation or pain detection thresholds, with increases in pain tolerance thresholds being most marked for long and/or repeated stimulation.[15,16] Diclofenac has smaller effects than opioids on threshold testing but has been shown to increase electric and thermal *tonic* pain tolerance thresholds.[43] Effects due to either of the postoperative analgesics are unlikely to explain group threshold differences, however, because of their similar use in all groups.

The quantification of neuroplasticity after surgery by quantitative sensory testing makes visible differences in the mechanisms of perioperative analgesic supplementation not reflected by clinical measures of pain experience. The preoperative state of pain processing may provide the basis for predictions about postsurgical nociceptive neuroplasticity. In the surgical context, these results demonstrate the efficacy of preemptive fentanyl in inhibiting excitatory nociceptive neuroplasticity, suggest a limited ability of postoperative morphine to suppress established central sensitization, and reveal that ketorolac, as used, may have little impact on the development of nociceptive central sensitization. Compared to clinical pain measures such as pain scores or analgesic use, QST measures of surgical neuroplasticity provide complementary but different information giving insight into the mechanisms involved in the postoperative consequences of nociception. Thus, QST-measured neuroplasticity could in the future provide a basis for the desirable shift from symptom-based to mechanism-based approaches to perioperative pain management. Further research will be needed to explore these possibilities.

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