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Prediction of Postoperative Pain by Preoperative Nociceptive Responses to Heat Stimulation

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Background: **Despite major advances in the understanding of the neurobiologic mechanisms of pain, the wide variation in acute pain experience has not been well explained. Therefore, the authors investigated the potential of a preoperatively induced heat injury to predict subsequent postoperative pain ratings in patients undergoing knee surgery.**

Methods: **Twenty patients were studied. The burn injury was induced 6 days before surgery with a contact thermode (12.5 cm^2, 47°C for 7 min). The sensory testing, before and 1 h after the injury, included pain score during induction of the burn, secondary hyperalgesia area, thermal and mechanical pain perception, and pain thresholds. Postoperative analgesia consisted of ibuprofen and acetaminophen. Pain ratings (visual analog scale) at rest and during limb movement were followed for 10 days after surgery.**

Results: **The burn injury was associated with development of significant hyperalgesia. There was a significant correlation between preoperative pain ratings during the burn injury and early (0–2 days, area under the curve) and late (3–10 days, area under the curve) postoperative dynamic pain ratings during limb movement.**

Conclusion: **The results of this study suggest that the pain response to a preoperative heat injury may be useful in research in predicting the intensity of postoperative pain. These findings may have important implications to identify patients at risk for development of chronic pain and to stratify individuals for investigations of new analgesics.**

IMPROVEMENT in postoperative pain treatment remains an elusive and major challenge, despite recent progress in the understanding of nociceptive pathophysiology.[1] One of the intriguing clinical observations is the wide variation in patient experience of pain after similar types of surgical injury.[2–4] Because optimal pain relief is important to an improved postoperative outcome[5] and the severity of postoperative pain may correlate with the development of a chronic pain state,[6] techniques to predict the intensity of postoperative pain are desirable. Such predictive methods may be useful in the allocation of additional resources to patients at potential risk for experiencing severe postoperative pain, but they also may serve as a screening procedure in pharmacologic trials of new analgesics by reducing the number of individuals required to assess the efficacy.

Previous efforts to predict postoperative pain have focused on age, gender, anxiety level, and neuroticism.[3,4,7–9] However, the sensitivity of these parameters has not been adequate for their use in a clinical context, although elderly patients generally have lower pain ratings and postoperative morphine requirements than do younger patients.[7,9] Conversely, preoperative anxiety[3] and neuroticism[4] seem to be associated with higher postoperative pain ratings.

The postoperative experience of pain is a combination of physiologic (nociceptive), psychologic, and behavioral components.[2] Thus, it may be hypothesized that assessment of pain perception to a preoperative minor physical injury may predict subsequent postoperative pain ratings. We therefore compared preoperative nociceptive responses to a first-degree heat injury[10] with postoperative pain ratings in patients undergoing arthroscopic knee surgery.

Patients and Methods

Patients

After obtaining approval of the Ethical Committees of Frederiksberg and Copenhagen Municipalities, Copenhagen, Denmark, written informed consent was obtained from 20 healthy patients scheduled for arthroscopic repair of the anterior cruciate ligament on an outpatient basis. Preoperative sensory assessment data from the first 17 patients have been reported in a companion article,[11] which also contains a detailed description of the burn injury and assessment methods.

Study Design

Because of the exploratory nature of the study, a formal calculation of sample size could not be made, but the group of 20 patients was considered sufficient to account for potential dropouts and allow for a reasonable clinically relevant estimate. Two or 3 weeks before surgery, the patients participated in a 30-min training session with quantitative sensory testing, experienced the burn injury, and made pain ratings with a horizontally held visual analog scale (VAS) anchored by "no pain" (0) and "the worst imaginable pain" (100).

On the 2 days before the burn injury, the standard postoperative pain treatment with 800 mg ibuprofen every 8 h and 1 g paracetamol every 6 h was given to

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allow for similar study conditions for preoperative and postoperative pain perception. On day 6 before surgery, the 2-h study session was made, and the patients were not aware of the results of the sensory testing.

Procedures

Sensory testing was performed before and 1 h after induction of the injury. Mechanical pain threshold and mechanical pain perception (VAS) within the burn area were assessed with von Frey monofilaments. Heat pain threshold was assessed with a contact thermode using a baseline temperature of 32°C. Heat pain perception (VAS) was evaluated with a 10-s 45°C heat stimulus in the burn area.

The first-degree burn injury was induced on the medial aspect of the calf contralateral to the surgical side with a 25 × 50-mm thermode (7 min at 47°C). Patients rated pain intensity at the start and every minute during the burn. The area of secondary hyperalgesia developing around the burn injury was assessed by a rigid von Frey monofilament.[10,11]

Surgery was performed under propofol–sufentanil general anesthesia. The repair of the anterior cruciate ligament was performed by a standardized transarthroscopically assisted three-incision approach.[11] At the end of surgery, 40 ml bupivacaine, 2.5 mg/ml, was given intraarticularly and incisionally, followed by administration of 30 mg ketorolac intravenously. Standard postoperative pain treatment was started in the postoperative recovery room with oral ibuprofen and paracetamol. Patients were discharged from the recovery room 4–6 h after surgery and continued taking 800 mg ibuprofen every 8 h and 1 g paracetamol every 6 h for 7 days. In addition, patients were instructed to use a cooling device (Cryo/Cuff®; Aircast, Inc., Boca Raton, FL) at least four times a day, starting 24 h after surgery.

All patients were asked to complete a pain questionnaire for the 2 days before the burn injury and for the 10 days after surgery. The patients assessed pain (VAS) once daily, except for the first and second postoperative days, on which the patients noted pain three times daily, during rest, and during dynamic conditions (*i.e.*, thigh flexion, knee flexion, walking, and staircase climbing). The maximal value at each time point was used in the analysis of dynamic pain ratings. On day 10, the sutures were removed, and the investigator, unaware of the preoperative results, reviewed the pain diary with the patient.

Statistical Analyses

Data distribution was evaluated for normality by the Kolmogorov-Smirnov test, version 10.0.7 (SPSS, Inc., Chicago, IL). Analyses of VAS ratings over time were based on the area under the curve (AUC; VAS · h). Baseline data before the burn and before surgery were compared with corresponding data after the burn and after surgery by using the Wilcoxon signed-rank test. In multiple comparisons, the Bonferroni correction was used. For bivariate rank correlation analysis, Spearman ρ was used. Values are recorded as median, with 95% CI in parentheses. $P < 0.05$ was considered to be statistically significant.

Results

Six women and 14 men with a median age of 28 yr (24–33 yr) were studied. No complications related to the burn injury or surgery were observed.

Preoperative Assessments

Preoperative median dynamic and resting pain ratings were 6 (VAS, 0–13) and 0 (VAS, 0–5), respectively. The median pain rating during the burn injury was 28 (VAS, 21–45). The burn injury caused significant hyperalgesia, leading to significant decreases in mechanical pain threshold (from von Frey No. 18 [18–18 von Frey No.] to 15 [14–17 von Frey No.], $P < 0.0001$) and heat pain threshold (from 46.3°C [43.9°–47.9°C] to 41.7°C [40.2°–43.8°C], $P < 0.00001$) and significant increases in mechanical pain perception (from 1 [VAS, 0–9] to 18 [VAS, 10–30], $P < 0.0003$) and heat pain perception (from 16 [VAS, 6–27] to 51 [VAS, 38–65], $P < 0.00001$). All patients developed circumscript secondary hyperalgesia with a median area of 52 cm^2 (41–77 cm^2).

Postoperative Pain Ratings

The median dynamic pain rating increased significantly after surgery to 47 (VAS, 26–69, $P < 0.01$, Bonferroni corrected) on days 0–2 and to 33 (VAS, 18–62, $P < 0.02$) on days 3–10. The median resting pain rating increased significantly after surgery to 33 (VAS, 16–47, $P < 0.0001$, Bonferroni corrected) on days 0–2 and to 9 (VAS, 4–34, $P < 0.002$) on days 3–10. Dynamic pain ratings were at all time points significantly higher than resting pain ratings (VAS, $P < 0.01$, Bonferroni corrected).

Correlations

Correlation analysis showed a significant relationship between the preoperative pain ratings (AUC, VAS · h) during the burn injury and the postoperative dynamic pain ratings (AUC, VAS · h) on days 0–2 (Spearman ρ, 0.65 [0.30–0.85], $P < 0.01$) and days 3–10 (Spearman ρ, 0.57 [0.17–0.81], $P < 0.01$) (figs. 1 and 2). The corresponding analyses of preoperative pain ratings (AUC, VAS · h) during the burn injury and postoperative resting pain ratings (AUC, VAS · h) also showed a significant correlation on days 0–2 (Spearman ρ, 0.60 [0.21–0.81], $P < 0.01$) and days 3–10 (Spearman ρ, 0.59 [0.20–0.82], $P < 0.01$).

The correlations between the preoperative assess-

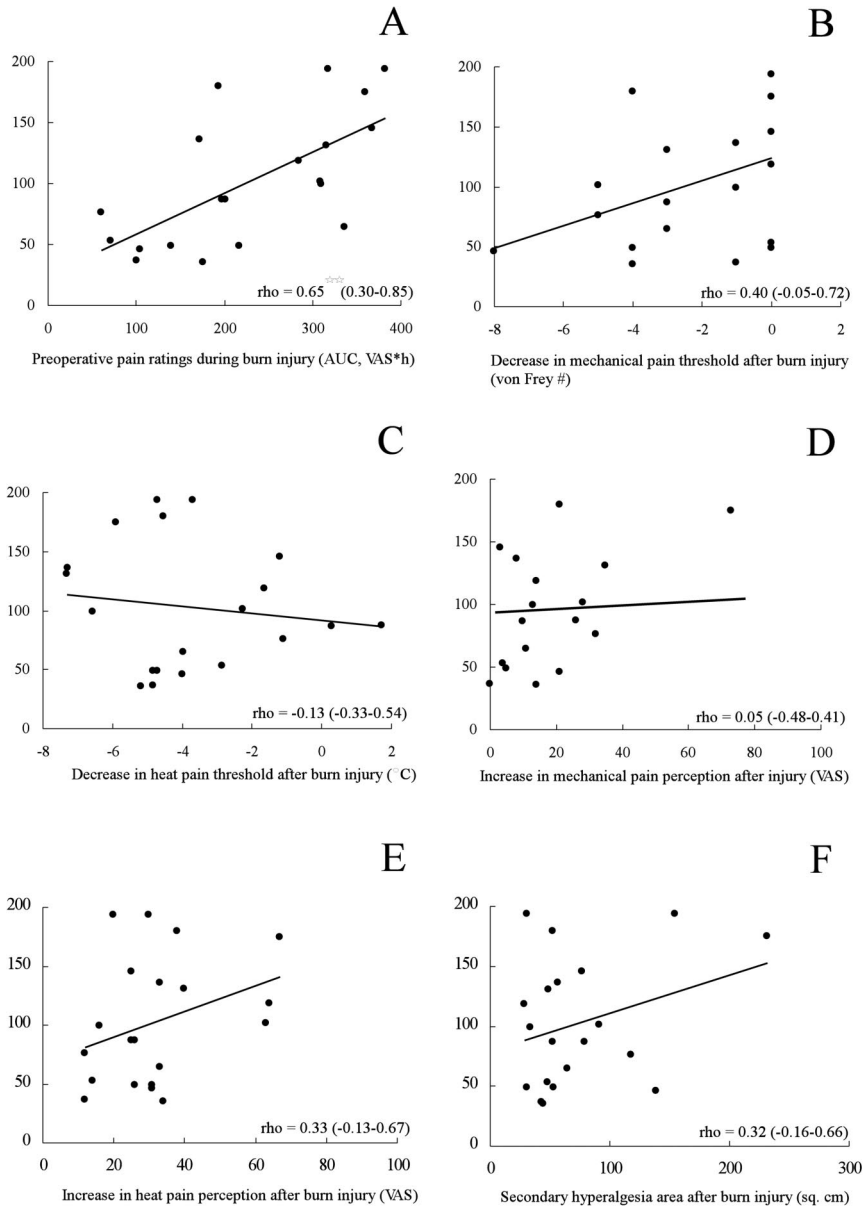

Fig. 1. Correlation between early (0–2 days) postoperative dynamic pain ratings (visual analog scale [VAS], area under the curve [AUC] [VAS · h], *ordinate*) and preoperative sensory assessments after the burn injury (*abscissa*): pain ratings during preoperative burn injury (*A*, VAS, AUC [VAS · h], Spearman ρ [95% CI], $^{**}P < 0.01$), decrease in mechanical pain threshold (*B*, von Frey No., not significant), decrease in heat pain threshold (*C*, not significant), increase in mechanical pain perception (*D*, °C, not significant), increase in heat pain perception (*E*, VAS, not significant), and area of secondary hyperalgesia (*F*, cm^2, not significant).

ments of changes (postburn − preburn values) in mechanical pain threshold, heat pain threshold, mechanical pain perception, heat pain perception, and area of secondary hyperalgesia, and the postoperative pain ratings were not statistically significant (figs. 1 and 2; only data for dynamic pain ratings are shown). There were no significant correlations between preoperative and postoperative pain ratings at rest ($P > 0.1$, Bonferroni corrected) or during dynamic conditions ($P > 0.1$, Bonferroni corrected).

Discussion

This study shows, for the first time, that nociceptive responses to a preoperatively applied, controlled heat injury have a significant predictive value in assessing pain responses after arthroscopic knee surgery. The predictive power is much higher than that reported previously in relation to age, gender, anxiety,[12] depression,[13] neuroticism,[3,4,7–9] and sensitivity to a cold pressor test.[4]

The preoperative heat injury is associated with an inflammatory response[10] and induces an integrated psychophysical pain response comparable to the pain response after the larger surgical injury. It is noteworthy that the pain responses during application of the heat injury correlated best with subsequent postoperative pain responses, whereas more elaborate assessments of nociceptive function by heat and mechanical pain thresholds and by development of secondary hyperalgesia showed less predictive value. Although the postinjury neuroplastic response mediating secondary hyperalgesia has been hypothesized to increase pain,[1] other studies

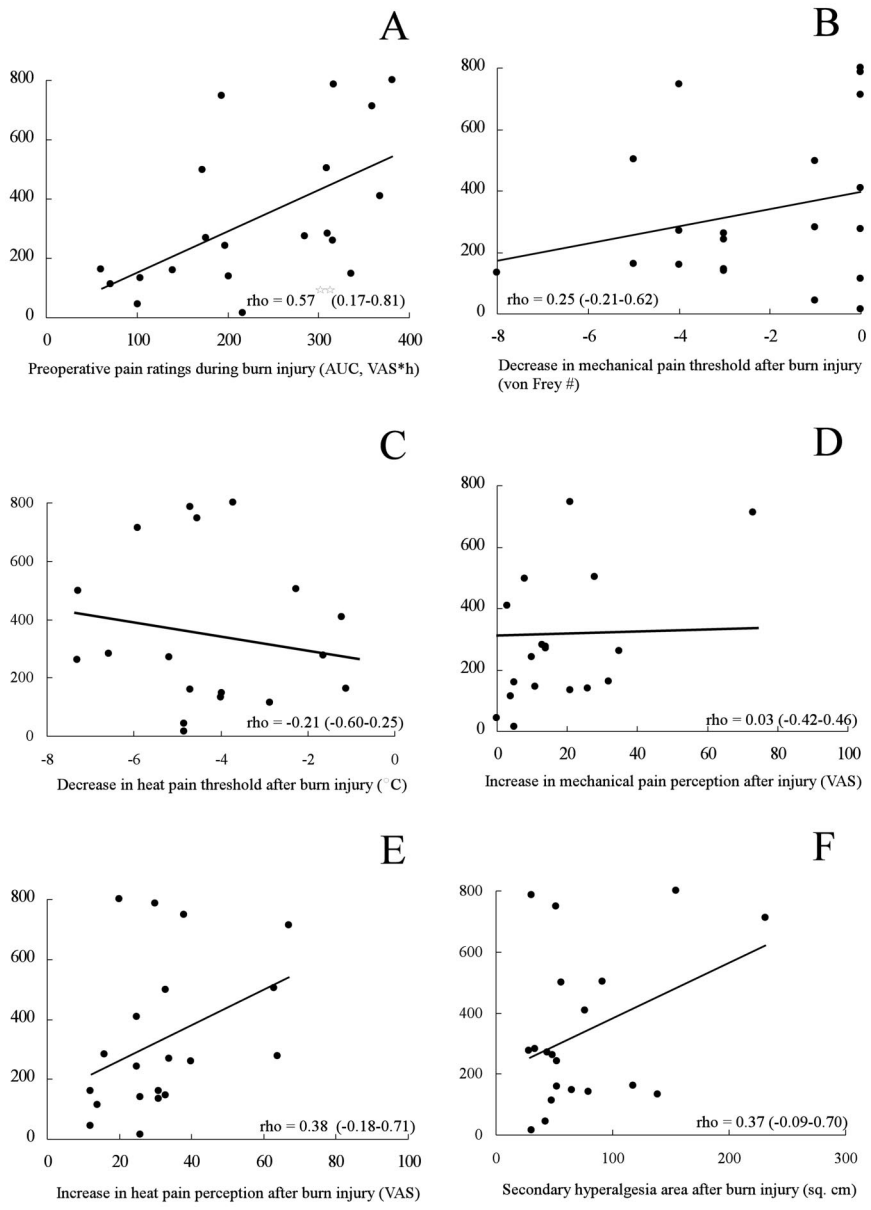

Fig. 2. Correlation between late (3–10 days) postoperative dynamic pain ratings (visual analog scale [VAS], area under the curve [AUC] [VAS · h], *ordinate*) and preoperative sensory assessments after the burn injury (*abscissa*): pain ratings during preoperative burn injury (*A*, VAS, AUC [VAS · h], Spearman ρ [95%CI], ** $P < 0.01$), decrease in mechanical pain threshold (*B*, von Frey No., not significant), decrease in heat pain threshold (*C*, not significant), increase in mechanical pain perception (*D*, °C, not significant), increase in heat pain perception (*E*, VAS, not significant), and area of secondary hyperalgesia (*F*, cm^2, not significant). The only significant correlation observed was with pain ratings during preoperative burn injury (*A*, ** $P < 0.01$).

with surgical patients have also shown a lack of relationship between incisional hyperalgesia and postoperative pain intensity.[14]

Our study does not allow separation into the relative role of the various factors responsible for the wide variation in patient experience of pain to a well-defined injury.[2] Obviously, further studies are needed to assess the differential role of the peripheral and spinal mechanisms of pain and cortical representation.[15]

Our findings, when confirmed, may have important clinical implications because this simple test, or modifications thereof, could be applied to identify those patients at risk for developing high-intensity postoperative pain. Such stratification of patients may be important in allocating treatment resources to patients at risk and in identifying relevant groups of individuals to be included in trials of new analgesics. Thus, previous studies have usually consisted of a nonselective group of individuals, which may include relatively low pain responders, thereby introducing lower sensitivity in the trials and consequently requiring larger study samples to interpret the results. Finally, our results may lead to the development of preoperative methods of identifying patients prone to moderate- to high-intensity postoperative pain, because such patients have been shown to be at a higher risk for the development of chronic pain.[6,16] Thus, preoperative identification of such high-risk patient populations for developing chronic pain may facilitate studies of the effect of early aggressive analgesic therapy to reduce the development of chronic pain.[6]

In summary, this study in a limited number of patients with relatively small, well-defined surgical injury indi-

cates a predictive value of nociceptive responses to a preoperative heat injury in the assessment of intensity of acute postoperative pain. This simple technique may have potential in future studies on acute pain physiology and pain therapy.

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