Anesthesiology 2003; 99:1152–7

Arthroscopic Knee Surgery Does Not Modify Hyperalgesic Responses to Heat Injury

Mads U. Werner, M.D., Ph.D., Preben Duun, M.D.,† Otto Kraemer, M.D.,† Birgit Lassen, R.N.A.,‡ Henrik Kehlet, M.D., Ph.D.§*

Background: **Experimental studies suggest that surgical injury may up- or down-regulate nociceptive function. Therefore, the aim of this clinical study was to evaluate the effect of elective arthroscopically assisted knee surgery on nociceptive responses to a heat injury.**

Methods: **Seventeen patients scheduled to undergo repair of the anterior cruciate ligament and 16 healthy controls were studied. The first burn injury was induced 6 days before surgery, and the second burn was induced 1 day after surgery with a contact thermode (12.5 cm^2, 47°C for 7 min) placed on the medial aspect of the calf contralateral to the surgical side. Ibuprofen and acetaminophen were given for 2 days before the first burn injury and again from the time of surgery. In the controls, the two burn injuries were separated by 7 days. Sensory variables included cumulated pain score during induction of the burn (visual analog scale), secondary hyperalgesia area, and mechanical and thermal pain perception and pain thresholds assessed before and 1 h after the burn injury.**

Results: **The heat injuries induced significant increases in pain perception ($P < 0.001$) and decreases in pain thresholds ($P < 0.02$). Baseline heat pain thresholds were higher during the second burn injury in patients ($P < 0.001$) and controls ($P < 0.01$). However, there were no significant differences in pain to heat injury ($P > 0.8$), secondary hyperalgesia areas ($P > 0.1$), mechanical and thermal pain perception ($P > 0.1$), or mechanical and thermal pain thresholds ($P > 0.08$) in the burn area before surgery compared to after surgery.**

Conclusion: **Arthroscopic knee surgery did not modify nociceptive responses to a contralaterally applied experimental burn injury.**

TISSUE injury is associated with peripheral and central changes in the nociceptive system leading to primary hyperalgesia in the inflammatory area and secondary hyperalgesia in neighboring noninjured tissue, which may contribute to an increase in pain perception.[1] These pain-sensitizing mechanisms have been well documented in the incisional area after surgery.[2–6] However, noxious stimulation *per se* may also attenuate pain perception by activation of supraspinal descending systems with widespread inhibition of nociceptive transmission in the spinal cord, *i.e.*, diffuse noxious inhibitory controls (DNICs) or stress-induced analgesia.[7,8] Few clinical studies have systematically evaluated nociceptive responses to various stimuli beyond the hyperalgesia territories associated with surgery. A study in hysterectomy patients of nociceptive electromyographic reflexes after electrical stimulation of the sural nerve indicated a decrease in pain threshold,[9] whereas a study in patients undergoing herniated disc surgery demonstrated an increase in electrical pain threshold.[10] In two studies using pressure algometry at a distant control site, no difference in pain thresholds was demonstrated preoperatively *versus* postoperatively.[2,11] However, in these studies, the stimulus has been of a noninflammatory origin. Therefore, the aim of the current study was to evaluate in detail the nociceptive responses to a validated burn model[12] applied before and after standardized knee surgery to assess whether nociceptive functions were up- or down-regulated postoperatively.

Materials and Methods

The protocol was approved by the regional Ethical Committee (Copenhagen, Denmark). After written informed consent, 18 medication-free, otherwise healthy patients scheduled to undergo arthroscopic repair of the anterior cruciate ligament on an outpatient basis and 16 healthy nonsurgical volunteers serving as controls were included. All subjects participated before inclusion in a 30-min training and information session and became familiar with the burn injury, quantitative sensory testing, and ratings of pain perception with a visual analog scale (VAS; scale, 0–100 mm; fig. 1). All sensory testing was performed in a quiet laboratory environment with a temperature of 21°–23°C. During measurements, the subjects rested comfortably in a reclined chair and were not aware of results of the sensory testing during any part of the study.

Study Design

The number of subjects required to demonstrate a difference of 20% of the mean for thermal and mechanical pain thresholds and secondary hyperalgesia areas between study days was calculated to be 16 for $2\alpha = 0.05$ (type I error of 5%) and $\beta = 0.20$ (type II error of 20%, *i.e.*, a power of 80%) based on a methodologic study of the burn model.[12] Eighteen patients were chosen to account for potential dropouts.

* Director of Acute Pain Service, Department of Anesthesiology, † Assistant Professor, Department of Orthopedic Surgery, ‡ Research Associate, Acute Pain Laboratory, Departments of Anesthesiology and Surgical Gastroenterology, § Professor, Department of Surgical Gastroenterology.

Received from the Departments of Anesthesiology, Orthopedic Surgery, and Surgical Gastroenterology, Hvidovre University Hospital, Copenhagen, Denmark. Submitted for publication October 9, 2002. Accepted for publication April 22, 2003. Supported by grant No. 22010160 from the Danish Medical Research Council, Copenhagen, Denmark. Presented in part at the World Congress of the International Association for the Study of Pain, San Diego, California, August 21, 2002.

Address reprint requests to Dr. Werner: Department of Oncology, University Hospital, SE 221 85 Lund, Sweden. Address electronic mail to: madswerner@medscape.com.

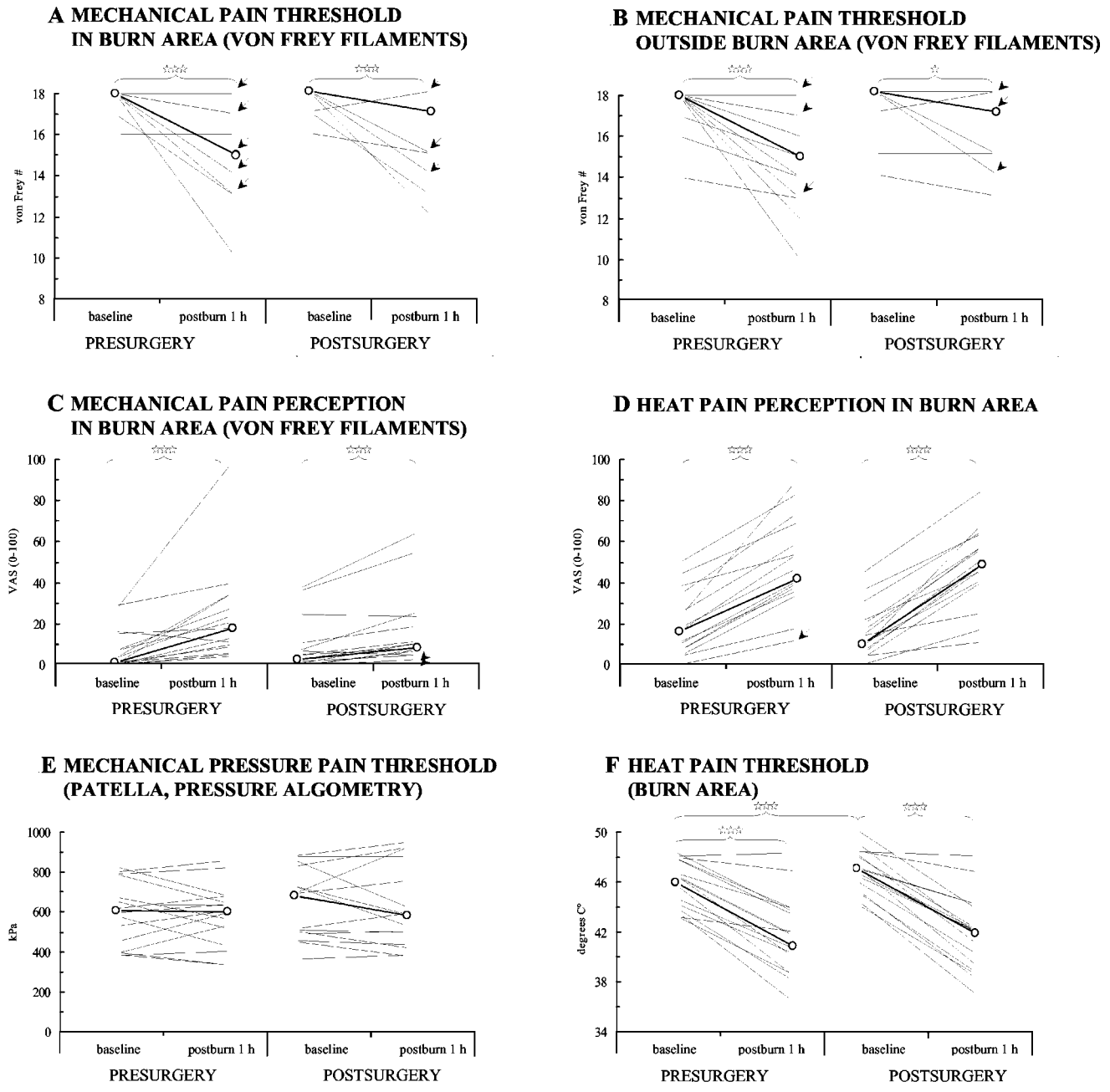

Fig. 1. Presurgery *versus* postsurgery sensory assessments after burn injury. Assessments were made before (*baseline*) and 1 h after (*postburn 1 h*) the burn injury. (*A*) Mechanical pain threshold in the burn area (von Frey monofilaments), (*B*) mechanical pain threshold outside the burn area (von Frey monofilaments), (*C*) mechanical pain perception in burn area (von Frey monofilaments), (*D*) heat pain perception in burn area, (*E*) pressure pain threshold (patella, pressure algometry), and (*F*) heat pain threshold (*lines with circles* = median; *stars* = $P < 0.005$; *arrows* = coincidence of data sets). VAS = visual analog scale.

In all subjects, the two burn injuries were separated by 7 days. In the patients, the first burn injury was induced 6 days before surgery, and the second burn was induced 1 day after surgery. All patients received, for 2 days before the first burn injury, the standard postoperative pain treatment with 800 mg ibuprofen every 8 h and 1 g acetaminophen every 6 h. The control volunteers were unmedicated. Assessments on the two study days were identical and included, in chronological order, assessment of area of secondary hyperalgesia, mechanical pain threshold for punctate stimuli, mechanical pain perception for punctate stimuli, heat pain threshold, heat pain perception, and mechanical pressure pain threshold. Assessments were obtained immediately before (baseline) and 1 h after induction of the burn injury.

Burn Procedure

Burn injuries were induced on the medial aspect of the calf contralateral to the surgical side in the patients and on the nondominant side in the nonsurgical volunteers

with a 25 × 50-mm thermode (Modular Sensory Analyzer; Somedic AB, Hörby, Sweden), as previously described.[12] The areas were carefully delineated with a ruler, and both burn injuries were made on the same location. The thermode was applied for 7 min at 47°C with standardized pressure (49 mmHg), causing a first-degree burn injury. Subjects rated pain intensity on a horizontal VAS (0–100 mm), anchored by "no pain" (0 mm) and "the worst imaginable pain" (100 mm), at the start of the injury and every minute during the burn.

Mechanical Assessments

The area of secondary hyperalgesia developing around the burn injury was assessed by a rigid von Frey monofilament (nominal buckling force 640 mN [No. 17]; Senselab Aesthesiometer; Somedic AB). The border was determined by stimulating well outside the area along eight linear paths converging toward the central part of the burn.[13] The patient was instructed to indicate a definite change to discomfort or pain during stimulation. The eight demarcating points of mechanical secondary hyperalgesia were traced onto a transparent acetate sheet, and the areas were calculated using a vector-based algorithm (Meditec®; Meditec, Copenhagen, Denmark).

The mechanical pain threshold within the burn area and 3–5 mm outside the burn area was assessed by stimulation with progressively rigid calibrated von Frey monofilaments in ascending order starting with No. 10 (No. 10 = 15 mN, No. 11 = 27 mN, No. 12 = 46 mN, No. 13 = 82 mN, No. 14 = 130 mN, No. 15 = 296 mN, No. 16 = 393 mN, No. 17 = 640 mN; Senselab Aesthesiometer). The *mechanical pain threshold* was defined as the lowest force that elicited a sensation of pain or discomfort. Eight stimuli applied with a rate of 0.5 Hz were made with each von Frey filament until at least four of the stimuli caused pain or discomfort. From this initial threshold, the up-and-down method was used for two additional assessments.[14] The median of the three assessments was reported as the mechanical pain threshold. If von Frey filament No. 17 did not elicit a sensation of pain or discomfort, the observation was assigned the value of 18.

The mechanical pain perception (VAS, 0–100 mm) was assessed by five stimuli of a rigid von Frey filament (No. 17) in the burn area and 3–5 mm outside the burn area. Pressure pain threshold was assessed with a handheld electronic pressure algometer (Somedic AB) with a circular stimulation probe (0.28 cm^2) applied at the superior margin of the ipsilateral patella at an angle of 45° to the skin with the supported knee in 45° flexion.[11] Pressure was increased by 75 mmHg s^{-1}, and the patient was instructed to indicate when the sensation changed to pain. Pressure pain thresholds were assessed in triplicate, and the median value was used in the analysis.

Thermal Assessments

The heat pain threshold was assessed by the 12.5-cm^2 thermode in the burn area,[13] and the subjects were instructed to indicate when the sensation of warmth changed to pain. Assessments were made in triplicate with randomized interstimuli intervals of 4–6 s, starting from a baseline temperature of 32°C, with a ramp rate of 1°C/s and a cutoff limit of 50°C. Heat pain perception (VAS) was evaluated with a 10-s 45°C heat stimulus in the burn area with an initial ramp rate from baseline temperature of 2.5°C/s.

Anesthesia, Surgery, and Postoperative Analgesia

Premedication was not given. Induction of anesthesia was with 2–3 mg/kg propofol and 1–2 μg/kg sufentanil, and ventilation was with air in oxygen (fraction of inspired oxygen [F_{IO_2}] = 0.4). Anesthesia was maintained with an infusion of 3–4 mg/kg propofol and incremental doses of 0.5–1.0 μg/kg sufentanil. The repair of the anterior cruciate ligament was performed by a standardized three-incision approach, transarthroscopically assisted, using autograft bone–patella–tendon–bone fixated by titanium interference screws. At the end of surgery, 40 ml bupivacaine, 2.5 mg/ml, was given intraarticularly and incisionally followed by 30 mg ketorolac intravenously. Postoperative analgesia was with 800 mg oral ibuprofen every 8 h and 1 g acetaminophen every 6 h.

Statistical Analysis

Presurgery data, *i.e.*, baseline and changes from baseline (1 h after burn − baseline), were compared with corresponding postsurgery data using the Wilcoxon signed-rank test. Comparisons of VAS measurements during the burn were based on the area under curve. Values are median (25%–75% interquartile range) unless otherwise stated. $P < 0.05$ was considered statistically significant.

Results

Demographics

Data from one patient (patient 10) were excluded because of readmission on day 1 after surgery because of severe anxiety and pain. Therefore, the second burn injury was not made. The median ages of the patients and the controls were 27 (25–32) and 31 (27–40) yr, respectively ($P > 0.1$). The male/female ratio was 14/4 for the patients and 13/1 for the controls ($P > 0.2$).

Preburn Assessments

Resting pain (VAS) on the morning before the presurgery burn injury was 1 (0–5) and before the postsurgery burn injury, 40 (21–69) ($P < 0.0001$). Baseline values for the presurgery burn injury compared to the postsurgery

Table 1. Sensory Assessments in the Control Group

	First Burn Injury		Second Burn Injury		*P* Values	
	Baseline	1 h after Burn	Baseline	1 h after Burn	Comparison of Baseline Values	Comparison of Δ Values
Mechanical pain threshold in burn von Frey No.	18 (17–18)	15 (13–15)	18 (18–18)	15 (15–16)	0.16	0.08
Mechanical pain threshold outside burn, von Frey No.	18 (18–18)	15 (14–15)	18 (17–18)	15 (14–16)	0.45	0.12
Mechanical pain perception in burn, VAS	8 (5–14)	36 (27–43)	4 (3–11)	27 (17–41)	0.30	0.13
Heat pain threshold, °C	43.8 (42.3–46.0)	40.9 (39.1–44.2)	47.1 (43.1–49.0)	43.1 (41.5–45.3)	0.01	0.92
Heat pain perception, VAS	24 (21–33)	50 (36–60)	12 (7–25)	40 (29–62)	0.001	0.05
Pressure pain threshold, mm Hg	4,188 (3,698–4,988)	4,185 (3,645–5,258)	4,718 (3,608–5,760)	4,515 (3,045–5,265)	0.30	0.16
Pain perception during burn, VAS*	25 (24–30)		29 (21–36)		0.20	—
Secondary hyperalgesia area, cm^2	—	75 (60–92)	—	103 (61–146)	0.41	—

n = 16.

* Scale: 0–100 mm.

Δ Values = (1 h after burn − baseline) values; VAS = visual analog scale (score); von Frey No. = number of von Frey monofilaments.

burn injury did not differ in regard to mechanical pain threshold and pain perception to punctate stimuli (figs. 1A–C, $P > 0.1$), heat pain perception (fig. 1D, $P = 0.06$), or mechanical pressure pain threshold (fig. 1E, $P > 0.2$). However, postsurgery baseline values for heat pain threshold, 47.0°C (45.9°–48.1°C), were significantly higher compared to presurgery values, 46.0°C (44.3°–47.9°C) (fig. 1F, $P < 0.001$).

In the control group, there was no difference in baseline values for mechanical pain threshold, mechanical pain perception, or mechanical pressure pain threshold, but a significant increase in heat pain threshold (table 1, $P = 0.01$) and a significant decrease in heat pain perception (table 1, $P = 0.001$) were observed.

Pain during Induction of Burn

There was no difference in median VAS scores during induction of the presurgery burn injury compared to the postsurgery burn injury, 28 (20–45) *versus* 29 (22–34), respectively (fig. 2A, $P > 0.8$). In the control group, the median VAS score during the first and second burn injuries was 25 (24–30) and 29 (21–36), respectively ($P > 0.2$).

Postburn Assessments

All patients developed circumscript areas of secondary hyperalgesia with no significant difference between the first and second burns (fig. 2B, $P > 0.1$). Mechanical pain threshold for punctate stimuli decreased significantly in the burn area and outside the burn area (figs. 1A and B, $P < 0.02$) but without differences between the preoperative and postoperative burns ($P > 0.08$). Mechanical pain perception increased significantly (fig. 1C, $P < 0.001$) after both burn injuries but without differences between preoperative and postoperative assessments ($P > 0.1$). The burn injuries induced a significant decrease in heat pain threshold (fig. 1F, $P < 0.0001$) and a significant increase in heat pain perception (fig. 1D, $P < 0.0001$) but without differences between the preoperative and the postoperative assessments ($P > 0.5$). The mechanical pressure pain thresholds did not differ before and after surgery (fig. 1E, $P > 0.8$).

In the control group, the burn injuries induced secondary hyperalgesia and significant changes in mechanical pain threshold ($P < 0.0001$), mechanical pain perception ($P < 0.002$), heat pain threshold ($P < 0.001$), and heat pain perception ($P < 0.0001$) but without

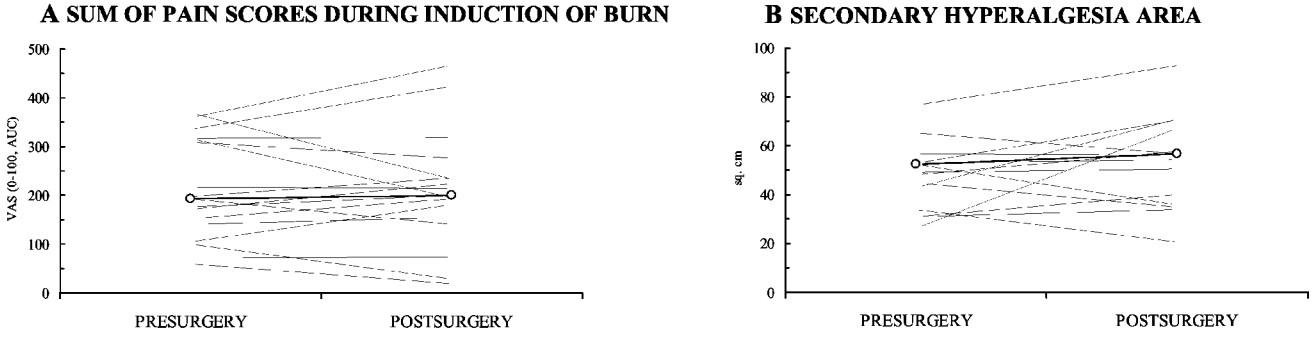

Fig. 2. Presurgery *versus* postsurgery (*A*) sum of pain scores during induction of burn injury (area under the curve [AUC], median) and (*B*) secondary hyperalgesia areas. VAS = visual analog scale.

significant changes between the first and second burn injuries (table 1).

Discussion

The main finding of this study was that arthroscopic knee surgery did not seem to modify hyperalgesic responses to an experimental heat injury applied at a site distant to the incisional area. We are not aware of any previous study systematically examining effects of surgery on nociceptive responses to a controlled inflammatory injury. The first-degree burn injury model, which is consistently associated with development of primary and secondary hyperalgesia, has been validated[12] and used in a number of physiologic and pharmacodynamic studies.[13]

Interpretation of the postoperative data requires careful comparison with data from the control group. Although nearly all sensory parameters were unchanged after surgery, a highly significant postoperative increase in baseline heat pain detection threshold was seen. This was also observed in the control group, and therefore, the increase in baseline value does not seem related to surgery *per se* but more likely represents habituation. A decrease in heat pain threshold has previously been observed in the burn injury model even when two burn injuries were made 21 days apart.[12] A significant decrease in baseline heat pain perception, probably also due to habituation, was observed in the control group, and a similar trend was noted in the surgical group ($P = 0.06$). Data from the control group thus corroborate our findings that arthroscopic knee surgery does not seem to modify hyperalgesic responses to an experimental inflammatory injury.

Evaluation of punctate pain thresholds with von Frey monofilaments does have its limitations because in a number of patients, even the most rigid monofilament (No. 17) did not evoke pain or discomfort at baseline measurements ($n = 14$) or at postburn measurements ($n = 4$). These patients were assigned an arbitrary value of 18.[12] Thus, pain thresholds could be regarded as a composite measure of hyperalgesia, *i.e.*, in patients with a baseline threshold of 17 or less, or allodynia, *i.e.*, in patients with a baseline threshold of 18. However, in 16 patients and all controls, the method demonstrated an adequate sensitivity by demonstration of an increase in pain perception after the burn injury.

Studies of postoperative neuroplasticity responses differ in regard to testing algorithms, stimulation methods, and stimulation sites.[2–4,6,9–11,15–21] Our findings are in general agreement with two studies of patients undergoing herniorrhaphy[2] and hysterectomy[11] using pressure algometry in the incisional area and in a distant area. In both of these studies, no difference between preoperative and postoperative pain thresholds at the control site was demonstrated. In another hysterectomy study with von Frey monofilaments, no change in touch detection threshold or pain threshold was observed in the control area postoperatively.[19] However, this study only reported relative values and may have lacked sensitivity because no significant changes in sensory thresholds in the incisional area were observed after surgery. Thermal thresholds and thermal pain thresholds have been tested in dental surgery.[22] Thresholds in skin overlying the pain area did not differ from a contralaterally control area, but unfortunately, no preoperative control was reported. In a study of abdominal surgery with preoperative controls, both thermal and heat pain thresholds adjacent to the surgical incision decreased after surgery,[23] while no differences were observed at a distant control site. There was no change in mechanical thresholds.

The findings of an essentially unchanged postoperative sensitivity to mechanical and thermal stimulation of the skin distant to the surgical site are in contrast with a number of studies with electrical nerve stimulation, which have demonstrated an increase[15] or no change[9] in electromyographic reflex threshold,[18] an increase in sensory threshold,[10,17] an increase in pain threshold,[10,18] or a reduced pain threshold[9] after surgery. These discrepancies are not easy to reconcile, but painful mechanical and thermal stimuli activate nociceptors and low-threshold afferents, while electrical stimulation directly activates nerve fibers, including larger Aβ fibers.[9] Thus, activity in large diameter fibers may suppress or facilitate nociceptive transmission depending on the sensitization state of dorsal horn neurons.[1] Furthermore, pain *per se*[15] and analgesics, opioids[15] and paracetamol,[24–26] may affect reflex thresholds and electrical pain thresholds, making interpretation in a postoperative setting difficult.

In the current study, we sought to compensate for any effect of analgesics on sensory and pain thresholds by administering the standard postoperative pain treatment, paracetamol and ibuprofen, for 2 days before the presurgery burn injury. The possibility of residual effects of the opioid-based anesthesia on sensory assessments in association with the postsurgery burn injury cannot be excluded, but it seems unlikely considering the pharmacokinetics and the small doses of sufentanil used. Furthermore, such single-dose interventions have not been shown to alter postoperative pain responses, as demonstrated from a number of randomized studies of preemptive analgesia.[27]

Decreases in mechanical pain thresholds in the incisional or periincisional areas are well documented.[2–4,6,11,21] In the current study, assessments were made in a contralateral segment to the surgical injury, and it may be argued that posttraumatic changes in nociceptive function predominantly takes place in the ipsilateral segment of injury, thereby explaining our negative findings. However, several experimental studies have indicated a central hyperexcitability of the contralateral flexor reflex after

injury.[28–30] In animal preparations, it has been observed that noxious heating of the skin may activate α-motoneurons in a contralateral segment,[31] indicating the potential of a "cross-talk" at the spinal level. In addition, intense noxious stimulation may activate the DNIC system and produce a powerful and widespread heterotopic inhibition of wide dynamic range neurons in the dorsal horn.[32] DNIC-like effects have been induced in experimental[33] and clinical pain.[34] Activation of DNIC requires a high-intensity nociceptive input, and it may be argued that the postoperative pain before the second postsurgery burn injury was of too low an intensity to activate DNIC because of the relatively small trauma of arthroscopic surgery. In a study of ischemia-induced DNIC on experimental, electrically induced pulpal pain,[35] the pain intensity of the conditioning stimulus was 59 (VAS, 0–100 mm) compared to the surgical pain of 40 before the second burn injury in the current study. However, in the current study, knee surgery caused clinically significant postoperative pain and was therefore expected to induce functional changes at the spinal level.

The impression that a segmental nociceptive input may generate effects beyond the hyperalgesia territories is corroborated by recent findings that injury-induced neuroplastic changes with c-fos generation[36] and generation of cyclooxygenase 2 in the spinal cord takes place in both the ipsilateral and contralateral sides.[37]

In conclusion, arthroscopic knee surgery did not modify nociceptive responses to a contralateral experimental burn injury.

References

1. Dickenson AH: Gate control theory of pain stands the test of time. Br J Anaesth 2002; 88:755–7
2. Dahl JB, Rosenberg J, Molke JF, Kehlet H: Pressure pain thresholds in volunteers and herniorrhaphy patients. Acta Anaesthesiol Scand 1990; 34:673–6
3. Richmond CE, Bromley LM, Woolf CJ: Preoperative morphine pre-empts postoperative pain. Lancet 1993; 342:73–5
4. Tverskoy M, Oz Y, Isakson A, Finger J, Bradley EL Jr, Kissin I: Preemptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. Anesth Analg 1994; 78:205–9
5. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A: Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997; 41:1124–32
6. Ilkjaer S, Bach LF, Nielsen PA, Wernberg M, Dahl JB: Effect of preoperative oral dextromethorphan on immediate and late postoperative pain and hyperalgesia after total abdominal hysterectomy. Pain 2000; 86:19–24
7. Danziger N, Rozenberg S, Bourgeois P, Charpentier G, Willer JC: Depressive effects of segmental and heterotopic application of transcutaneous electrical nerve stimulation and piezo-electric current on lower limb nociceptive flexion reflex in human subjects. Arch Phys Med Rehabil 1998; 79:191–200
8. Kosek E, Ordeberg G: Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. Pain 2000; 88:69–78
9. Dahl JB, Erichsen CJ, Fuglsang-Frederiksen A, Kehlet H: Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers. Br J Anaesth 1992; 69:117–21
10. Wilder-Smith OH, Tassonyi E, Senly C, Otten P, Arendt-Nielsen L: Surgical pain is followed not only by spinal sensitization but also by supraspinal antinociception. Br J Anaesth 1996; 76:816–21
11. Moiniche S, Dahl JB, Erichsen CJ, Jensen LM, Kehlet H: Time course of subjective pain ratings, and wound and leg tenderness after hysterectomy. Acta Anaesthesiol Scand 1997; 41:785–9
12. Pedersen JL, Kehlet H: Hyperalgesia in a human model of acute inflammatory pain: A methodological study. Pain 1998; 74:139–51
13. Pedersen JL: Inflammatory pain in experimental burns in man. Dan Med Bull 2000; 47:168–95
14. Dixon WJ: The up-and-down method for small samples. Am Stat Assoc J 1965; 60:967–78
15. Willer JC, Bergeret S, Gaudy JH: Epidural morphine strongly depresses nociceptive flexion reflexes in patients with postoperative pain. ANESTHESIOLOGY 1985; 63:675–80
16. Ekblom A, Hansson P: Pain intensity measurements in patients with acute pain receiving afferent stimulation. J Neurol Neurosurg Psychiatry 1988; 51: 481–6
17. Lund C, Hansen OB, Kehlet H: Effect of surgery on sensory threshold and somatosensory evoked potentials after skin stimulation. Br J Anaesth 1990; 65:173–6
18. Peters ML, Schmidt AJ, Van den Hout MA, Koopmans R, Sluijter ME: Chronic back pain, acute postoperative pain and the activation of diffuse noxious inhibitory controls (DNIC). Pain 1992; 50:177–87
19. Collis R, Brandner B, Bromley LM, Woolf CJ: Is there any clinical advantage of increasing the pre-emptive dose of morphine or combining pre-incisional with postoperative morphine administration? Br J Anaesth 1995; 74:396–9
20. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A: Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997; 41:1124–32
21. McConaghy PM, McSorley P, McCaughey W, Campbell WI: Dextromethorphan and pain after total abdominal hysterectomy. Br J Anaesth 1998; 81:731–6
22. Ekblom A, Hansson P: Thermal sensitivity is not changed by acute pain or afferent stimulation. J Neurol Neurosurg Psychiatry 1987; 50:1216–20
23. Weinbroum AA, Gorodezky A, Niv D, Ben Abraham R, Rudick V, Szold A: Dextromethorphan attenuation of postoperative pain and primary and secondary thermal hyperalgesia. Can J Anaesth 2001; 48:167–74
24. Piguet V, Desmeules J, Dayer P: Lack of acetaminophen ceiling effect on R-III nociceptive flexion reflex. Eur J Clin Pharmacol 1998; 53:321–4
25. Piletta P, Porchet HC, Dayer P: Central analgesic effect of acetaminophen but not of aspirin. Clin Pharmacol Ther 1991; 49:350–4
26. Carnes PL, Cook B, Eleazer PD, Scheetz JP: Change in pain threshold by meperidine, naproxen sodium, and acetaminophen as determined by electric pulp testing. Anesth Prog 1998; 45:139–42
27. Moiniche S, Kehlet H, Dahl JB: A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: The role of timing of analgesia. ANESTHESIOLOGY 2002; 96:725–41
28. Woolf CJ: Evidence for a central component of post-injury pain hypersensitivity. Nature 1983; 306:686–8
29. Cook AJ, Woolf CJ, Wall PD, McMahon SB: Dynamic receptive field plasticity in rat spinal cord dorsal horn following C-primary afferent input. Nature 1987; 325:151–3
30. Hartell NA, Headley PM: Preparative surgery enhances the direct spinal actions of three injectable anaesthetics in the anaesthetized rat. Pain 1991; 46:75–80
31. Cook AJ, Woolf CJ: Cutaneous receptive field and morphological properties of hamstring flexor alpha-motoneurones in the rat. J Physiol 1985; 364: 249–63
32. De Broucker T, Cesaro P, Willer JC, Le Bars D: Diffuse noxious inhibitory controls in man: Involvement of the spinoreticular tract. Brain 1990; 113(pt 4):1223–34
33. Le Bars D, Willer JC, De Broucker T: Morphine blocks descending pain inhibitory controls in humans. Pain 1992; 48:13–20
34. Sigurdsson A, Maixner W: Effects of experimental and clinical noxious counterirritants on pain perception. Pain 1994; 57:265–75
35. Kojo I, Pertovaara A: Effect of tourniquet-induced ischemia on cutaneous thermal thresholds. Acta Neurol Scand 1986; 74:383–6
36. Ji RR, Woolf CJ: Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain. Neurobiol Dis 2001; 8:1–10
37. Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, Bonventre JV, Woolf CJ: Interleukin-1beta-mediated induction of COX-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 2001; 410:471–5