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Short title : Peripheral sensitization with orthopedic surgery

Implication statement : Peripheral sensitization plays important role in pain associated with knee arthroplasty, both in the pre and postoperative period

Abstract

Background: Quantitative sensory testing (QST), which allows a better characterization of sensory deficits and painful symptoms, may offer additional information on the pathophysiology of postoperative pain.

Methodology: Twenty patients scheduled for total knee anthroplasty were evaluated clinically and with QST before surgery, at one and four days, and at one and four months after surgery. Clinical evaluation included preoperative pain and inflammation of operative knee, postoperative assessment of pain at rest and during movement (Visual Analog Scale score), cumulative morphine consumption, and circumference and temperature of both knees. QST included thermal and mechanical (pressure) pain threshold measurements and assessment of responses to suprathreshold stimuli. Brush-evoked allodynia was also evaluated. Measurements were taken on the operative knee, contra lateral knee, and on the hand as a control site.

Results: All patients had prolonged and severe pain before surgery and inflammation of operative knee. **Preoperative QST provided evidence of heat hyperalgesia in the inflammatory area on the operative knee, but absence of punctate or brush-evoked allodynia in the adjacent non inflamed area**. Patients had intense postoperative pain, mostly induced by movement. **Primary heat hyperalgesia was present on the operative knee on the first and fourth days after surgery, and was associated with punctate mechanical allodynia**

in the inflammatory area, but not in the adjacent non inflamed area. Postoperative morphine consumption was correlated with preoperative heat hyperalgesia (r=0.63; *P*=0.01). QST was normalyzed at the 4-month evaluation and only 4 patients had moderate knee pain induced by movement at that time.

Conclusion: **Heat hyperalgesia was the predominant QST symptom associated with perioperative pain after total knee arthroplasty and was predictive of postoperative morphine consumption**

Key words: anesthesia, knee arthroplasty, quantitative sensory testing, primary hyperalgesia.

Introduction

Variation in patients' experiences with pain after similar types of surgical operations is well established (1, 2). Possible factors that may influence the postoperative pain intensity are preoperative pain intensity (3, 4), age (5), sex (4), the patient's personality characteristics (4) and education or information about the surgery (6). However, the role of these factors and the neurophysiological mechanisms by which they could interfere with the nociceptive systems remain elusive.

Postoperative pain involves not only peripheral mechanisms, most notably the sensitization of nociceptors due to inflammation, but also secondary central mechanisms, including hyperexcitability of nociceptive neurons (i.e., central sensitization) (7, 8). These mechanisms would play a major role in postoperative pain, including both spontaneous pain and allodynia (i.e. pain due to a stimulus which normally does not provoke pain) and/or hyperalgesia (i.e. an increased response to a stimulus which is normally painful) (7). In particular, peripheral sensitization would explain the hyperalgesia observed at the incision site (primary hyperalgesia), while central sensitization would provide a major mechanism of secondary hyperalgesia at distant non inflammatory sites (9-11).

Results from experimental studies in both animals and humans have suggested that heat and punctuate mechanical hyperalgesia are clinical correlates of the peripheral sensitization of nociceptors (mediated by A-delta and C fibers) in the inflamed primary hyperalgesia area (10, 12). In contrast, brush-evoked

pain (mechanical dynamic allodynia) observed in the non-inflamed area of secondary hyperalgesia, would best reflect the abnormal excitability of central nociceptive processing (i.e. central sensitization), since it is induced by the activation of large tactile A-beta fibers (10, 13). Detailed sensory examinations thus have the potential to identify underlying mechanisms of postoperative pain.

Quantitative sensory testing (QST), based on the measurements of detection and pain thresholds, is the best way to identify and quantify hyperalgesia. These psychophysical tests have already been used in the perioperative period and have proven valuable in assessing primary and secondary hyperalgesia (14-22).

The goal of the present study was to analyse further the influence of preoperative pain and hyperalgesia (primary and secondary) on early and chronic postoperative pain and to identify putative predictive factors of the severity of postoperative pain. We performed a prospective study with QST before and after total knee arthroplasty, combined with clinical evaluation of acute and chronic pain. Total knee arthroplasty was chosen because it is often associated with intense preoperative inflammatory pain that can develop into chronic pain (23).

Methods

Patients

With approval of the local ethics committee (Comité de Protection des Personnes, Boulogne Billancourt) and written informed consent, we recruited 20 consecutive patients scheduled for total knee arthroplasty. Inclusion criteria were total knee arthroplasty indicated because of knee arthrosis and surgery performed under general anesthesia. The exclusion criteria were previous surgery or trauma of the knee, preoperative use of opioids, or mental disorders preventing an accurate understanding of the tests.

Anesthesia, surgery, and postoperative pain relief

All patients were given hydoxyzine, 100 mg before surgery. Surgery was performed under balanced general anesthesia combining propofol, sufentanil, a muscle relaxant, and sevoflurane. The same surgeon performed each operation. Postoperative pain was controlled by intravenous morphine patient-controlled analgesia (PCA) in combination with intravenous acetaminophen (1 g every 6 hours; Perfalgan® UPSA-BMS laboratory, Rueil Malmaison, France) and nefopam, a non opioid analgesic drug (20 mg every 4 hours; Acupan® Biocodex Laboratory, Paris, France). Intravenous treatment was discontinued 48 hours after surgery. No patient was given a peripheral nerve block or non-steroidal anti-inflammatory drugs.

Study design

Clinical and quantitative sensory evaluations were performed on the operative knee, the contra lateral knee, and the right hand one day before surgery (D0), then at one day (D1), four days (D4), 1 month (M1), and 4 months (M4) after surgery.

Clinical evaluation

The circumference of both knees, as well as the surface temperature of the hand and both knees, was monitored at each follow-up visit. Skin temperature at each site was measured at the time of pain testing with Thermopoint device (Protechnique, Quebec). Pain was evaluated at rest and on movement (flexion/extension of the knee during physical therapy) by a 100-mm visual analog scale (VAS) graduated from 0 (no pain) to 100 mm (worst imaginable pain). Pain scores were recorded the day before surgery, then every 4 hours for 48 hours after surgery, at 4 days after surgery and at the follow-up visits at M1 and M4, and during all physical therapy sessions. The cumulative doses of morphine consumed via PCA were recorded at 24 and 48 hours. Physical therapy was started 24 hours after surgery with passive and active mobilization of the operative knee. The active angle of flexion was recorded during hospitalization and at the follow-up visits at M1 and M4. Chronic pain was defined as an operative knee VAS pain score > 30 mm at the M4 visit.

Quantitative sensory testing

Psychophysical testing was performed in a quiet room at a constant

temperature (22°C) by the same investigator (VM). Measurements included determination of thermal (heat and cold) and punctuate mechanical pain thresholds and the responses to suprathreshold thermal stimuli.

Mechanical pain thresholds were measured on the operated knee in the middle of the patella; 1 cm lateral to the midline. This location was chosen because in our patients it was always located in the area of maximal inflammation determined clinically (i.e. redness, swelling). Measurements were also taken in the adjacent non-inflamed area in the proximal direction, which in our patients was always located at least 5 cm above the top of the incision of the operative knee. We also investigated tactile allodynia (dynamic pain) using a paintbrush (three strokes). We considered tactile allodynia to be present if stroking the skin provoked a distinctly painful sensation.

Thermal pain threshold were measured on the operative knee in the area of maximal inflammation (i.e. in the middle of the patella; 1 cm lateral to the midline).

Control measurements for mechanical and thermal pain threshold were performed in two remote sites: the contra lateral knee (stimulation on the patella; 1 cm lateral to the midline) and the palmar aspect of the right hand.

Mechanical pain threshold

Pain thresholds for punctuate mechanical stimuli were assessed using calibrated von Frey hairs (Bioseb, Chaville France). Care was taken to avoid

stroking the skin with the hair and to apply only a pressure stimulus. The patients were instructed to close their eyes during the procedure. The von Frey filaments were applied (at least twice) in ascending and descending order of stiffness. The pain threshold was defined as the lowest pressure the patient considered painful. The force required to bend the filaments (0.057 to 140 g) was converted into log units.

Thermal pain threshold

Thermal sensations were assessed with a Somedic thermotest (Somedic AB, Stockholm, Sweden), using the Marstock method (24). Briefly, a contact thermode of Peltier elements measuring 25 x 50 mm was applied to the skin. The baseline temperature of the thermode was adjusted to the patient's skin temperature. Thresholds were measured according to the method of limits described previously by Fruhstorfer et al (24): stimuli of increasing or decreasing intensities were applied; for each stimulus, the subject was instructed to press a button that reversed the thermal stimulation, as soon as the stimulation became painful, indicating the pain thresholds. The interval between stimuli was 15 to 20 seconds for hot stimuli and 20 to 30 seconds for cold stimuli. The maximum and minimum temperatures were set at 50 °C and 4 °C. A thermal rate of change of 1°C/sec was used. All thresholds were calculated as the average of three successive determinations.

Supraliminal thermal stimulation

A series of suprathreshold cold and hot thermal stimuli were applied

according to a method previously described in detail (25). Each stimulus had duration of 2 seconds and the intensity was increased above the pain threshold by 2 and 4°C for hot stimuli and decreased by 5°C below the pain threshold for cold stimuli. After each stimulus, patients were asked to rate the pain intensity on a VAS. The patients could stop the stimulus at any time. If a VAS score of 80 or more was reported with a lower intensity stimulus, greater stimuli were not applied. In these cases, the same VAS score was assigned to the higher stimulus intensity to allow analysis of the cumulative group data.

Statistical analysis

Data are expressed as means ± SEM. We used paired t-tests with a Bonferroni adjustment for multiple comparisons, for comparison of (circumference, temperature, pain thresholds) and Wilcoxon's signed ranked test for comparison of VAS scores. Relationships between two variables were tested using the Spearman correlation test. Repeated-measures ANOVA was used to analyze the stimulus-response curves obtained for suprathreshold mechanical or thermal stimuli. $P < 0.05$ was considered statistically significant.

Results

20 patients (1 man, 19 women) were included. Age was 69 ± 2 years old; weight was 74 ± 14 kilograms. Surgery duration was 115 ± 26 minutes. Before surgery, average pain induced by movement was severe [mean VAS score: 61 ± 6 mm (10-80)], whereas average pain at rest was mild [mean VAS score: 16 ± 4 mm (0-50)]. Pain had been present for an average of 3.8 ± 3.3 years (1-15). The circumference of the operative knee was significantly greater than the contra lateral knee (43 ± 1.3 cm versus 41.6 ± 1.2 cm, $P = 0.0003$) (Figure 1). However, skin temperature of the operative knee was similar to that of the contra lateral one (32.2 ± 0.3 versus 31.9 ± 0.5 °C) (Figure 2).

Preoperative quantitative sensory testing (QST)

The pain thresholds to heat, cold, and mechanical punctuate stimuli were similar on the operative knee, the contra lateral knee and the hand (Table 1). No brush-allodynia was observed in the inflamed or adjacent non inflamed areas.

The responses to suprathreshold heat stimuli were significantly increased on the operative knee compared with the contra lateral knee, indicating preoperative heat hyperalgesia (figure 3). In contrast, the responses to suprathreshold cold stimuli were similar on the two knees (results not shown).

Postoperative Clinical data

The intensity of postoperative pain on D1 and D4 was moderate at rest but severe (VAS score > 60) during movement (figure 4). In contrast, the mean pain

intensity, at rest or during movement, was very mild at M1 and M4 (Figure 4). At M4, four patients reported moderate pain (VAS score < 50) during movement. None of the preoperative or postoperative clinical data was predictive of persistent pain at M4.

Morphine use was 60 ± 18 mg (29-83) over the first 24 hours after surgery

Active operative knee flexion was 77 ± 5 degrees (40-95) on D4, 96 ± 2 degrees (70-100) at M1 and 106 ± 2 (85-125) degrees at M4.

Compared with the contra lateral knee, both the temperature and circumference of the operative knee were significantly greater from D1 to M1 (Figure 1, Figure 2). The maximum temperature increase in the operative knee was observed on D1; the maximum increase in circumference occurred on D4. By M4, both the temperature and circumference had returned to baseline values. Temperature was stable for the hand and the contra lateral knee throughout the measurement period.

Postoperative Quantitative sensory testing

In comparison with preoperative values, mechanical and cold pain thresholds were significantly decreased on the operative knee, in the immediate postoperative period, while heat pain threshold were not significantly altered (Table 1). These changes suggesting static punctuate mechanical and cold allodynia were observed in the inflammatory area, and not in the adjacent area, were no longer observed at M1 or M4. There was no brush allodynia in the

inflammatory operative area or adjacent area.

On D1 and D4, the responses to suprathreshold heat, but not cold, stimuli were increased on the operative side as compared with the contra lateral side (Figure 5 A and B). **The heat hyperalgesia response was not significantly different from that measured preoperatively and was not observed at M1 (Figure 5C) or M4.**

No significant changes in the thermal, mechanical pain thresholds, or responses to supraliminal thermal stimuli were observed in the postoperative period in the contra lateral knee or hand, confirming that hyperalgesia was strictly limited to the inflammatory area on the operated side.

Relationship between pre-and postoperative clinical and quantitative sensory data

No correlation was detected between preoperative clinical and quantitative sensory data. In particular there was no relationship between pain intensity (at rest or during movement) and heat hyperalgesia (i.e., VAS scores) or signs of inflammation measured by knee circumference and local temperature.

Preoperative pain intensity during movement directly correlated with postoperative pain intensity during movement at D1 (Rho = 0.6; $P = 0.02$) **(Figure 6 A),** but not at D4. No such correlation was observed for pain at rest.

No correlation was observed between preoperative thermal and

mechanical pain thresholds and postoperative clinical data. However, preoperative heat hyperalgesia (VAS scores) correlated with PCA morphine use over the first 24 hours (Rho = 0.63; $P = 0.01$) **(Figure 6 B).**

Discussion

In this prospective study, we systematically analyzed thermal and mechanical pain thresholds and the responses to suprathreshold thermal stimuli, applied locally and at distant sites, before and for up to 4 months after total knee arthroplasty. Preoperatively, all the patients reported knee pain that was more intense during movement concurrently with primary **heat** hyperalgesia, but not with secondary hyperalgesia. After surgery, intense pain, mostly during movement, was observed in the early but not late postoperative period, and coexisted with increased signs of local inflammation and primary hyperalgesia (i.e., local mechanical punctate allodynia, and heat hyperalgesia) but, again, not with secondary hyperalgesia. Our data, thus, show that heat hyperalgesia, reflecting primary hyperalgesia, is a predominant symptom of perioperative pain associated with total knee arthroplasty. The pathophysiological significance of this finding is supported by our finding that the intensity of heat hyperalgesia was predictive of postoperatve morphine consumption.

Before surgery, patients had prolonged pain that was associated with a characteristic inflammation of the operative knee, as indicated by swelling and increased temperature. Our QST analysis revealed that these inflammatory signs were associated with severe local heat hyperalgesia, but no other significant sensory alteration; in particular, there was no mechanical allodynia at distant sites. It has long been demonstrated, both in experimental and pathological models of inflammation in animals and humans, that heat hyperalgesia is mostly

due to the sensitization of peripheral nociceptors by pronociceptive mediators released locally in inflamed tissue (e.g., prostaglandins, cytokines, bradykinin) (10, 12). Thus, in our patients, peripheral mechanisms may have been sufficient to explain preoperative chronic knee pain due to osteoarthritis. However, one cannot formally exclude on the basis of our study that non-clinically detectable secondary central processes also contributed.

Heat hyperalgesia was still present in the early postoperative period. Thus, peripheral sensitization may still be a predominant mechanism of postoperative pain. In accordance with this hypothesis, we found that preoperative heat hyperalgesia directly correlated with postoperative morphine consumption. Heat hyperalgesia was associated with postoperative punctuate mechanical allodynia in the inflammatory area, which might reflect an increased peripheral sensitization after surgery. In contrast with other studies concerning other types of surgeries (19, 20, 26, 27) we did not detect postoperative segmental secondary hyperalgesia in our patients. This supports the hypothesis that peripheral mechanisms played the predominant pathophysiological role in early postoperative pain. This may be specific of major knee surgery, where postoperative pain is mainly induced by peripheral inflammation. In addition, we did not detect any modification of extrasegmental pain threshold when previous studies testing secondary hyperalgesia in extrasegmental area also found no modification (28) or inhibition (18, 29).

From a clinical perspective, the present data suggest, in accordance with a previous study (30), that measurement of heat hyperalgesia preoperatively may have some predictive value regarding postoperative pain and, therefore, anticipate perioperative analgesic requirement. We also found a correlation between the intensity of pain induced by movement pre- and post-operatively, which may also prove clinically useful. These results are in agreement with those of previous studies on the prognostic value of preoperative pain for immediate postoperative pain intensity, with other types of surgery (3, 4).

Despite the severity of both preoperative inflammation and pain, the prevalence of chronic pain was relatively low in our patients. This is in accordance with the incidence of complex regional pain syndrome after total knee arthroplasty reported in a previous study (21% at 1 month and 13% at three months) (23). In contrast, a significantly higher incidence of chronic pain has been reported after other types of surgery with or without preoperative pain and inflammation (31). Moreover, all our patients had severe prolonged pain before surgery, and only 20% described moderate pain on movement 4 months after surgery. Thus, preoperative pain, inflammation, or the combination of the two do not seem sufficient to contribute to the development of chronic pain. It has been suggested that the presence of postoperative secondary hyperalgesia may be predictive of the development of chronic pain (11, 32). In keeping with this hypothesis, our data tend to indicate that the lack of secondary hyperalgesia is associated with reduced incidence of postoperative chronic pain. This finding

should be verified in future studies in larger groups of patients, since it could have an important impact on perioperative analgesic treatment strategies.

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Table 1. Postoperative quantitative data.

		Hand	Contra lateral knee	Operative knee
Mechanical PT (log unit)				
	D0	3.6 ± 0.1	3.9 ± 0.2	3.9 ± 0.0
	D1	3.4 ± 0.1	4.1 ± 0.0	3.6 ± 0.1** ‡
	D4	3.2 ± 0.2	3.9 ± 0.1	3.6 ± 0.1* ‡
	M1	3.5 ± 0.1	3.8 ± 0.1	3.9 ± 0.1
	M4	3.6 ± 0.2	4.1 ± 0.1	3.8 ± 0.2
Heat PT (°C)				
	D0	42.4 ± 0.6	43.3 ± 1	43.1 ± 0.8
	D1	42.1 ± 0.4	43.9 ± 0.7	43.3 ± 0.7
	D4	41.4 ± 0.8	42.8 ± 1.0	42.5 ± 0.8
	M1	41.9 ± 0.6	41.9 ± 0.8	41.3 ± 0.8
	M4	41.9 ± 0.6	41.4 ± 1.2	42.1 ± 1
Cold PT (°C)				
	D0	14.2 ± 1.6	16 ± 2.3	16.9 ± 2.6
	D1	14.8 ± 0.4	16.4 ± 2.5	23.5 ± 2.5 ** ‡
	D4	15.2 ± 0.6	16.1 ± 2.2	18.1 ± 2.4
	M1	15.3 ± 0.6	16.4 ± 2.5	17.1 ± 2.9
	M4	16.9 ± 0.8	16.8 ± 3.2	17.4 ± 3.9

Paired t-test: * $P < 0.05$. ** $P < 0.01$ operative knee versus contra lateral knee

Paired t-test: ‡ $P < 0.01$ operative knee versus preoperative value (D0)

PT: pain threshold, DO: preoperative day, D1: 1 day after surgery, D4: 4 days after surgery, M1: 1 month after surgery, M4: 4 months after surgery.

Figure Legends

Figure 1 Knee circumference (cm) on the preoperative day (D0), on the 1st and 4th day after surgery (D1 and D4), and the 1st and 4th month after surgery (M1 and M4)

Paired t-test: ** $P < 0.01$ operative knee versus contra-lateral knee

Figure 2 Knee temperature (°C) on the preoperative day (D0), on the 1st and 4th day after surgery (D1 and D4), and the 1st and 4th month after surgery (M1 and M4)

** $P < 0.01$ operative knee versus contra-lateral knee

Figure 3 Preoperative responses to heat stimuli applied to the operative and contra-lateral knees at different intensities: pain threshold (temperature value determined previously for each patient), pain threshold + 2°C and pain threshold + 4°C

Anova: $P < 0.01$ operative knee versus contra-lateral knee

Figure 4 Postoperative pain intensity (visual analog pain scale (VAS) score) at rest and during movement the 1st and 4th day after surgery (D1 and D4), and 1st and 4th month after surgery (M1 and M4).

Figure 5 Postoperative responses on the 1st (D1; Figure 5A), 4th day (D2; Figure 5B) and 1st month after surgery (M1; Figure 5C) to heat stimuli applied to the operative and contra-lateral knees at different intensities: pain threshold (temperature value determined previously for each patient), pain threshold + 2°C and pain

threshold + 4°C). Anova: $P < 0.05$ operative knee versus contra-lateral knee for D1 and D4; no significant difference for M1

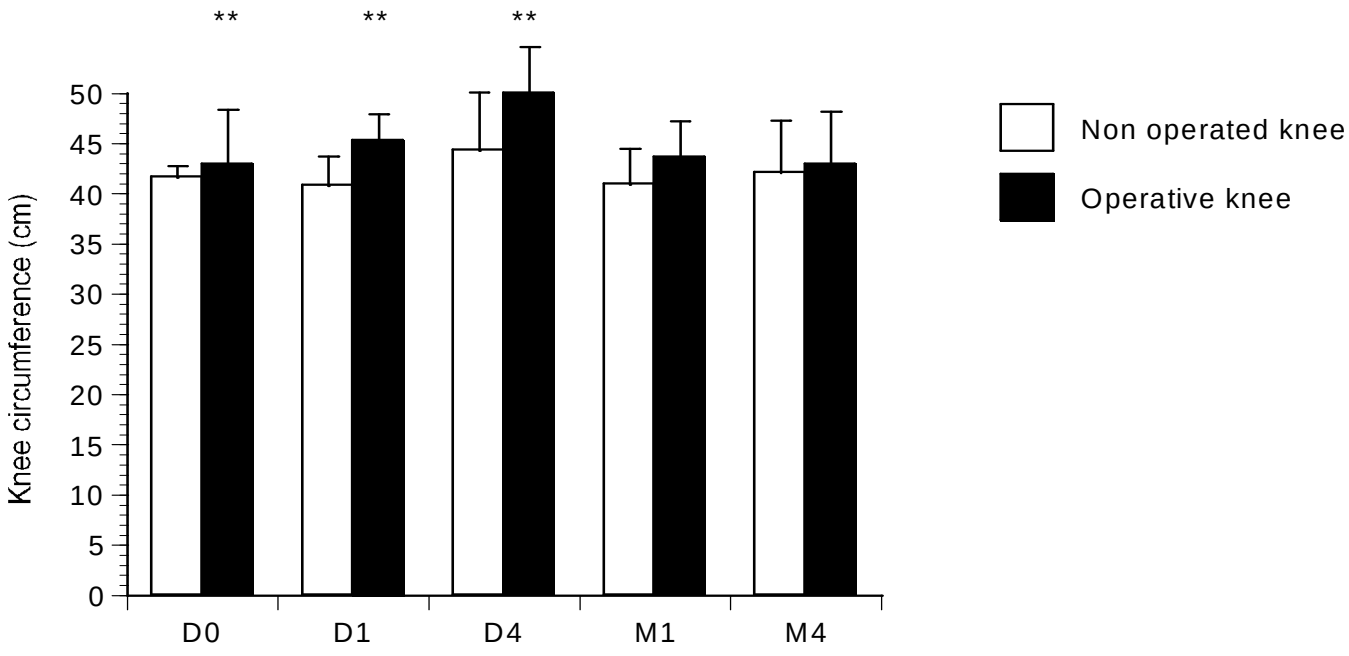
Figure 6 A. Association between the visual analog pain score on movement after surgery at D1 and the visual analog pain score on movement before surgery at D-1

Spearman correlation test : Rho = 0.6; $P = 0.02$

B. Association between the 24 hours cumulative morphine patient controlled analgesia and the VAS pain score after heat stimulation before surgery at D-1

Spearman correlation test : Rho = 0.63; $P = 0.01$

Figure 1


**
**
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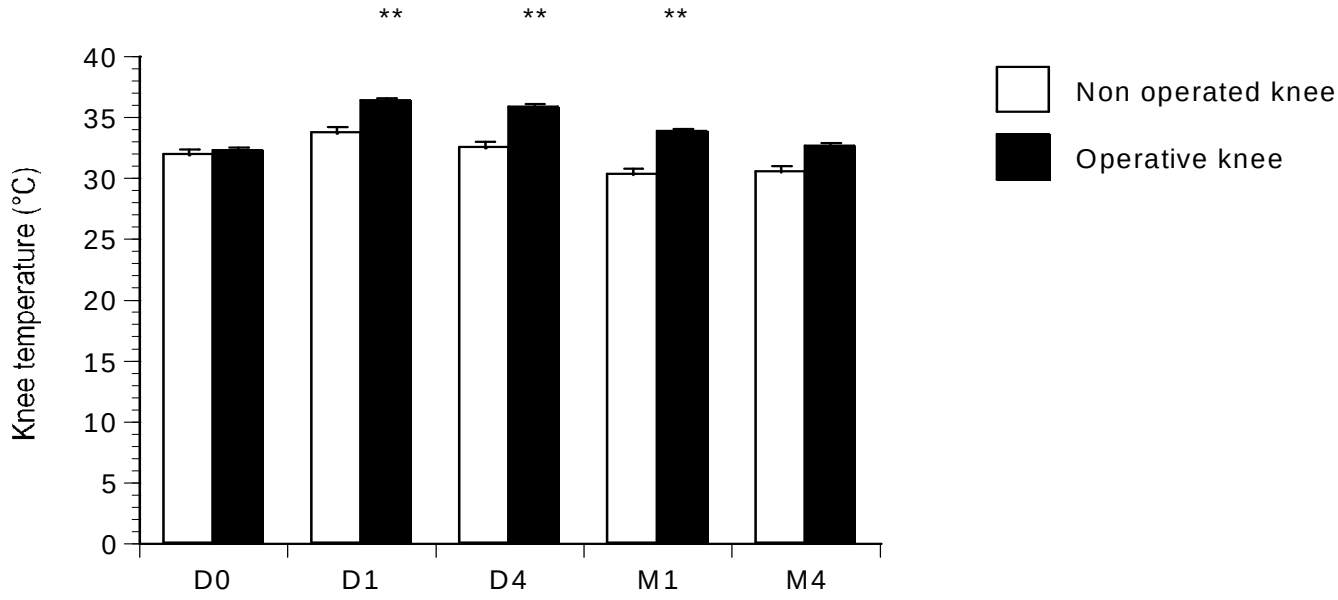
Knee circumference (cm)
50
45
40
35
30
25
20
15
10
5
0
D0
D1
D4
M1
M4
Non operated knee
Operative knee

Figure 2


**
**
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Knee temperature (°C)
40
35
30
25
20
15
10
5
0
D0
D1
D4
M1
M4
Non operated knee
Operative knee

Figure 3

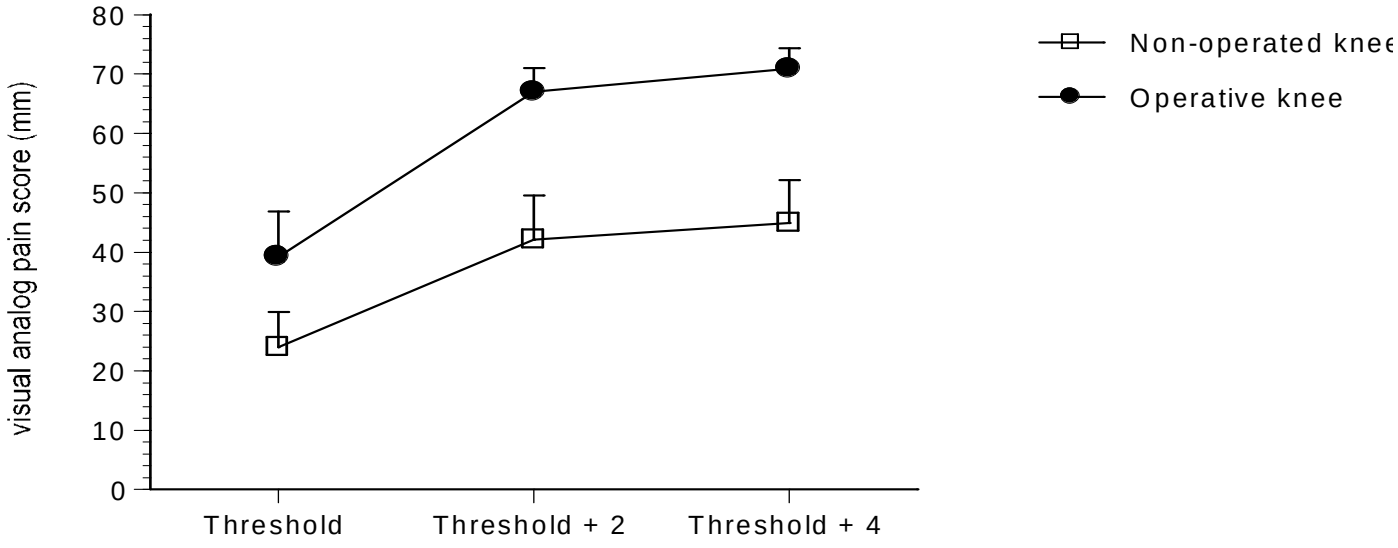

visual analog pain score (mm)
80
70
60
50
40
30
20
10
0
Threshold
Threshold + 2
Threshold + 4
Non-operated knee
Operative knee

Figure 4

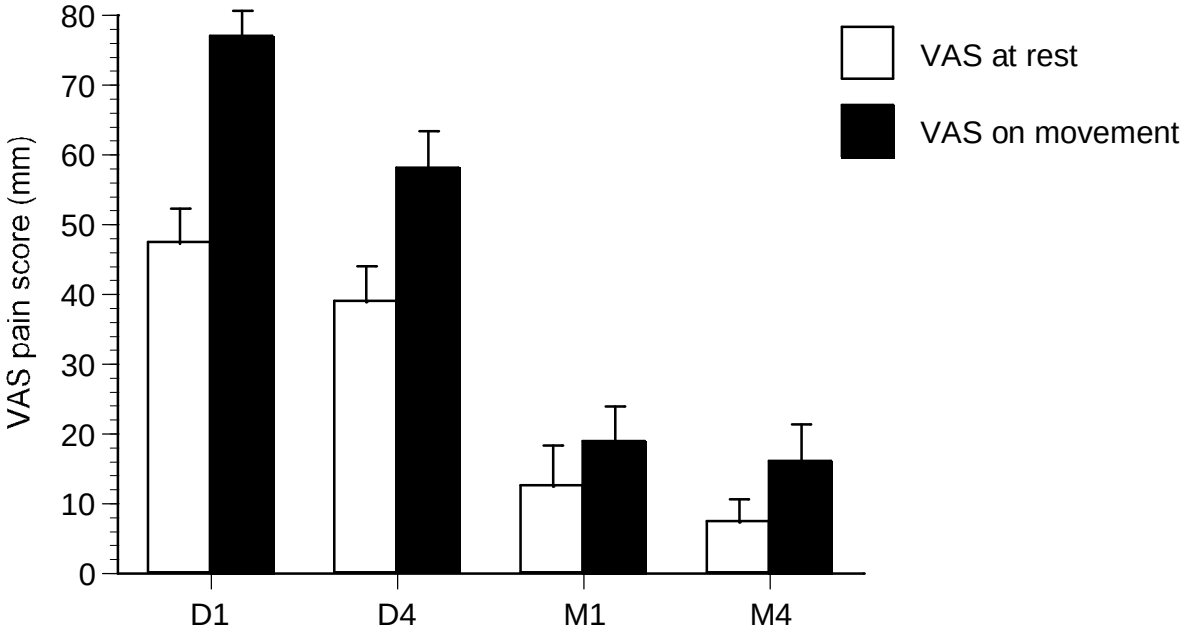

VAS pain score (mm)
80
70
60
50
40
30
20
10
0
D1
D4
M1
M4
VAS at rest
VAS on movement

Figure 5 A

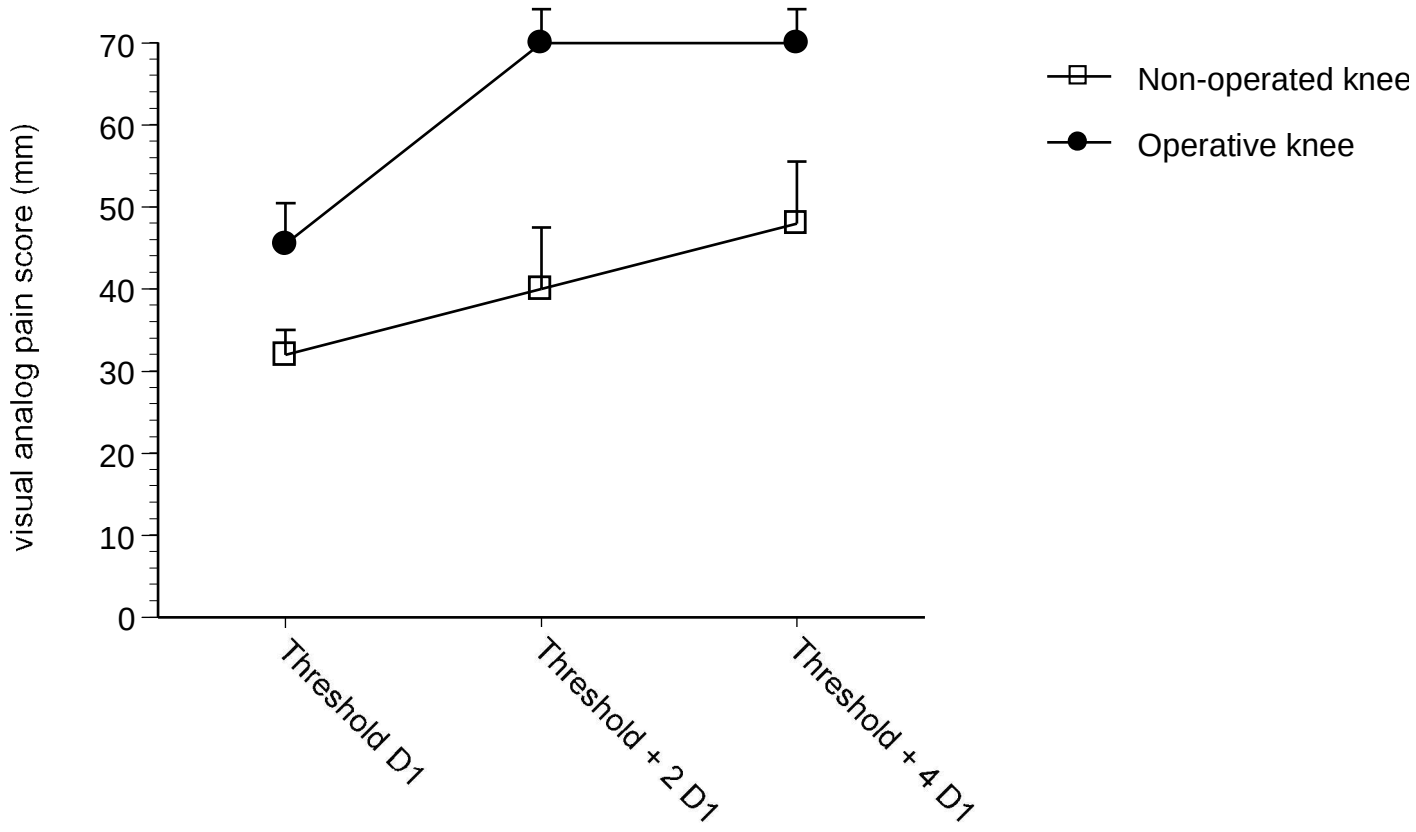

visual analog pain score (mm)
70
60
50
40
30
20
10
0
Threshold D1
Threshold + 2 D1
Threshold + 4 D1
Non-operated knee
Operative knee

Figure 5 B

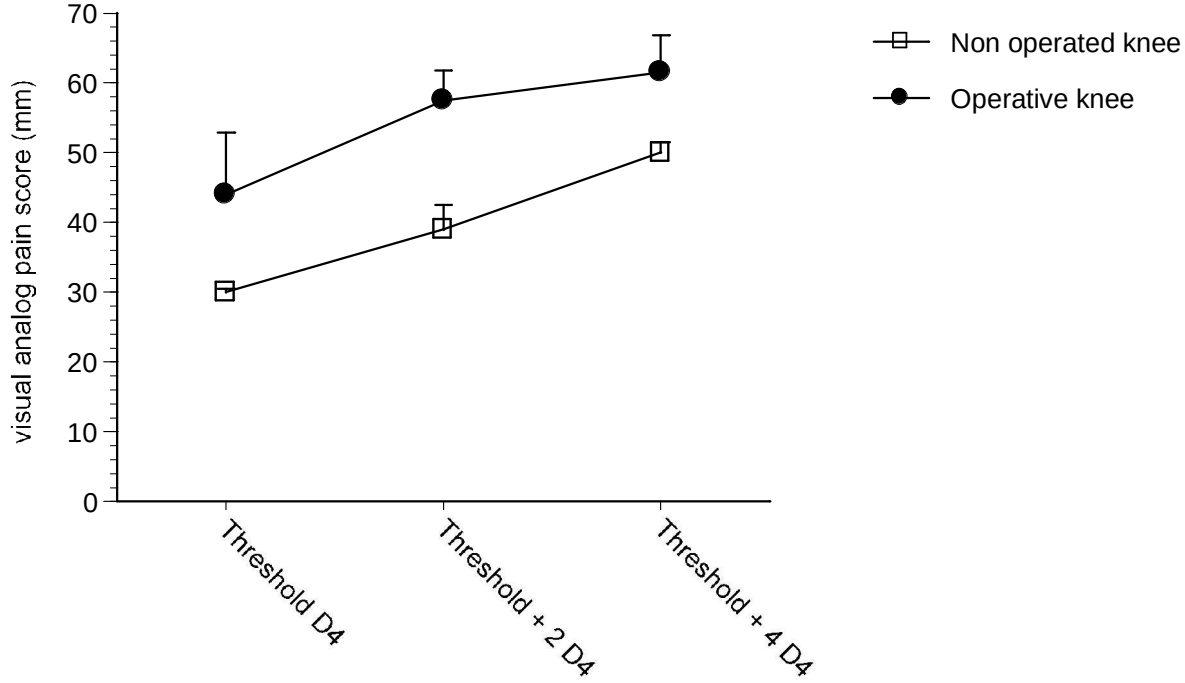

70
60
50
40
30
20
10
0
visual analog pain score (mm)
Threshold D4
Threshold + 2 D4
Threshold + 4 D4
Non operated knee
Operative knee

Figure 5 C

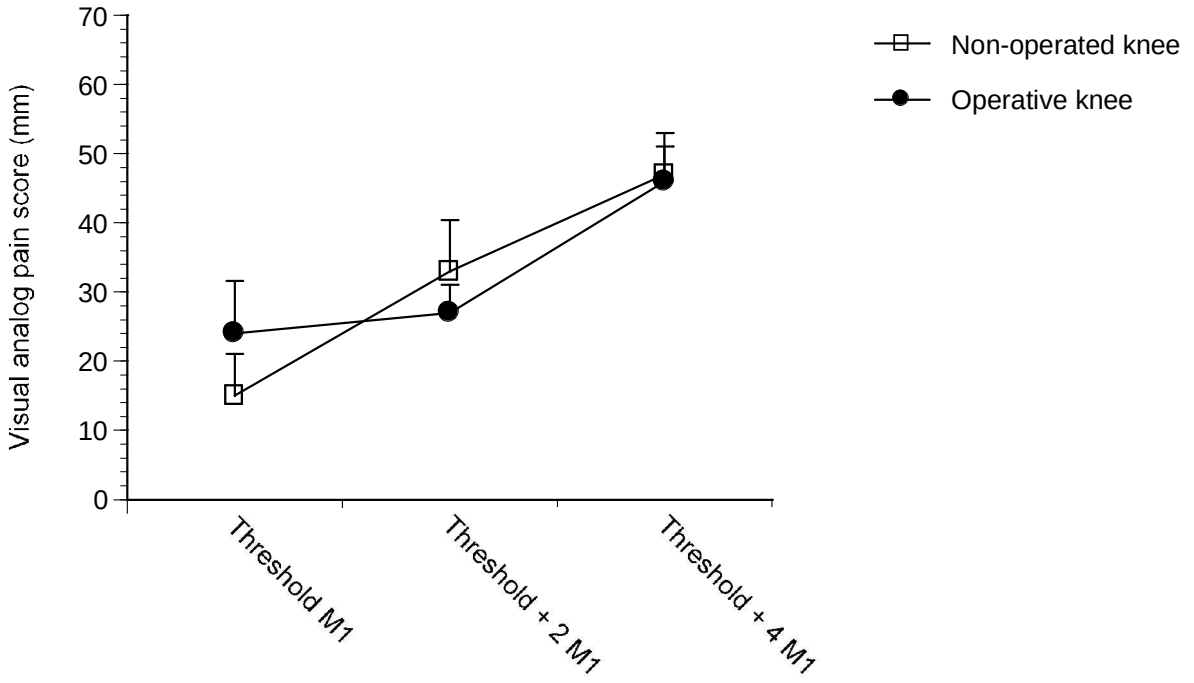
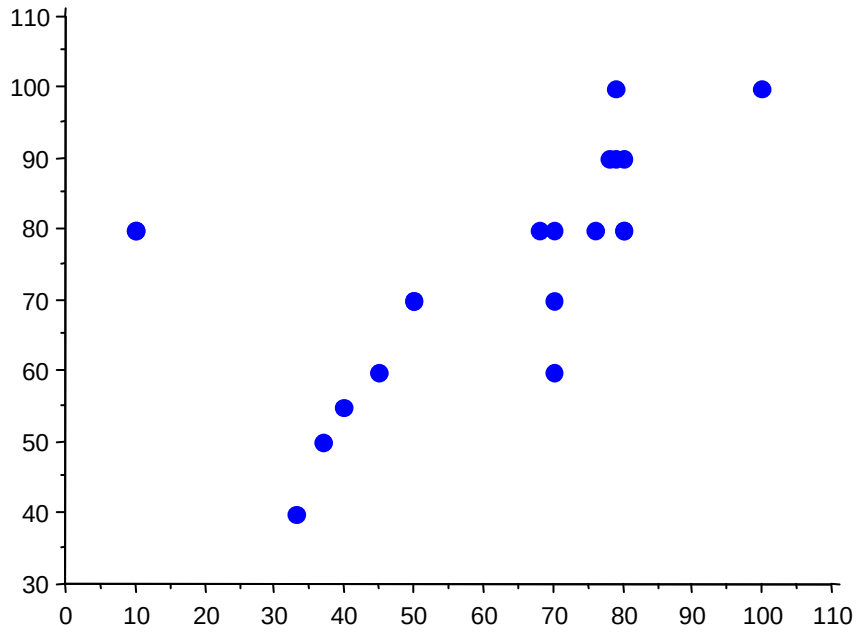

70
60
50
40
30
20
10
0
Visual analog pain score (mm)
Threshold M1
Threshold + 2 M1
Threshold + 4 M1
Non-operated knee
Operative knee

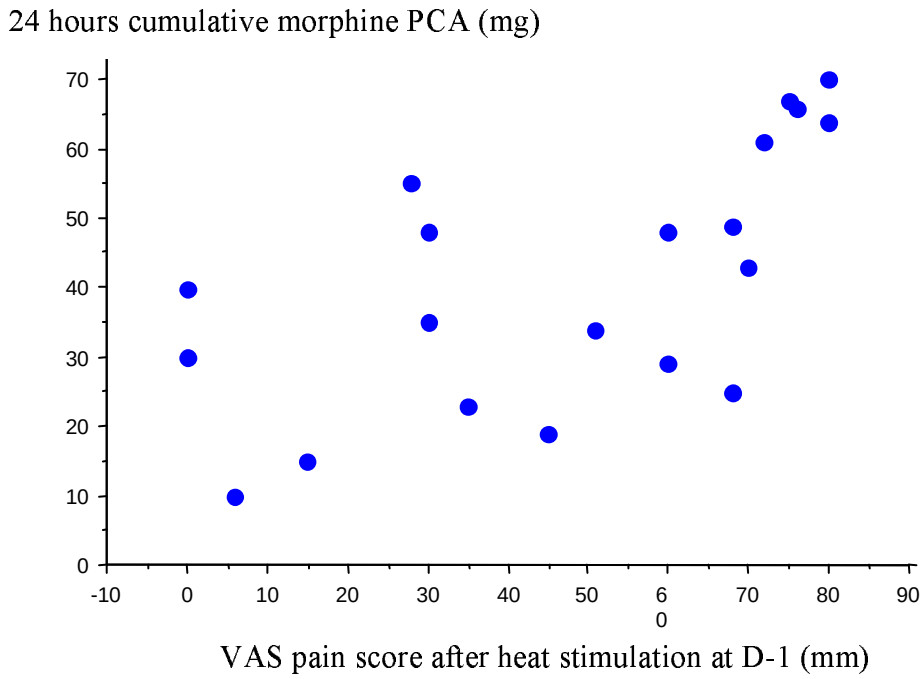
Figure 6 A

VAS pain score on movement at D1 (mm)



VAS pain score on movement at D-1 (mm)

Figure 6 B


24 hours cumulative morphine PCA (mg)
70
60
50
40
30
20
10
0
-10
0
10
20
30
40
50
60
70
80
90
VAS pain score after heat stimulation at D-1 (mm)