

Mechanisms of Postoperative Pain: Clinical Indications for a Contribution of Central Neuronal Sensitization

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Background: **The relative importance of different nociceptive mechanisms for the intensity, duration, and character of postoperative pain is not well established. It has been suggested that sensitization of dorsal horn neurones may contribute to pain in the postoperative period. We hypothesized that wound hyperalgesia in postoperative patients and experimentally heat-induced secondary hyperalgesia share a common mechanism, sensitization of central neurones, and consequently, that the short-acting opioid remifentanil would have comparable effects on hyperalgesia in both conditions.**

Methods: **In a randomized, controlled, double-blind trial, we assessed mechanical hyperalgesia in skin bordering the surgical wound, and an area of experimentally heat-induced secondary hyperalgesia on the thigh, in 12 patients who underwent abdominal hysterectomy within 5 days prior to the investigation. Observations were made before and during a drug challenge with remifentanil, which has been demonstrated to reduce the area of heat-induced secondary hyperalgesia in volunteers.**

Results: **The area of skin with surgically-induced mechanical hyperalgesia, the area of heat-induced secondary hyperalgesia, and pain during cough, were significantly reduced during remifentanil infusion compared with placebo ($P = 0.008$, $P = 0.006$, and $P = 0.002$, respectively). The relative reduction (% of baseline) of the area of skin with surgically-induced hyperalgesia and heat-induced secondary hyperalgesia during infusion of remifentanil was significantly associated ($R^2 = 0.72$, $P = 0.001$).**

Conclusions: **Although remifentanil is not a highly targeted "antihyperalgesic," these results support the hypothesis that both wound hyperalgesia in postoperative patients and experimentally heat-induced secondary hyperalgesia may share common mechanisms, and that central neuronal sensitization may contribute to some aspects of postoperative pain. Antihyperalgesic drugs should be further developed and evaluated in clinical trials of postoperative pain.**

THE relative importance of different nociceptive mechanisms for the intensity, duration, and quality of postoperative pain is not well characterized. As a result, treatment is often empirical, which may contribute to the well-documented inadequate management of pain in surgical patients.

In theory, pain in the perioperative period represents an operation of multiple mechanisms, including nociceptive transduction, sensitization of peripheral somatic and visceral nociceptive nerve terminals and central neurons, and loss of local and descending inhibition of neurons in the brainstem and spinal cord.[1] In particular, it has been suggested that central neuronal sensitization plays an important role in postoperative pain.[2] As suggested recently, a rational approach to improving the treatment of pain may be to identify the contributing mechanisms, to target treatment specifically at these mechanisms, and to measure the effect of this treatment.[3]

Evidence for the presence of a particular pain mechanism in the clinical setting, however, will at best be indirect, since no diagnostic tools so far are available to identify a given mechanism in a given patient.[3] In this study, assessment of mechanical hyperalgesia in skin bordering the surgical wound was combined with parallel assessments of area of heat-induced secondary hyperalgesia in the same postoperative patient. The placebo-controlled observations were made before and during a drug challenge with the short-acting opioid remifentanil, which has been demonstrated to reduce the area of heat-induced secondary hyperalgesia in volunteers.[4] We hypothesized that mechanical hyperalgesia in skin surrounding the wound in postoperative patients and heat-induced secondary hyperalgesia share a common mechanism, sensitization of central neurons. Consequently, remifentanil would have comparable effects on the area of hyperalgesia in both conditions. The design and description of the present trial adhere to the "Consolidated Standards of Reporting Clinical trials" (CONSORT) statement.[5]

Materials and Methods

Participants

Women aged 18–75 yr, ASA class I–II, who underwent total abdominal hysterectomy (simple or radical, with general anesthesia) through a vertical or horizontal incision within the 5 days prior to the investigation were eligible for the study. Only patients who had been free from opioids for 8 h prior to assessments were included in the study. Patients were not included if they were unable to cooperate, had a known allergy to remifentanil, a history of drug or alcohol abuse, chronic pain, daily intake of analgesics or corticosteroids, or diabetes. Patients were recruited from the Department of Gynecology, Herlev University Hospital, during the period from August 2001 to January 2002. Written informed consent was obtained from all patients, and the study was approved by the Regional Ethics Committee, and The Danish National Health Board.

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Table 1. Study Procedures

Time (min)	Action
0–10	Baseline assessment of: • Surgical-induced mechanical hyperalgesia, wound • Heat-induced secondary hyperalgesia, thigh • Pain during cough
10–35	IV-infusion of remifentanil 0.10 $\mu g \times kg^{-1} \times min^{-1}$, or placebo
25–35	Assessment of: • Surgical-induced mechanical hyperalgesia, wound • Heat-induced secondary hyperalgesia, thigh • Pain during cough
35	Assessment of: • Sedation • Nausea • Oxygen saturation • Blood pressure
36–70	Pause
70–80	Baseline assessment of: • Surgical-induced mechanical hyperalgesia, wound • Heat-induced secondary hyperalgesia, thigh • Pain during cough
80–105	IV-infusion of remifentanil 0.10 $\mu g \times kg^{-1} \times min^{-1}$, or placebo
95–105	Assessment of: • Surgical-induced mechanical hyperalgesia, wound • Heat-induced secondary hyperalgesia, thigh • Pain during cough
105	Assessment of: • Sedation • Nausea • Oxygen saturation • Blood pressure

For further details, see text.

Interventions

The study was performed in a quiet room with patients in a semisupine position. Each patient was familiar with the study procedures before measurements were initiated.

The study procedures are displayed in table 1. Two successive sessions were separated by a wash-out period of 35 min (t1/2, remifentanil, 3–10 min). In each session, baseline measurements were performed, and an IV-infusion with remifentanil 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or placebo (isotonic saline) was administered for 25 min. Measurements of hyperalgesia and pain were performed during the last 10 min of these infusions, followed by assessment of side-effects.

Assessments and Outcomes

Hyperalgesia in Relation to the Surgical Wound. The skin bordering the wound, with surgically-induced mechanical hyperalgesia, was assessed with a 21.5 gauge von Frey hair, by stimulating along two linear paths at right angles to the cranial right and left side (horizontal incisions), or right upper and lower side (vertical incisions) of the surgical wound, in steps of 5 mm at intervals of 1 s, starting well outside the hyperalgesic area. Stimulations continued toward the wound until patients reported a clear change in sensation ("burning," "tenderness," "more intense pricking"). The distance (in mm) from the wound, where sensations changed, was measured, and a mean value for the two assessments was calculated and used for statistical comparison.

Experimental Secondary Hyperalgesia

Induction of secondary hyperalgesia was performed with a computer-controlled thermode (12.5 cm^2) (Thermotest; Somedic A/B, Hörby, Sweden). Hyperalgesia was induced with the thermode placed on the center of the anterior side of the dominant thigh at 45°C. After 3 min of heating, the area of skin with secondary hyperalgesia was quantified with a 21.5 gauge von Frey hair.[6] The borders of skin with hyperalgesia to mechanical stimulation were determined by stimulating along four linear paths arranged radially around the stimulation site in steps of 5 mm at intervals of 1 s. Stimulation started in normal skin and continued toward the stimulation site until subjects reported a clear change in sensation. The distances were measured for later surface area calculations, and the thermode was removed.

Pain, Adverse Effects, and Vital Signs

Pain during cough was assessed on a visual analogue scale (VAS, 0 mm = no pain, 100 mm = worst pain imaginable). Sedation and nausea were rated on a 4-point verbal scale (none, mild, moderate, severe). Noninvasive blood pressure was assessed before, during, and immediately after drug infusions. Oxygen saturation and 3 lead electrocardiogram was monitored continuously during the study.

Randomization and Blinding

The study was conducted with a randomized, double-blind, placebo-controlled, cross-over design. Randomization was performed according to a computer generated block-randomization schedule. In six patients, the order of infusion was remifentanil-placebo, while in the other six it was placebo-remifentanil. Information about order of infusion was concealed in closed envelopes, and study medication was prepared in identical syringes by a person not involved in the investigation. Participants were assigned consecutively to a group according to their number. No person was aware of their group assignment until all patients had been included, and assessments were completed.

All assessments of hyperalgesia were performed by the same investigator (J. Dirks), who was separated from visual contact with the patient by a screen. Another investigator managed the blinded drug infusions and assessments of vital signs, and interviewed patients about pain and side effects.

Study Population Size

From previous observations, the anticipated area of skin with secondary hyperalgesia during heat sensitization of the thigh was 200 cm^2, with an intraindividual SD

Table 2. Demographic and Operative Data

Age (yr, median [range])	58 (27–74)
Height (cm, median [range])	167 (155–179)
Weight (kg, median [range])	60 (44–135)
Surgical procedure (N, hysterectomy–radical hysterectomy)	9/3
Incision (N, horizontal–transverse)	6/6

of 55.[6] Remifentanil reduced the area of hyperalgesia with more than 50% in another study.[4] Based on these figures, approximately 12 patients were required to demonstrate a 25% reduction in the area of hyperalgesia, with a power of 90%, and a type 1 error of 5%.

Statistical Methods

The prospectively defined primary outcome measure was an association between relative reduction from baseline of area of hyperalgesic skin surrounding the surgical wound (measured as distance from wound in mm) and area of heat-induced secondary hyperalgesia on the thigh, during remifentanil infusion. Data are presented as medians with lower and upper quartiles. Variables were evaluated using linear regression, and the Wilcoxon rank sum test for paired data. $P < 0.05$ was considered statistically significant. Calculations were performed using SPSS 10.0 for Windows (SPPS, Chicago, Illinois, USA). The statistical analysis was performed by the investigators.

Results

Twelve patients were included, and all patients completed the study. Demographic and operative data are shown in table 2.

Mechanical hyperalgesia in skin bordering the surgical wound and heat-induced secondary hyperalgesia on the thigh were easily detectable in all patients. Secondary hyperalgesia after heat-induced sensitization lasted only shortly after the thermode was removed, and there were no spontaneous sensations or sensitization in the skin prior to the next thermal sensitization.

Baseline values of area of skin with surgically-induced mechanical hyperalgesia (distance in mm from wound), area of skin with heat-induced secondary hyperalgesia, and pain during cough, were comparable between preremifentanil and preplacebo assessments ($P = 0.59$, $P = 0.84$, and $P = 0.39$, respectively) (fig. 1). We observed a significant association between baseline values of area of skin with surgically-induced mechanical hyperalgesia, and area of skin with heat-induced secondary hyperalgesia, prior to remifentanil infusions ($R^2 = 0.55$, $P = 0.006$, Fig. 2). No significant association was observed between baseline values of pain during cough and area of skin with surgically-induced mechanical hyperalgesia ($R^2 = 0.04$, $P = 0.52$).

The area of skin with surgically-induced mechanical hyperalgesia, as well as the area of skin with heat-induced secondary hyperalgesia, and pain during cough, were significantly reduced during remifentanil infusion compared with placebo ($P = 0.008$, $P = 0.006$, and $P = 0.002$, respectively) (Fig. 1). The relative reduction (% of baseline) of the area of skin with surgically-induced hyperalgesia and heat-induced secondary hyperalgesia, during infusion of remifentanil, was significantly associated ($R^2 = 0.72$, $P = 0.001$, Fig. 3). No significant association was observed between remifentanil-induced reduction in pain at cough and reduction of the area of skin with surgically-induced hyperalgesia ($R^2 = 0.03$, $P = 0.61$).

Nine of the 12 patients experienced mild (N = 6) or moderate (N = 3) sedation during remifentanil infusion, compared with 2 of 12 patients who experienced moderate sedation during placebo infusion ($P = 0.01$). None of the patients experienced nausea during infusions, and blood pressure and oxygen saturation were stable throughout the study.

Discussion

There has been much debate on the possible role of central neuronal sensitization in postoperative pain. Experimental studies have demonstrated that tissue injury results in hyperexcitability of dorsal horn neurons, and it has been suggested that similar alterations may play an important role in clinical pain states.[1,2] Accordingly, "antihyperalgesic" methods and drugs, including "preemptive analgesia"[2,7] and *N*-methyl-D-aspartic acid receptor antagonists,[8] have been evaluated in a large number of clinical trials of postoperative pain. Results have been conflicting, and it is still not known whether this mechanism is of clinical importance.

The burn injury model employed in the current study is well-documented in clinical trials,[6] and there is convincing evidence from parallel studies of humans and animals that heat-induced secondary hyperalgesia is a result of altered central processing of afferent activity because of sensitization of dorsal horn neurones.[9–11] Several clinical studies have further demonstrated that the area of heat- and/or capsaicin-induced secondary hyperalgesia is reduced by opioids,[4,12,13] including remifentanil.[4]

Primary and secondary hyperalgesia have been demonstrated in a rat model of incisional pain,[14,15] whereas similar alterations in relation to surgical incisions in humans are less well characterized. Mechanical hyperalgesia in skin surrounding the surgical wound has been described as distressing, and has been said to interfere with general well-being and normal clothing wear, but such reports are anecdotal. Hyperalgesia to von Frey hair stimulation adjacent to surgical incisions in humans has been reported previously.[16–18] These findings included reduced pain thresholds,[16] or altered sensations ("burning," "tenderness")[17,18] at varying distances (5–10 cm)

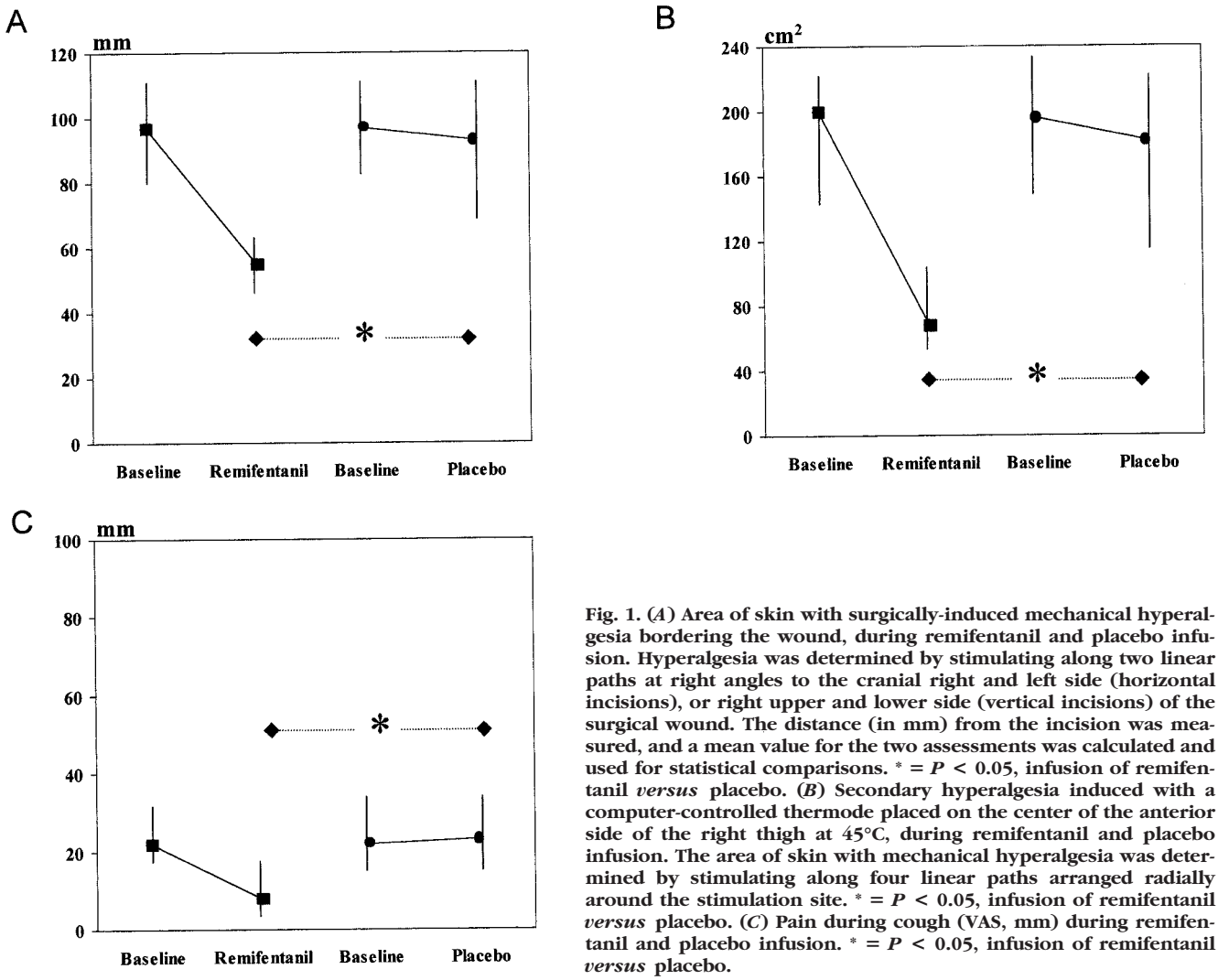

Fig. 1. (*A*) Area of skin with surgically-induced mechanical hyperalgesia bordering the wound, during remifentanil and placebo infusion. Hyperalgesia was determined by stimulating along two linear paths at right angles to the cranial right and left side (horizontal incisions), or right upper and lower side (vertical incisions) of the surgical wound. The distance (in mm) from the incision was measured, and a mean value for the two assessments was calculated and used for statistical comparisons. * = $P < 0.05$, infusion of remifentanil *versus* placebo. (*B*) Secondary hyperalgesia induced with a computer-controlled thermode placed on the center of the anterior side of the right thigh at 45°C, during remifentanil and placebo infusion. The area of skin with mechanical hyperalgesia was determined by stimulating along four linear paths arranged radially around the stimulation site. * = $P < 0.05$, infusion of remifentanil *versus* placebo. (*C*) Pain during cough (VAS, mm) during remifentanil and placebo infusion. * = $P < 0.05$, infusion of remifentanil *versus* placebo.

from the surgical wounds, and were detectable for up to 3 months after surgery.[18] In one study, the decrease in the pain threshold was prevented by morphine administered before, but not after, surgery.[16] In another study, the area of skin with hyperalgesia was smaller in patients during infusion of ketamine compared with placebo.[17] Both morphine and ketamine have been demonstrated to reduce secondary hyperalgesia in human pain models.[12,19] The findings from the above studies of surgical patients, however, are only indirect evidence that hyperalgesia bordering a surgical incision is caused by sensitization of central neurones, and is thus secondary hyperalgesia. Direct evidence for such a relationship requires assessments of neuronal activity at the spinal cord level. Consequently, the importance of central neuronal sensitization in postoperative pain has not been proven by these studies, nor from the above-mentioned antihyperalgesic method, or drug trials.

In the current study we observed a close and highly significant association between the relative reduction of area of skin with mechanical hyperalgesia surrounding the surgical wound and heat-induced secondary hyperalgesia during infusion of remifentanil in postoperative patients. In addition, baseline values of area of skin with mechanical hyperalgesia surrounding the surgical wound and area of heat-induced secondary hyperalgesia were associated. Although still indirect, these findings are the hitherto most explicit indications that experimentally, heat-induced, secondary hyperalgesia, and surgically-induced mechanical hyperalgesia share a common mechanism, central neuronal sensitization. We were not able to demonstrate a statistically significant association between a composite measure of pain (during cough) assessed on a visual analogue scale, and the area of skin with surgically-induced mechanical hyperalgesia. In the sense that surgically-induced mechanical hyperalgesia might compromise the overall well-being of the postoperative patient, however, our findings further support the suggestion that central sensitization of dorsal horn neurones contribute to postoperative pain.

It should be reiterated, though, that the present findings do not definitely identify central sensitization to

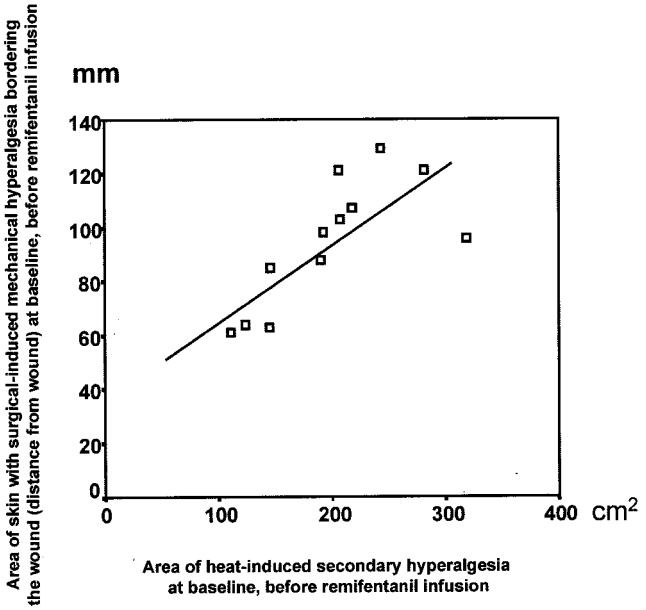

Fig. 2. Relation between area of heat-induced secondary hyperalgesia (cm^2), and area of surgically-induced mechanical hyperalgesia bordering the wound (distance from wound in mm) at baseline, before remifentanil infusion. Linear regression, $R^2 = 0.55$, $P = 0.006$.

account for surgically-induced mechanical hyperalgesia. Mechanical hyperalgesia bordering the surgical wound may reflect other mechanisms such as peripheral sensitization, or disinhibition of central neurones. In addition, the effects of opioids such as remifentanil are due to actions at receptors at both peripheral, spinal, and supraspinal sites. Since opioids are not highly targeted antihyperalgesics, their ability to reduce clinical manifestations of hyperalgesia is not evidence that such hyperalgesia is due to sensitization of central neurones. Different pain mechanisms are not independent, and a drug-induced alteration of one clinical manifestation is not evidence for an effect on one particular underlying mechanism.[3] Finally, although side effects during remifentanil infusion were limited, blinding may have been lost in some patients.

Despite these limitations, our findings support the hypothesis that mechanical hyperalgesia surrounding the wound in postoperative patients, and experimentally, heat-induced, secondary hyperalgesia, share a common mechanism, and that central neuronal sensitization may contribute to some aspects of postoperative pain. The clinical implications of these findings are that antihyperalgesic drugs and methods should be further developed and evaluated in clinical trials of postoperative pain. In particular, combinations of antinociceptive and antihyperalgesic medication may provide additive or synergistic effects.

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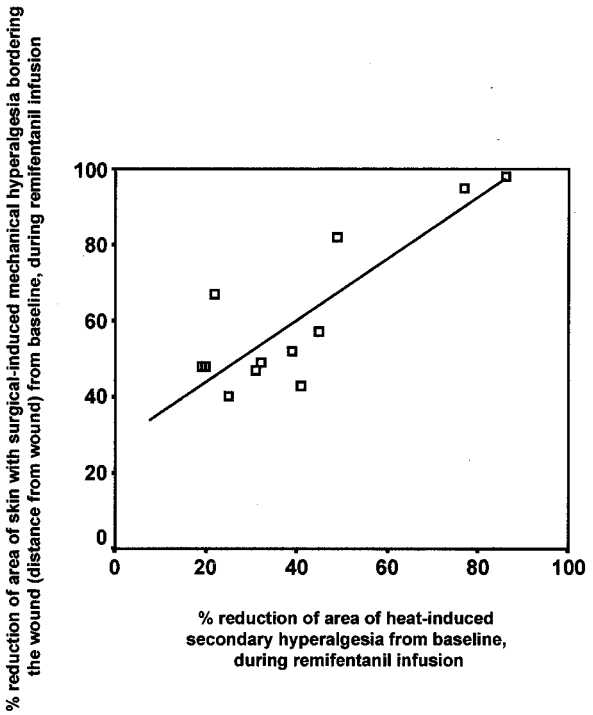

Fig. 3. Relation between percent reduction from baseline of heat-induced secondary hyperalgesia, and area of surgically-induced mechanical hyperalgesia bordering the wound (distance from wound in mm), during remifentanil infusion. Linear regression, $R^2 = 0.72$, $P = 0.001$.

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