The Effect of Wound Instillation of a Novel Purified Capsaicin Formulation on Postherniotomy Pain: A Double-Blind, Randomized, Placebo-Controlled Study

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BACKGROUND: Acute postoperative pain is common after most surgical procedures. Despite the availability of many analgesic options, postoperative pain management is often unsatisfactory. Purified capsaicin (ALGRX 4975 98% pure) has demonstrated prolong inhibition of C-fiber function in *in vitro*, preclinical, and clinical studies, and may be an effective adjunct to postoperative pain management.

METHODS: We performed a single-center, randomized, double-blind, placebo-controlled study of the analgesic efficacy of a single intraoperative wound instillation of 1000 μg ultrapurified capsaicin (ALGRX 4975) after open mesh groin hernia repair in 41 adult male patients. The primary end-point was average daily visual analog scale (VAS) pain scores during the first week after surgery assessed as area under the curve (AUC). Pain was recorded twice daily in a pain diary for 4 wk. Physical examination and laboratory tests were done before and 1 wk after surgery, together with recordings of adverse events up to 28 days. Adverse events were recorded. Data were also analyzed using a mixed-effects analysis with NONMEM.

RESULTS: VAS AUC was significantly lower during the first 3 days postoperatively ($P < 0.05$), but not for the whole 1 or 4 wk postoperatively. Mixed-effects analysis with NONMEM revealed that pain scores were significantly lower ($P < 0.05$) in the capsaicin group during the first 4 days. No clinically significant serious adverse events were observed, although a mild transient increase in liver enzymes was seen more often in the capsaicin-treated group.

CONCLUSION: In the setting of a well-defined analgesic protocol standard, VAS AUC analysis and a mixed-effect analysis showed superior analgesia of capsaicin relative to placebo during the first 3–4 days after inguinal hernia repair.

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Adult groin hernia surgery is one of the most common operations, with an annual rate of approximately 2800 per million in the United States.[1] Although there is little intraoperative morbidity, acute postoperative pain has been shown to be the most prominent factor in extending recovery and delaying return to everyday functions.[2–6] Present evidence-based analgesic therapy combines infiltration with local anesthetics, systemic nonsteroidal antiinflammatory drugs or cyclooxygenase-2 inhibitors, acetaminophen, and opioids for rescue pain management.* Despite this multimodal approach, analgesia is often unsatisfactory.[7]

ALGRX 4975 is a novel, long-acting, non-opioid analgesic for moderate to severe pain. The active ingredient in ALGRX 4975 is ultrapurified natural capsaicin, which is known for the ability to induce stinging and burning algesia.[8] Ultrapurification is accomplished using high-pressure liquid chromatography. This process removes dihydrocapsaicin and other capsaicinoids, resulting in ≥98% pure capsaicin. Repetitive or intense exposure to capsaicin results in a selective, reversible loss of nociceptive nerve endings (C-fibers).[9] This ability to induce reversible long lasting nociceptor inhibition makes capsaicin a potentially useful topical analgesic. Volunteer studies have shown that nociceptive C-fiber regeneration occurs within 4–16 wk, adequate to provide analgesia for the full period of recovery after surgery.[9–11]

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We designed this single-center, double-blind, parallel-group, placebo-controlled, randomized trial of the analgesic efficacy of a single wound instillation of 1000 μg ultrapurified capsaicin (ALGRX 4975) during open groin hernia repair, to test the primary hypothesis that capsaicin would provide superior analgesia during the first week after surgery.

METHODS

This phase two, single-center, randomized, double-blind, placebo-controlled, parallel-group study was approved by the Danish Medicines Agency, the local ethics committee, and data handling authorities, and monitored according to the principles of Good Clinical Practice by a clinical research organization (Norma, Hørsholm, Denmark). The trial was registered with www.ClinicalTrials.gov (NCT00146198) before enrollment. After providing written informed consent, 42 adult male patients from an ambulatory hernia clinic scheduled to undergo Lichtenstein mesh repair of an inguinal hernia were enrolled in the study. Inclusion criteria were: male 18–70-yr-of-age, primary groin hernia planned to undergo Lichtenstein mesh repair, ability to use pain scales, ASA class I or II based upon medical history, physical examination, and screening laboratory results, willing to take oral pain medication (acetaminophen, ibuprofen) for the first week, and willing to fill out a diary for 4 wk after surgery. Exclusion criteria were as follows: a previous lower abdominal surgical procedure, presently taking bupivacaine, acetaminophen, ibuprofen, or tramadol, a medical condition likely to alter wound healing or pain ratings, systolic blood pressure more than 150 or diastolic more than 95 mm Hg, contraindication to general anesthesia, bilateral hernia repair, a history of drug or alcohol abuse within the past 2 yr, use of antihypertensive, antidepressant, or psychotropic drugs that has not been stable for 3 mo, and use of an investigational drug within 3 mo or scheduled to receive an investigational drug other than ALGRX 4975 during the study period.

Current use of the following drugs resulted in exclusion: digoxin, antiarrhytmics except β-blockers, warfarin, theophylline, aminoglycosides, anticonvulsants, except benzodiazepines or lithium, pain medication, or central nervous system active drugs. Small-dose aspirin for cardiovascular protection was allowed.

Study Design

Screening Phase: One to 2 wk before surgery, patients were screened for eligibility by a physical examination including all major organ systems, arterial blood pressure, heart rate, and electrocardiogram (ECG). A standard hematology panel (complete blood count and differential count), a standard clinical chemistry panel, and a standard urine analysis panel with microscopic examination (only if dipstick was positive) were performed.

Blinding, Randomization, and Study Medication

The active study medication was purified (≥98%) capsaicin (ALGRX 4975, Anesiva, Inc., South San Francisco, USA). Based upon safety and efficacy data from pilot studies,[12–15] an instillation of 1000 μg purified capsaicin was chosen. Purified capsaicin was supplied as an open-label stock solution, and diluted with water for a maximum of 4 h before administration. Placebo (water) and capsaicin (both 15 mL after dilution) were colorless and odorless. Each patient was given a unique randomization number in the order they entered the study. This number was linked to a computer-randomized treatment sequence only known to two study nurses who prepared the study medication. The randomization code was generated to ensure that the appropriate number of subjects was randomly allocated to each treatment group, with a minimum of 20 in each group. A labeled vial of blinded study medication was handed to the investigator by the unblinded study nurse. During the study, the subject and the investigators/study staff were blinded to the study drug. In case of an emergency, separately blinded envelopes for each study subject were available for the investigator and the medical monitor.

Surgery and Anesthesia

A Lichtenstein mesh hernia repair was performed with the patient under general anesthesia. Anesthesia was induced with propofol 2–3 mg/kg, and remifentanil 0.5–1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Anesthesia was maintained with a propofol infusion of 0.3–0.6 $mg \cdot kg^{-1} \cdot h^{-1}$ and a remifentanil infusion of 0.3–1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Near the end of the repair, a combined local infiltration and ilioinguinal nerve block[16] using 40 mL 0.25% bupivacaine was administered at least 10 min before the instillation of capsaicin or placebo. After suturing of the mesh, capsaicin or placebo was instilled for at least 1 min and left to dwell for 5 min, taking care to include the whole of the open wound from the subcutaneous layer down to the mesh, but not the surrounding skin. The wound was then closed with the capsaicin or placebo instilled. At the end of surgery, fentanyl 1.5 μg/kg was administered IV.

Postoperative Management

Pain was assessed in the postanesthesia pain unit, as described below. The patient was discharged 4 h postoperatively if a family member could be present for the first postoperative night. Otherwise the patient stayed in the hospital until the next morning. Before discharge, instructions regarding the pain diary were given to the patient and family member.

First Postoperative Day

A telephone call regarding pain and general well-being was made.

One Week Postoperatively

The patient was seen at the hospital and a physical examination, ECG, urine, and blood test similar to that

of the screening day were performed. Sutures were removed and the wound was evaluated. Adverse events (AEs) were recorded. The patient's pain diary was collected together with any acetaminophen, ibuprofen, or tramadol tablets not used.

Weeks 2 and 4

A telephone call regarding wound healing, analgesic efficacy, and AEs was made. At the 4-wk interview, the patients returned the pain diary in a prestamped envelope.

Pain Medication

According to our usual practice, patients were given the following pain medication for the first postoperative week; acetaminophen 1 g every 6 h and ibuprofen 600 mg every 8 h. Supplemental medication was tramadol 50 mg to be taken as needed (4–6 h apart maximum 200 mg daily). Pain medication was recorded in the diary. After 1 wk, all excess pain medicine was collected and compared with the diary recordings. Any need for pain medication beyond the first week was recorded in the diary for weeks 2–4.

AEs and Safety Analysis

Any untoward medical occurrence to a patient during the study (from randomization to 4 wk postoperatively) was recorded as an AE. This included any unfavorable and unintended sign including abnormal laboratory findings, symptoms, disease, injuries, adverse reactions, or exacerbations of preexisting illnesses. Laboratory findings were classified as above or below the normal range (age corrected).

Pain Recording

Pain ratings were recorded on a horizontal 100 mm Visual Analog Scale (VAS). Patients were instructed in the use of the scale at the screening visit, on the day of surgery, and on the day after surgery. Pain at rest and when rising from prone to sitting was recorded at the screening visit. Pain was recorded immediately after awakening from surgery and 4 h postoperatively. To standardize pain measurements, movement-associated pain from the wound when getting out of bed in the morning and getting into bed at night was recorded for 4 wk postoperatively in a pain diary.

Outcomes

The primary end-point was average daily VAS scores, assessed during movement upon arising in the morning and retiring in the evening, during the first week after surgery. Pain scores during the first week were chosen as a primary outcome based upon pilot studies[12–15] and the theoretical duration of c-fiber inhibition,[9] assuming high pain score in this period as seen in previous groin hernia studies.[4] Secondary end-points included: time to supplemental medication usage, average pain scores at individual intervals for the first 4 wk after surgery, area under the curve (AUC) pain scores from 4 h postoperatively to day 7 evening ($AUC_{day\ 7}$), AUC during the first 4 wk after surgery ($AUC_{week\ 4}$), and when (day and time) the AUC pain scores were no longer significantly different.

Statistics

A sample size of 20 per treatment group was planned in this study. This sample size would have 80% power to detect 24 mm treatment difference in pain VAS score at a 5% significance level, assuming the standard deviation of 26 mm. VAS pain scores are presented as medians with the 25th and 75th percentiles. We calculated AUC according to the trapezoidal rule[17] to obtain a summary measure and to analyze the differences in response between the purified capsaicin and placebo groups. The time point immediately after surgery was not included in the AUC calculations since not all patients were able to cooperate in giving a pain score at that time. Since the AUC pain scores were skewed and not normalized by logarithmic transformation, nonparametric testing was performed using Wilcoxon's signed rank test to compare groups. Differences in frequencies were compared using Fischer's exact test. P values <0.05 are considered statistically significant.

To control the assumption about the inter- and intraindividual variability across the VAS observation and its influence on statistical decision making, we also performed a *post hoc* nonparametric analysis of the VAS scores using nonlinear mixed effect modeling program NONMEM VI (Globomax LLC, Hanover, MD). The model parameters were typical VAS scores each postoperative day, and drug effect (if any), as described in Appendix.

RESULTS

Forty-two patients were randomized, of whom 41 who were treated received capsaicin or placebo. One patient was excluded before instillation of the study medication because no hernia was found during surgery and a herniorrhaphy was not performed. The two groups were similar regarding age, body mass index, preoperative pain, side of hernia, anesthesia time, and duration of surgery. Use of pain medication was the same in both treatment groups, with an equal amount of acetaminophen and ibuprofen taken during the entire duration of the study (Table 1).

VAS Pain Scores

The time course of pain throughout the study is shown in Figure 1. Inspection of the VAS scores shows a rapid decline in VAS score for both groups in the first days after surgery, as well as considerable intersubject variability in VAS scores. The average median VAS pain scores in the first week after surgery were 10.3 mm/d in the capsaicin group, and 13.9 mm/d in the placebo group ($P = 0.43$). Similarly, the average median VAS scores for weeks 1–4 after surgery were 3.8 mm/d in the capsaicin group, and 6.0 mm/d in the placebo group, $P = 0.89$. AUC pain scores for the first

Table 1. Demographics of 41 Patients Randomized for Treatment for Postherniotomy Pain by Instillation of 1000 μg Ultrapure Capsaicin (ALGRX-4975) or Placebo

	Capsaicin (n = 20)	Placebo (n = 21)
Preoperative pain median (range)		
Rest	0 (0–5)	0 (0–16)
Activity	0 (0–5)	0 (0–58)
Age, mean (yr)	50.7	49.5
Body mass index, mean (kg/m^2)	25.0	23.9
Anesthesia time (mean min, SD)	77.4 (16.5)	74.3 (16.8)
Surgery time (mean minutes, SD)	46.9 (9.6)	46.8 (14.1)
Ibuprofen use during the first week (mean no. tablets, SD)	20.8 (3.4)	21.2 (1.8)
paracetamol use during the first week (mean no. tablets, SD)	54.1 (3.7)	54.3 (5.5)

Pain at rest and during activity was scored after lying down for 10 min and immediately after sitting up using the abdominal muscles rather than the arms. All subjects were Caucasian males.

Ibuprofen tablets = 600 mg, Acetaminophen tablets = 500 mg.

week or the whole study were also not significantly different (P = 0.25 and 0.78, respectively).

However, a significant difference in the AUC favoring capsaicin was seen for the time period from 4 h until the morning of the third day postsurgery (AUC_{4h} – day 3 morn, P = 0.045), which appears consistent with the time course of median VAS pain scores shown in Figure 1. The differences in the distribution of VAS pain scores during the first 4 days are further evaluated in boxplots (Fig. 2), which illustrate lower pain scores at every time point in the capsaicin group compared with placebo as well as higher maximum pain scores at every time point in the placebo group. In both groups, median pain scores were low (<10 mm) after the third postoperative day. Pain scores immediately after surgery (0 h) were also low in the capsaicin and placebo group (median, 12.0 vs 13.5) (P = 0.77) and after 4 h (median, 6.5 vs 8.0) (P = 0.85), demonstrating the efficacy of the bupivacaine block in reducing pain from the operation.

The effect of ALGRX 4975 on the VAS scores versus placebo, and incorporating intersubject variability, was modeled using NONMEM, as described in Appendix. Models selectively examined the influence of capsaicin on VAS score each day after surgery. The optimal model demonstrated an analgesic effect of ALGRX 4975 on days 0, 1, 2, 3, and 4 and some residual effect until the end of the study (change −2LL = 204, $P < 0.0001$). The parameters of the final model are shown in Table 2. Figure 3 shows the individual modeled VAS score for both groups using the final model. The goodness of fit can be observed in Figures 3C and D. The typical population curves (Fig. 3E) demonstrated the analgesic effect of ALGRX 4975 on the VAS scores on days 0, 1, 2, and 3. After day 3, both groups had very little pain. Nevertheless, there was a slight, but statistically significant (P = 0.014), transient increase in pain in the subjects receiving capsaicin, which can also be seen on very close inspection of Figure 1.

Supplemental tramadol was used by four patients in the capsaicin group (a group total of 19 tablets) and by 3 in the placebo group (a group total of 22 tablets). All tramadol tablets were administered during the first five postoperative days, consistent with the greater levels of pain during this time period.

Safety Analysis

No adverse events rated as serious or severe were seen throughout the study period (Table 3). Eight (40%) cases of transient increases of aspartate aminotransferase to levels slightly above normal range were seen in the capsaicin patients versus 3 (14%) in the placebo group. The increases were just above the normal range (10–45 U/L) except in one patient (105 U/L). Alanine aminotransferase and alkaline phosphatase increases above normal were seen in the capsaicin or placebo group in 2 versus 1 patients and in 0 versus 1 patient, respectively (Table 4). All tests were normalized during the following week. Wound infection was seen in 2 (10%) patients in the capsaicin group and none in the placebo group. Postoperative nausea was reported by 4 (20%) patients in the capsaicin group versus 1 (5%) in the placebo group, dizziness in 5 (25%) versus 3 (14%), and headache by 6 (30%) versus 2 (10%). All except one patient in the capsaicin group with wound infection exhibited normal wound healing at week 2. Laboratory tests showed one case of urine positive for blood in each group and one case of bilirubin (placebo); however, the findings could not be reproduced the next day. No clinical relevant changes in ECG, heart rate, or arterial blood pressure were recorded.

DISCUSSION

Capsaicin specifically opens the nonselective cation channel, TRPV1 (formerly vanilloid receptor 1)[18] predominantly expressed by C-fiber polymodal nociceptors. The resulting flood of cations into the targeted neuron leads to a transient burst of action potentials, causing profound stinging, burning, and thermal and mechanical hyperalgesia,[8,10,19–21] followed by reversible desensitization potentially lasting for several weeks.[8,19] The desensitization is due to an intracellular accumulation of calcium that exceeds the buffering capacity of the mitochondria of the C-fiber,[22] causing osmotic lysis, resulting in loss of mitochondrial energy supplies, and disruption of pain (C-fiber) receptor terminals. During the period of pain-receptor regeneration, pain fibers are unable to transmit pain signals, resulting in a long-term decrease in sensitivity to noxious, mechanical, and thermal stimulation.[9,11] These analgesic effects of capsaicin have primarily been investigated after topical administration,[23–26] but

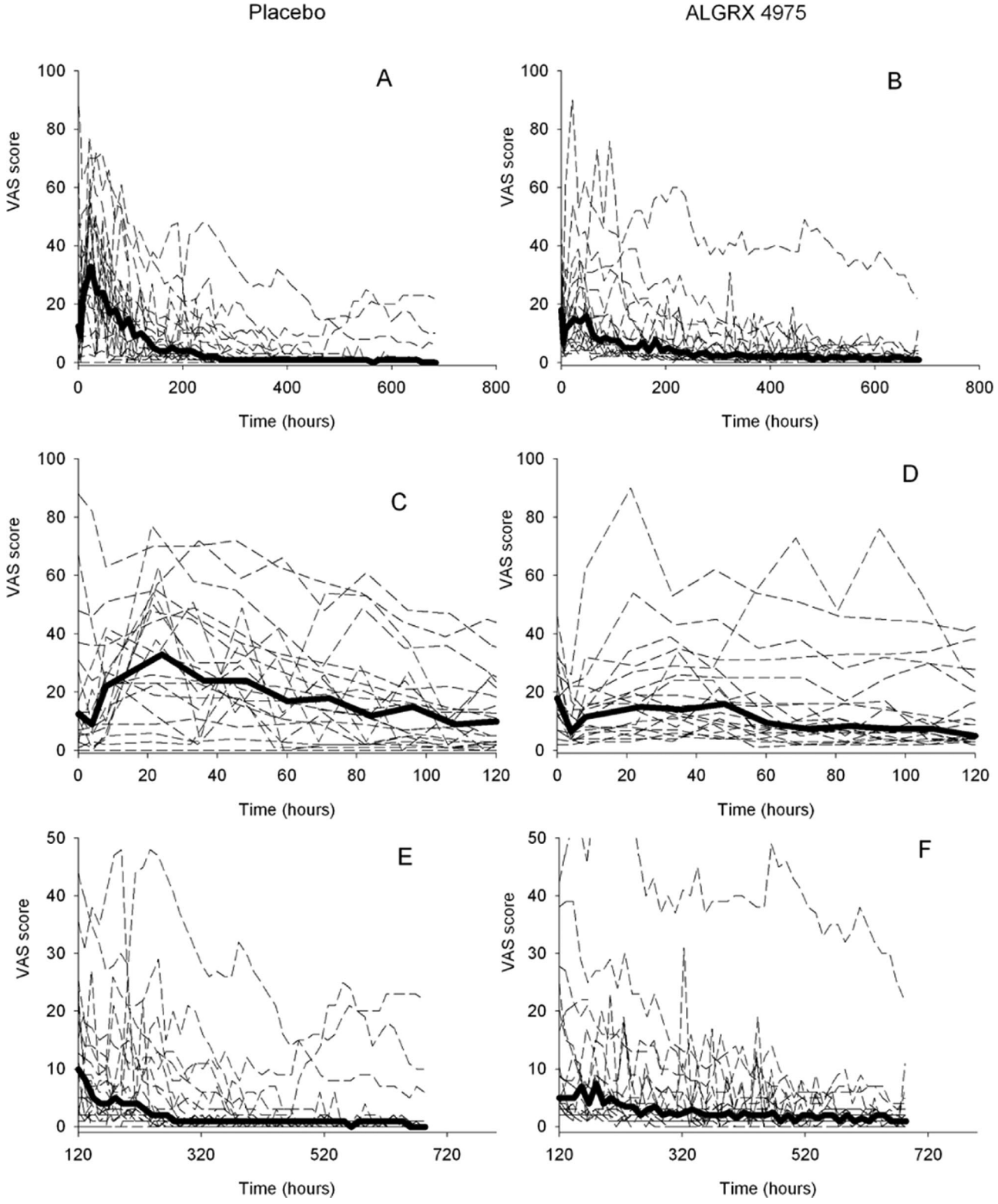

Figure 1. Individual (dashed line) and median (solid line) visual analog scale (VAS) pain scores in the placebo (A) and ALGRX 4975 (B) group for the entire time course of the study. C–F shows a detailed view of the study period.

topical treatment requires repetitive application and can be painful when administered.

When analyzing the primary and secondary endpoint of average pain during the first week and the whole study (28 days) using a classical Wilcoxon's signed rank test, the observed differences did not reach statistical significance, despite a visually obvious difference in the raw data (Fig. 1). The likely explanation was insensitivity of the statistical model to the repeated measures design of the study data, which permits differentiation of intersubject from intrasubject variability. To detect if capsaicin influences

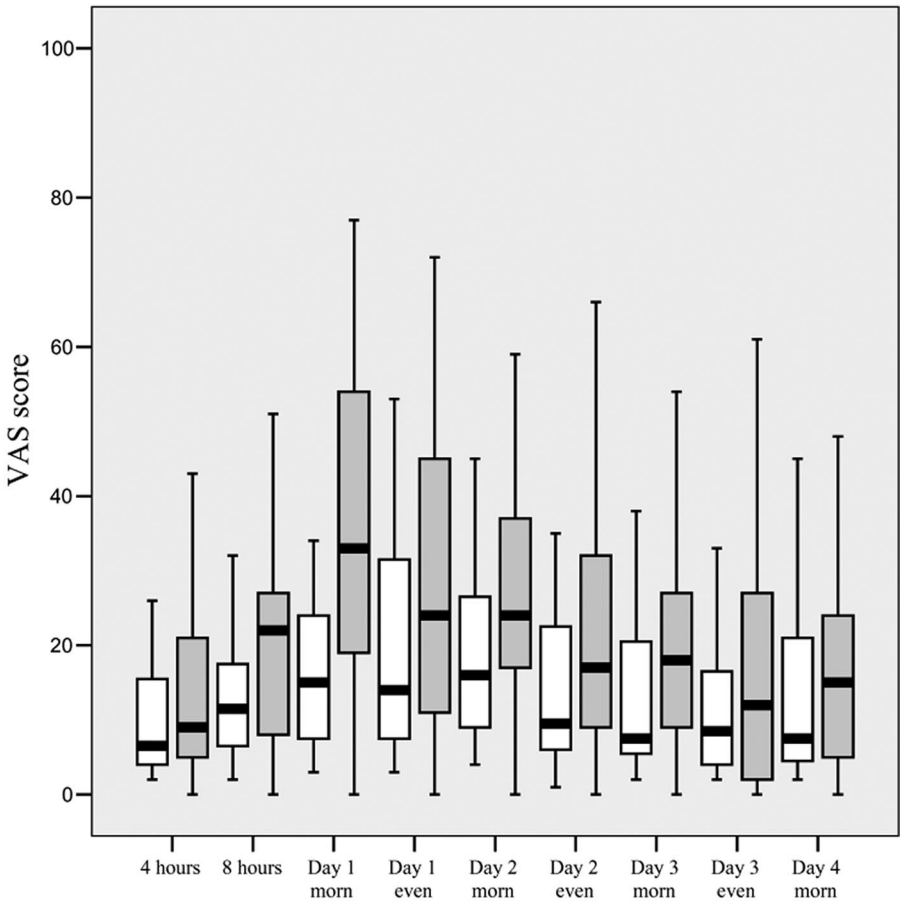

Figure 2. Detailed distribution of visual analog scale (VAS) pain scores during the first 4 days in patients with wound instillation of capsaicin (n = 20) or placebo (n = 21) during groin hernia repair. Horizontal bars represent median pain scores, boxes represent the 25th and 75th percentile range, and T-bars the 2.5th and 97.5th percentile range. Outliers are not shown.

Table 2. NONMEM Parameters for the Best Fitting Model

Model parameters	VAS
$\theta_{TV,\ placebo}$ day 0	17.1
$\theta_{TV,\ placebo}$ day 1	26.3
$\theta_{TV,\ placebo}$ day 2	21.8
$\theta_{TV,\ placebo}$ day 3	18.2
$\theta_{TV,\ placebo}$ day 4	13.2
$\theta_{TV,\ placebo}$ day >4	5.21
$\theta_{TV,\ capsaicin\ effect}$ day 0	−32%
$\theta_{TV,\ capsaicin\ effect}$ day 1	−26%
$\theta_{TV,\ capsaicin\ effect}$ day 2	−23%
$\theta_{TV,\ capsaicin\ effect}$ day 3	−16%
$\theta_{TV,\ capsaicin\ effect}$ day 4	+13%
$\theta_{TV,\ capsaicin\ effect}$ day >4	+56%
CV for all θ_{TV}	87%
Residual error (SD)	7.11

$\theta_{TV,\ placebo}$ = typical population visual analog scale (VAS) score in the placebo group for a specific day; $\theta_{TV\ capsaicin\ effect}$ = percent difference from placebo VAS attributable to ALGRX-4975, whereby a negative value means a lower VAS score compared with θ_{TV}; CV = coefficient of variation; SD = standard deviation.

the VAS trajectory for each patient compared with placebo, we developed a NONMEM pharmacodynamic model for VAS versus time, similar to that used by Flood and Daniel.[27] The NONMEM analysis demonstrated an analgesic effect of capsaicin on days 0, 1, 2, and 3, but with slightly higher pain scores on days 4 and 5.

However, when evaluating to the differences in typical curves (Fig. 3), we have to admit that although significant, the absolute decrease in VAS score is not that large. However, it would be wrong to dismiss purified capsaicin as a potential perioperative analgesic since the duration of pain relief for the primary end-point was chosen from results from experimental studies suggesting a longer analgesic effect[9] and assuming the presence of sufficient pain to adequately compare the capsaicin treated versus the placebo patients. Both explanatory *post hoc* analyses (AUC using nonparametric statistics and NONMEM) showed that wound instillation of purified capsaicin was superior to placebo as an add-on analgesic therapy for the first 3–4 days after groin hernia repair. The negative result on the primary and secondary end-points are attributable to the unexpected low VAS pain score of around 10 mm (0–100 mm Scale) beyond the third postoperative day. Given the low VAS score in both treatment groups, it is clear that there was insufficient remaining pain to provide more test sensitivity. Postoperative pain after hernia repair was adequately addressed by the concomitant pain medications of acetaminophen and ibuprofen during the rest of the first week beyond the third day after surgery. The measurable postsurgical pain associated with this procedure does not extend to 30 days.

No severe AEs were observed during the study period; however, slight increases in aspartate aminotransferase levels above the normal range were seen more often in the purified capsaicin group compared with controls, and all increases were

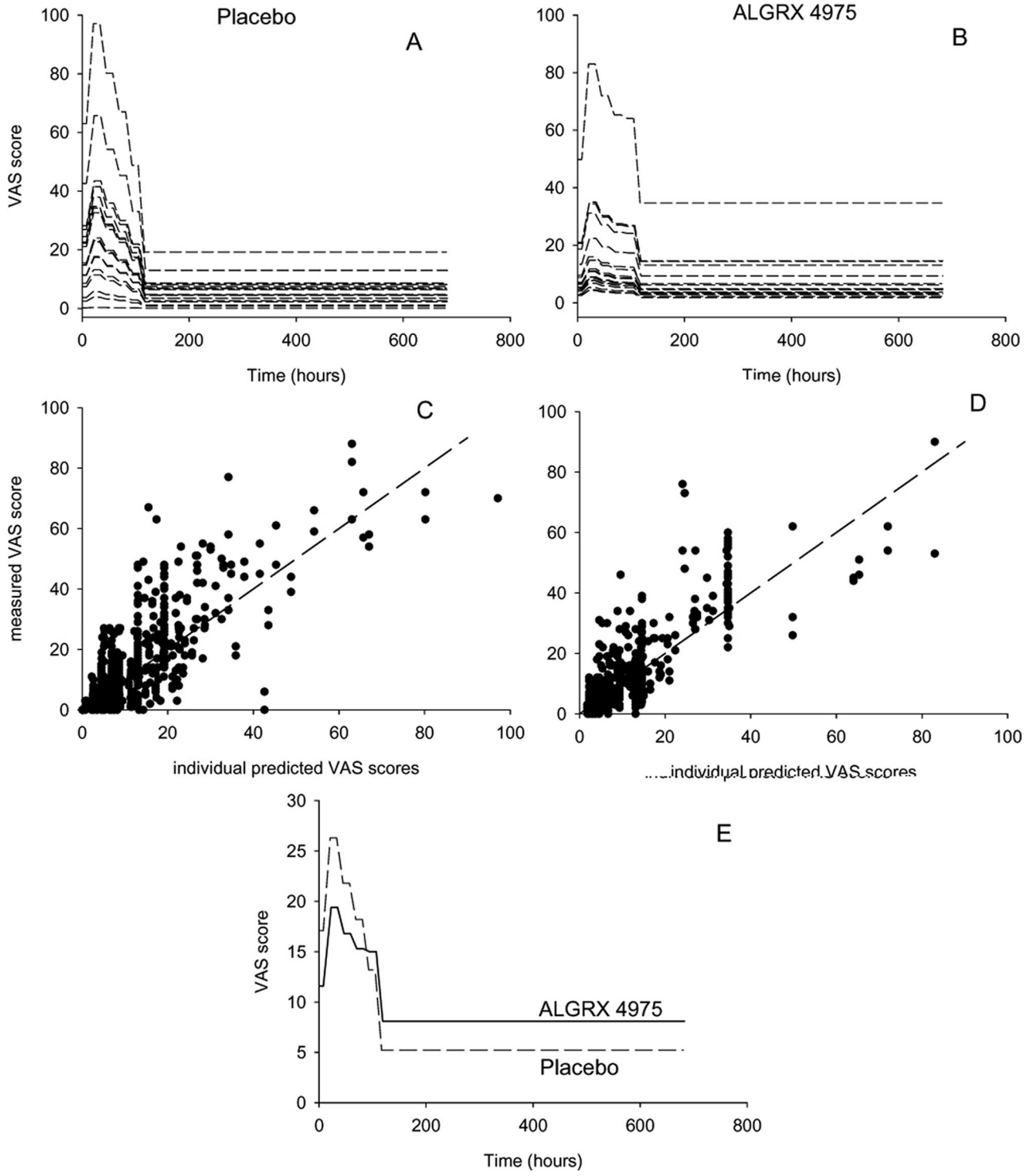

Figure 3. NONMEM modeling details. A, B shows the individual *post hoc* Bayesian predicted visual analog scale (VAS) pain scores from the best fitting model for the placebo (A) and ALGRX 4975 (B) group. C, D shows the individual measured versus predicted VAS scores from the best fitting model for the placebo (C) and ALGRX 4975 (D) group. E, the typical population predicted VAS scores by the best fitting model versus time for placebo and ALGRX 4975.

normalized within the following week. The aspartate aminotransferase elevations are in contrast to the previously reported studies of purified capsaicin where there were no treatment-related effects on laboratory safety variables.[12,13] However, the relatively small sample size was not powered to assess AEs.

The potential for an algesic response to capsaicin is well described in human studies of intradermal administration of capsaicin.[8,9,20,28] This response generally occurs when capsaicin first contacts the target tissue during its initial contact with TRPV1 receptors, immediately followed by desensitization of the TRPV1 receptors, resulting in analgesic response. The lack of

Table 3. Adverse Events (AE) Recorded the First 4 Postoperative Weeks in 41 Patients Randomized for Treatment for Postherniotomy Pain by Instillation of 1000 μg Ultrapure Capsaicin (ALGRX-4975) or Placebo

	No. of patients					
	Mild		Moderate		Severe	
Adverse event	Capsaicin (n = 20)	Placebo (n = 21)	Capsaicin (n = 20)	Placebo (n = 21)	Capsaicin (n = 20)	Placebo (n = 21)
Blood pressure increased	2	0	0	0	0	0
Dizziness	4	1	2	1	0	0
Fatigue	1	0	0	1	0	0
Hematoma	2	1	0	1	0	0
Headache	3	0	3	2	0	0
Skin hypoesthesia	0	0	19	17	0	0
Skin hyperalgesia	0	0	12	9	0	0
Postoperative infection	1	0	1	0	0	0
Abnormal wound healing	0	0	1	0	0	0
Postoperative nausea	1	1	3	0	0	0
Operative hemorrhage	0	1	0	0	0	0
Postoperative hematoma	16	19	3	1	0	0
Postoperative skin reaction	11	17	4	3	0	0
Urine positive for blood	1	1	0	0	0	0
Urine positive for bilirubin	0	1	0	0	0	0

The numbers in each column cannot be added because a subject may have had more than one AE. Hypoesthesia and hyperalgesia was assessed at 1 wk follow-up by stimulation with a von Frey fiber (Semmes-Weinstein monofilaments, Stoelting, IL, USA; nominal buckling 588.2 milliNewton).

Table 4. Changes in Liver Enzymes in 41 Patients Randomized for Treatment for Postherniotomy Pain by Instillation of 1000 μg Ultrapure Capsaicin (ALGRX-4975) or Placebo

	Capsaicin (n = 20)			Placebo (n = 21)		
	Preoperative	1 week postoperative	Change from baseline	Preoperative	1 week postoperative	Change from baseline
Aspartate aminotransferase (U/L) (normal range, 10–45 U/L)						
Mean	28.9	47.3	16.8	25.5	31.7	6.1
SD	11.6	25.7	22.0	10.1	12.6	10.5
Min	11	12	−6	12	12	−22
Median	28.5	47.5	10.0	22.0	27.0	6.0
Max	54	105	77	48	54	25
Alanine aminotransferase (U/L) (normal range, 10–40 U/L)						
Mean	26.2	37.7	11.5	28.3	31.0	2.7
SD	6.1	18.6	16.4	14.0	14.7	10.5
Min	17	19	−7	17	18	−35
Median	26.5	34.5	7.0	24.0	26.0	2.0
Max	39	91	63	48	85	20
Alkaline phosphatase (U/L) (normal range, 20–70 U/L)						
Mean	57.7	56.1	−1.6	69.0	70.7	1.7
SD	12.8	10.6	4.9	15.6	17.3	21.4
Min	28	34	−10	33	45	−17
Median	58.0	54.5	−3.0	67.0	67.0	−3.0
Max	80	92	6	96	121	98

U/L = units per liter; SD = standard deviation; min = minimum value; max = maximum value.

report of pain on application of capsaicin in this study is likely attributable to its intraoperative use while patients are under anesthesia. The slightly higher VAS scores in the capsaicin group from day 4–5 could be interpreted as the development of hyperalgesia. However, we do not believe this for the following reasons: First, the pain scores were very low compared with what is normally seen from capsaicin-induced hyperalgesia and judging from the AEs reported, hyperalgesia was not a specific finding in capsaicin-treated patients compared with controls. However, the short- and especially long-term effect of capsaicin instillation

on sensory functions needs to be investigated in future studies.

Purified capsaicin may be valuable for perioperative use if analgesia lasting a couple of days can be confirmed from other surgical models. Preliminary evidence for such an effect is only available from buniectomy.[12] However, other nonsurgical pain studies (intermetatarsal neuroma, lateral epicondylitis, and knee osteoarthritis) support the long-term analgesic effect of a purified capsaicin injection.[13–15] Similar to the bunionectomy study,[12] we successfully avoided the initial intense pain after purified capsaicin administration seen in other studies,[13–15] by first administering a local anesthetic.

The ideal regimen for the treatment of postoperative pain should target the pain at its origin, be of sufficient duration, have only local effects, be easy to administer, usable in ambulatory settings, cost-effective, and available to all patient categories. Unfortunately, such a regimen does not yet exist. In groin hernia repair, several techniques are used to diminish acute postoperative pain, but none is ideal.[7] Limitations include techniques that rely on single-dose wound injection of local anesthetics and those that are only effective for 4–6 hours, as well as the use of continuous wound perfusion with local anesthetics, which is costly.[29–32]

In conclusion, instillation of purified capsaicin resulted in superior analgesia to placebo with regards to average pain during the first 3–4 postoperative days after inguinal herniotomy. Future studies should address the potential use of capsaicin as a single treatment modality, in combination with a systemic rescue analgesic, in surgical models with intense and prolonged postoperative pain.

APPENDIX: THE NONMEM ANALYSIS AND CONTROL FILE OF THE FINAL MODEL

For the parameters, interindividual variability was modeled using a constant coefficient of variation model,

$$\theta_i = \theta_{TV} \cdot (1 + \eta_i)$$

where θ_i refers to the individual value of the parameter, θ_{TV} is the typical value of the parameter, and η is a normally distributed random variable with mean zero and a variance of ω^2 individual variability is reported as ω, the standard deviation (SD) of η in the log domain, which is approximately the coefficient of variation in the standard domain. Residual intraindividual variability was modeled using a standard additive error model,

$$DV_{obs} = DV_{exp} + \epsilon$$

where DV_{obs} refers to the observed dependent variable, and DV_{exp} refers to the predicted dependent variable, ϵ is normally distributed random variable with mean zero and variance σ^2. The objective function for the analysis was −2 log likelihood (−2LL). The possible therapeutic effect of capsaicin on the VAS score was modeled as a proportional effect (θ_j),

$$\theta_i = \theta_{TV} \cdot (1 + \eta_i) \cdot (1 + \theta_j)$$

A different θ_i was analyzed per day of therapy. However all θ_i's share the same η_i. Individuals are either above or below the typical (TV) VAS score (that's the "repeated measures" part of the analysis). For each day of therapy, an additional effect θ_j on the VAS score by capsaicin can be added or not. This additional effect for a specific day of therapy is significant compared with placebo if the difference in −2LL exceeds 3.84 when adding 1 parameter as a nested models ($P < 0.05$, χ^2 test, 1 degree of freedom). Various models were tested with a similar and different additional effect per therapeutic day (meaning a similar θ_j among days or a different θ_j among days). In the placebo group, θ_j is always zero.

The control file of the best-fitting model

```
$PROB Anesiva VAS Scores, Separate Drug Effect Each Day
$DATA vas.data.txt
$INPUT ID TIME POD VAS = DV TRT AGE
$PRED
IF (POD.EQ.0)
   TY=THETA(1)*(1+ETA(1))*(1+THETA(7)*TRT)
IF (POD.EQ.1)
   TY=THETA(2)*(1+ETA(1))*(1+THETA(8)*TRT)
IF (POD.EQ.2)
   TY=THETA(3)*(1+ETA(1))*(1+THETA(9)*TRT)
IF (POD.EQ.3)
   TY=THETA(4)*(1+ETA(1))*(1+THETA(10)*TRT)
IF (POD.EQ.4)
   TY=THETA(5)*(1+ETA(1))*(1+THETA(11)*TRT)
IF (POD.GT.4)
   TY=THETA(6)*(1+ETA(1))*(1+THETA(12)*TRT)

IPRED = TY
Y = IPRED + EPS(1)

$THETA
(0, 20,   100) ; Theta 01: POD 0
(0, 32,   100) ; Theta 02: POD 1
(0, 26,   100) ; Theta 03: POD 2
(0, 23,   100) ; Theta 04: POD 3
(0, 19,   100) ; Theta 05: POD 4
(0, 7,    100) ; Theta 06: POD >4
−0.1         ; Theta 07: Effect on POD0
−0.1         ; Theta 08: Effect on POD1
−0.1         ; Theta 09: Effect on POD2
−0.1         ; Theta 10: Effect on POD3
−0.1         ; Theta 11: Effect on POD4
−0.1         ; Theta 12: Effect on POD >4

$OMEGA 0.75      ; Between subject variability
$SIGMA 50        ; Residual variability
```

$ESTIMATION MAX = 1000 PRINT = 1 NOABORT METHOD = 1 SIG = 3
$TABLE ID TIME POD TRT AGE IPRED

REFERENCES

1. Rutkow IM. Demographic and socioeconomic aspects of hernia repair in the United States in 2003. Surg Clin North Am 2003;83:1045–51
2. Bay-Nielsen M, Thomsen H, Andersen FH, Bendix JH, Sorensen OK, Skovgaard N, Kehlet H. Convalescence after inguinal herniorrhaphy. Br J Surg 2004;91:362–7
3. Callesen T, Klarskov B, Bech K, Kehlet H. Short convalescence after inguinal herniorrhaphy with standardised recommendations: duration and reasons for delayed return to work. Eur J Surg 1999;165:236–41
4. Callesen T, Bech K, Nielsen R, Andersen J, Hesselfeldt P, Roikjaer O, Kehlet H. Pain after groin hernia repair. Br J Surg 1998;85:1412–4
5. Eklund A, Rudberg C, Smedberg S, Enander LK, Leijonmarck CE, Österberg J, Montgomery A. Short-term results of a randomized clinical trial comparing Lichtenstein open repair with totally extraperitoneal laparoscopic inguinal hernia repair. Br J Surg 2006;93:1060–8
6. Wellwood JM, Sculpher MJ, Stoker D, Nicholls GJ, Geddes C, Whitehead A, Singh R, Spiegelhalter D. Randomised controlled trial of laparoscopic versus open mesh repair for inguinal hernia: outcome and cost. BMJ 1998;317:103–10
7. Callesen T, Kehlet H. Postherniorrhaphy pain. Anesthesiology 1997;87:1219–30
8. Simone DA, Baumann TK, Lamotte RH. Dose-dependent pain and mechanical hyperalgesia in humans after intradermal injection of capsaicin. Pain 1989;38:99–107
9. Simone DA, Nolano M, Johnson T, Wendelschafer-Crabb G, Kennedy WR. Intradermal injection of capsaicin in humans produces degeneration and subsequent reinnervation of epidermal nerve fibers: correlation with sensory function. Neuroscience 1998;18:8947–59
10. Caterina MJ, Schumpelick V, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997;23:816–24
11. Nolano M, Simone DA, Wendelschafer-Crabb G, Johnson T, Hazen E, Kennedy WR. Topical capsaicin in humans: parallel loss of epidermal nerve fibers and pain sensation. Pain 1999;81:135–45
12. Cantillon M, Vause E, Sykes D, Tagoe M. Safety, tolerability and efficacy of intraoperative ALGRX 4975 in a randomized, double-blind, placebo-controlled study of subjects undergoing bunionectomy. J Pain 2005;6(suppl 1):S48
13. Cantillon M, Vause E, Sykes D, Russel R, Moon A, Hughes S. Preliminary safety, tolerability and efficacy of ALGRX 4975 in Osteoarthritis (OA) of the knee. J Pain 2005;6(suppl 1):S39
14. Diamond E, Richards P, Miller T. ALGRX 4975 reduces pain of intermetatarsal neuroma: Preliminary results from a randomized, double-blind, placebo-controlled, phase II multicenter clinical trial. J Pain 2006;7(suppl 1):41
15. Richards P, Vasko G, Stasko I, Lacko M, Hewson G. ALGRX 4975 reduces pain of acute lateral epicondylitis: Preliminary results from a randomized, double-blind, placebo-controlled, phase II multicenter clinical trial. J Pain 2006;7(suppl 1):3
16. Andersen FH, Nielsen K, Kehlet H. Combined ilioinguinal blockade and local infiltration anaesthesia for groin hernia repair–a double-blind randomized study. Br J Anaesth 2005;94:520–3
17. Matthews JN, Altmann DG, Campbell JN, Royston P. Analysis of serial measurements in medical research. BMJ 1990;300:230–5
18. Caterina MJ, Julius D. The vanilloid receptor: a molecular gateway to the pain pathway. Annu Rev Neurosci 2001;24:487–517
19. Carpenter SE, Lynn B. Vascular and sensory responses of human skin to mild injury after topical treatment with capsaicin. Br J Pharmacol 1981;73:755–8
20. Lamotte RH, Shain CN, Simone DA. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. J Neurophysiol 1991;66:190–211
21. Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D. The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron 1998;21:531–43
22. Dedov VN, Roufogalis BD. Mitochondrial calcium accumulation following activation of vanilloid (VR1) receptors by capsaicin in dorsal root ganglion neurons. Neuroscience 2000;95:183–8
23. Frerick H, Keitel W, Kuhn U, Schmidt S, Bredehorst A, Kuhlmann M. Topical treatment of chronic low back pain with a capsicum plaster. Pain 2003;106:59–64
24. Watson CP, Evans RJ. The postmastectomy pain syndrome and topical capsaicin: a randomized trial. Pain 1992;51:375–9
25. Tandan R, Lewis GA, Krusinski PB, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy. Controlled study with long-term follow-up. Diabetes Care 1992;15:8–14
26. Deal CL, Schnitzer TJ, Lipstein E, Seibold JR, Stevens RM, Levy MD, Albert D, Renold F. Treatment of arthritis with topical capsaicin: a double-blind trial. Clin Ther 1991;13:383–95
27. Flood P, Daniel D. Intranasal Nicotine for Postoperative Pain Treatment. Anesthesiology 2004;101:1417–21
28. Lamotte RH, Lundberg TER, Torebjork HE. Pain, hyperalgesia, and activity in nociceptive C units after intradermal injection of capsaicin. J Physiol 1992;448:749–64
29. LeBlanc KA, Bellanger D, Rhynes K, Hausmann M. Evaluation of continuous infusion of 0.5% bupivacaine by elastomeric pump for postoperative pain management after open inguinal hernia repair. J Am Coll Surg 2005;200:198–202
30. Oakley MJ, Smith JS, Anderson JR, Fenton-Lee D. Randomized placebo-controlled trial of local anaesthetic infusion in day-case inguinal hernia repair. Br J Surg 1998;85:797–9
31. Schurr MJ, Gordon DB, Pellino TA, Scanlon TA. Continuous local anesthetic infusion for pain management after outpatient inguinal herniorrhaphy. Surgery 2004;136:761–9
32. Sanchez B, Waxman K, Tatevossian R, Gamberdella M, Read B. Local anesthetic infusion pumps improve postoperative pain after inguinal hernia repair: a randomized trial. Am Surg 2004;70:1002–6