Lidocaine Patch (5%) in Treatment of Persistent Inguinal Postherniorrhaphy Pain

A Randomized, Double-blind, Placebo-controlled, Crossover Trial

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ABSTRACT

Background: Evidence-based pharmacological treatment options for patients with persistent inguinal postherniorrhaphy pain are lacking.

Methods: Twenty-one male patients, with severe, unilateral, persistent inguinal postherniorrhaphy pain, participated in a randomized, double-blind, placebo-controlled crossover trial, receiving lidocaine patch (5%) and placebo patch treatments in periods of 14 days separated by a 14-day wash-out period. Pain intensities (at rest, during movement, and pressure evoked [Numerical Rating Scale]) were assessed before treatment and on the last 3 days of each treatment period. Patients were *a priori* divided into two subgroups based on quantitative sensory testing (+/− thermal "hyposensitivity"). Skin biopsies for intraepidermal nerve fiber density assessment were taken at baseline, and quantitative sensory testing was performed before and after each treatment period. The primary outcome was change in pain intensity assessed as the difference in summed pain intensity differences between lidocaine and placebo patch treatments.

Results: There was no difference in summed pain intensity differences between lidocaine and placebo patch treatments in all patients (mean difference 6.2% [95% CI = −6.6 to 18.9%]; $P = 0.33$) or in the two subgroups (+/− thermal "hyposensitivity"). The quantitative sensory testing (n = 21) demonstrated an increased pressure pain thresholds after lidocaine compared with placebo patch treatment. Baseline intraepidermal nerve fiber density (n = 21) was lower on the pain side compared with the nonpain side (−3.8 fibers per millimeter [95% CI = −6.1 to −1.4]; $P = 0.003$). One patient developed mild erythema in the groin during both treatments.

Conclusions: Lidocaine patch treatment did not reduce combined resting and dynamic pain ratings compared with placebo in patients with severe, persistent inguinal postherniorrhaphy pain.

What We Already Know about This Topic

- Pain is common after inguinal hernia repair, and approximately 5% of patients suffer from severe postherniorrhaphy pain
- The nature of this pain is often neuropathic

What This Article Tells Us That Is New

- Lidocaine patches (5%) caused increased pressure pain threshold compared with placebo patch treatment
- However, lidocaine patch treatment did not lead to decreases in summed pain intensity differences

SEVERE, persistent pain after inguinal herniorrhaphy interfering with daily activities occurs in approximately 5% of patients and has a substantial impact on quality of life.[1–3] Detailed sensory assessments with quantitative sensory testing (QST) have indicated neuropathic pain components in persistent inguinal postherniorrhaphy pain (PIPP).[4,5]

Systemic pharmacological treatment with acetaminophen, nonsteroidal antiinflammatory drugs, opioids,

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anticonvulsants (*e.g.*, pregabalin and gabapentin), tricyclic antidepressants, and selective serotonin and norepinephrine reuptake inhibitors is used in the management of PIPP, despite the lack of procedure-specific evidence of efficacy from randomized studies. Lidocaine patches have been recommended as a first-line treatment option for localized neuropathic pain,[6] but there is a void in the literature with regard to postsurgical neuropathic pain. Topical treatment with a lidocaine patch (5%) has potential advantages due to the local action and low systemic exposure of lidocaine, leading to a low risk of systemic adverse events and drug interactions.[7] Presumably, the lidocaine patch reduces pain by acting on voltage-gated sodium channels on hyperactive or damaged nociceptors, thereby decreasing afferent nociceptive input.[7,8] In randomized studies, lidocaine patches were effective in patients with postherpetic neuralgia,[7] and open-label studies have suggested efficacy in other neuropathic pain conditions.[9] An analgesic effect of lidocaine patches in persistent postsurgical pain has been suggested,[10,11] but randomized controlled studies are lacking.

A classification of patients into predefined subgroups based on their sensory profiles has been proposed in studies assessing drug efficacy.[12,13] In a randomized, placebo-controlled crossover study in postherpetic neuralgia patients, Wasner *et al.*[14] demonstrated that lidocaine patches reduced pain in patients with impaired nociceptor function, as indicated by hypoalgesia to heat, but *not* in patients with preserved/sensitized nociceptor function. According to this QST profile-based approach, patients in the current study were *a priori* divided into two subgroups according to their thermal thresholds: one group *with* thermal "hyposensitivity" and another group *without* thermal "hyposensitivity." Thus, in the current study, we tested the hypothesis that lidocaine patch treatment would reduce pain in PIPP and that the analgesic efficacy would be different in subgroups of patients based on sensory profiles. The aims of the study were *first* to investigate the effects of lidocaine patches on pain and sensory thresholds for the treatment of PIPP and *second* to evaluate sensory profile-dependent differences in analgesic efficacy of the lidocaine patch. In addition, skin punch biopsies with baseline assessments of intraepidermal nerve fiber density (IENFD) were included to morphologically complement the patients' sensory profile.

Materials and Methods

This randomized, double-blind, placebo-controlled, crossover study was approved by the Ethics Committee of the Capital Region of Denmark (H-2-2011-051), the Danish Medicines Agency (EudraCT-Nr. 2011-001258-27), and The Danish Data Protection Agency. The study was registered on ClinicalTrials.gov (NCT01443325). It was conducted in compliance with guidelines for Good Clinical Practice and was monitored by the Copenhagen University Hospital Good Clinical Practice Unit. The study was conducted at the Rigshospitalet, Multidisciplinary Pain Centre, between September 2011 and June 2012. Patients included in the study were referred to the Multidisciplinary Pain Centre by a surgeon or general practitioner. All patients gave written informed consent to participate in the study. Inclusion criteria specified male patients, aged 18 yr or more, with severe unilateral PIPP (Numerical Rating Scale [NRS, 0–10] >6) for more than 6 months. Concomitant analgesics were permitted, provided that patients had received a stable regimen for at least 4 weeks before study entry and were maintained on a stable dose during the study. Exclusion criteria were known allergy to local anesthetic drugs or vehicle ingredients in the patches, inflamed or injured skin at the application site, severe cardiac impairment, use of class I antiarrhythmic drugs (*e.g.*, tocainide and mexiletine), known severe hepatic disorder, known severe renal impairment, known recurrent hernia, alcohol or drug abuse, known diseases impairing central or peripheral nerve function, bilateral groin pain, inability to understand Danish, signs of cognitive impairment, or inability to understand and cooperate with study requirements. Patients were recruited in a 1:1 ratio according to their thermal sensory profile in the groin region evaluated with assessments of warmth detection threshold, cool detection threshold, heat pain threshold, and cold pain threshold. Patients with 3 or more increased thermal thresholds were classified as patients with thermal "hyposensitivity." Patients with 2 or less increased thresholds (including normal or decreased thresholds) were classified as patients *without* thermal "hyposensitivity." An increased thermal threshold was defined by a side-to-side difference in threshold of 2°C or more compared with the contralateral side or a control site (lower arm) in patients who were bilaterally operated.

Randomization and Blinding

Randomization was performed by Herning Hospital Pharmacy (Herning, Denmark) using a computer-generated randomization list.** Block randomization with block sizes of four patients was used. The lidocaine 5% patches and the placebo patches appeared identical and were packed by the hospital pharmacy in identical small plastic boxes. The patients and the investigators were blinded to the treatment sequence throughout the study.

Pain Ratings and Sleep Interference

Patients recorded pain ratings and sleep interference in a diary. Pain intensity was recorded on an NRS (0 = no pain and 10 = worst pain imaginable) twice-daily (morning and evening) on the last 3 days before treatment and on the last 3 days in each treatment period. Pain intensity was evaluated during three standardized conditions: at rest in the supine position, during transition from supine to sitting position,

** Available at: www.randomization.com. Accessed July 16, 2013.

and during the patient's palpation of the most painful area in the groin. In addition, sleep interference due to pain was evaluated every morning in the last 3 days before treatment and on the last 3 days in each treatment period with the Daily Sleep Interference Scale (0–10, 0 = pain did not interfere with sleep, 10 = pain completely interfered with sleep).[15] Patients were telephonically contacted at 14-day intervals by the research nurse and reminded about the 3-day assessment period.

Questionnaires

Patients completed questionnaires, assessing secondary endpoints, before and after each patch treatment period. The self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (S-LANSS)[16] was used for evaluation of neuropathic pain. Psychological factors were assessed with the Hospital Anxiety and Depression Scale [17] and the Pain Catastrophizing Scale.[18]

Sensory Mapping

Before sensory testing, hair in the inguinal and suprapubic regions was cautiously trimmed with a surgical clipper (3M 9671, St. Paul, MN). Sensory mapping in the inguinal area was performed with a 25°C metal roll (Somedic AB, Hörby, Sweden; width 3.2 cm), moved in linear paths at a rate of 1–2 cm/s from skin with normal cool sensation into the inguinal area to indicate sensory changes. Changes in cool perception (hypoesthesia, hyperesthesia) were indicated by a marker on the skin, and subsequently the mapped areas were transferred to a transparent sheet. Area assessment was performed with a computer-assisted drawing program (Canvas 12.0; ACD Systems, Seattle, WA).

QST

The QST testing area included the point of maximum pain, and the assessments were made in both inguinal regions. Thermal detection and pain thresholds (warmth detection threshold, cool detection threshold, and heat pain threshold) were assessed with a computer-controlled thermode (Somedic AB; $2.5 \times 5.0\,cm^2$). Baseline temperature was 32°C, and thermal stimuli were applied at a rate of ±1°C/s and the cutoff limits were set at 50° and 5°C for heat and cold assessments, respectively. A heat stimulus (5 s at 47°C, ramp rate 1°C/s) was applied to assess the suprathreshold heat pain perception evaluated by the patient (NRS, 0–10). Pressure pain threshold was assessed at the point of maximum pain using a pressure algometer (Somedic AB; 1-cm^2 felt-tipped probe) applied perpendicularly to the skin, until pain was reported or the pressure exceeded the cutoff value (350 kPa). All QST parameters were tested in triplicate and median values were used. Sensory mapping and QST were performed before and after each treatment period (fig. 1).

Skin Biopsies

After the QST assessments at the first clinical visit, two 3-mm punch biopsies (disposable biopsy punch; Miltex, York, PA) were taken, using a sterile technique during local anesthesia with 10 mg/ml of mepivacaine (AstraZeneca AB, Södertälje, Sweden). The biopsies were taken at the point of maximum pain, and on the contralateral side as a control, and IENFD was assessed in accordance with previously described techniques.[19,20] The skin biopsies were fixed in 4% paraformaldehyde, washed in phosphate buffer solution, and stored in 10% sucrose with 0.1 M phosphate buffer solution at 4°C. The biopsies, blinded with regard to side, were subsequently forwarded to the Department of Neurology, University of Würzburg, Würzburg, Germany, for analyses. Cryostat sections (50 μm) were immunoreacted with the panneuronal marker PGP9.5 (1:800; UltraClone, Wellow, United Kingdom) and visualized with Cy3-labeled anti-rabbit antibodies (1:100; Amersham Biosciences, Piscataway, NJ), and counted using a Zeiss Axiophot 2 microscope (Wetzlar, Germany) and Spot advanced software (Windows Version 4.5; Sterling Heights, MI).

Treatment Procedure

The lidocaine 5% patches (Versatis, $14 \times 10\,cm^2$; Grünenthal GmbH, Aachen, Germany) contain 700 mg (5% w/w) of lidocaine. Lidocaine is continuously released at the site of patch application. The systemic uptake is low with approximately 3% reaching systemic circulation.[9] Patch treatment started 14 days after skin biopsies were taken to allow time for wound healing. At the first and third clinical visit, patients received a small plastic box with patches for the next treatment period. Patients were instructed to apply one patch in the groin region with the point of maximum pain in the center of the patch. The patch was applied for 12 h/day followed by a patch-free

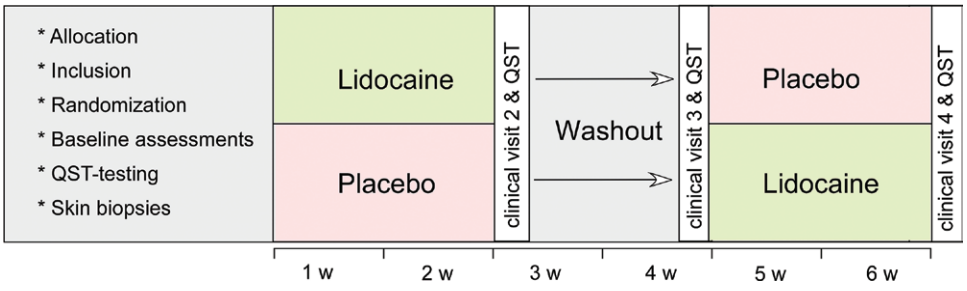

Fig. 1. Study algorithm. QST = quantitative sensory testing.

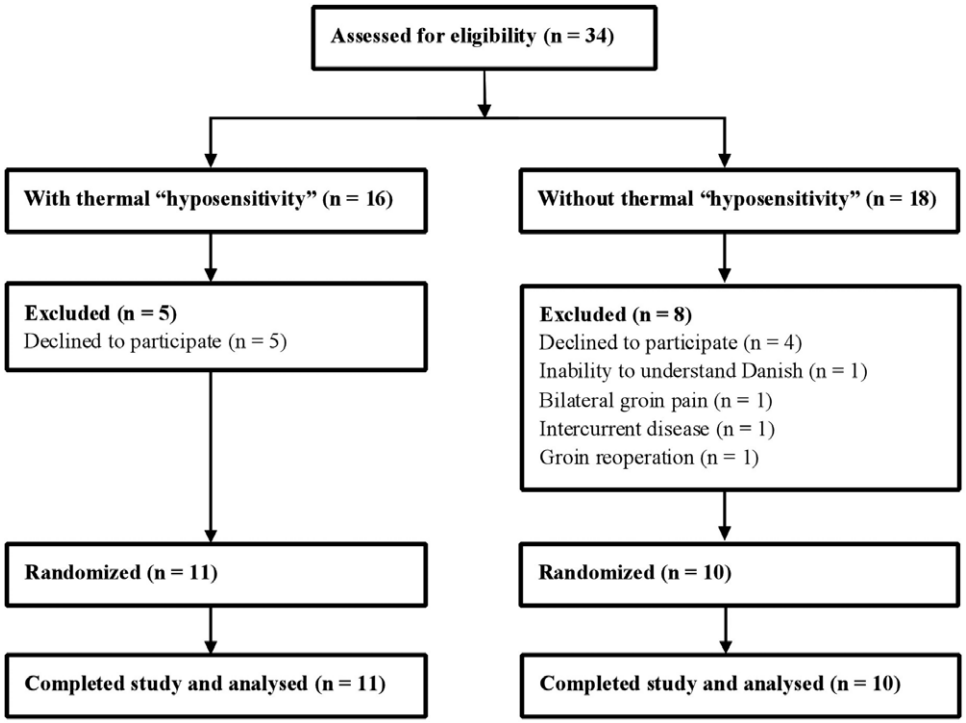

Fig. 2. Flow diagram of patients in the study.

interval of 12 h. Each treatment period lasted 14 days separated by a 14-day wash-out period to reduce carry-over effects (fig. 1). Clinical visits with QST assessments and questionnaires were scheduled at days 15–17, days 25–27, and days 43–45 after start of the first treatment period. A time margin of 3 days was allowed.

Table 1. Baseline Patient Characteristics

	With Thermal "Hyposensitivity" (n = 11)	Without Thermal "Hyposensitivity" (n = 10)	All Patients (n = 21)
Age (yr)*	59 (15)	55 (12)	57 (13)
BMI (kg/m^2)*	25 (2)	25 (4)	25 (3)
Duration of pain (mo)†	49 (25–67)	47 (32–73)	47 (29–70)
Primary/recurrent operation, *n*‡	9/2	7/3	16/5
Open mesh/laparoscopic, *n*‡	10/1	6/4	16/5
Unilaterally/bilaterally operated, *n*	7/4	5/5	12/9
Exploratory surgery for pain, yes/no, *n*	6/5	4/6	10/11
Concomitant pain medication, yes/no, *n*	4/7	5/5	9/12
Acetaminophen, *n*	3	3	6
NSAIDs, *n*	3	2	5
Gabapentin, *n*	0	1	1
Tricyclic antidepressant, *n*	0	1	1
Opioids, *n*	1	3	4
Baseline pain ratings§			
Pain at rest (NRS)	5 (2–7)	7 (5–8)	6 (4–7)
Pain during movement (NRS)	5 (2–8)	8 (5–9)	7 (5–8)
Pain during palpation (NRS)	8 (5–9)	8 (5–9)	8 (6–8)

* Mean (SD). † Median (25–75% interquartile range). ‡ Pain-generating inguinal hernia operation. § Pain ratings at baseline assessed at rest in the supine position, during transition from supine to sitting position, and during the patient's palpation of the most painful area in the groin. Values are medians (95% CI).

BMI = body mass index; NRS = Numerical Rating Scale; NSAID = nonsteroidal antiinflammatory drugs.

Table 2. Changes in Pain Intensity Presented as SPID for Lidocaine and Placebo Patch Treatments, and the Estimated Effect Size

	Lidocaine	Placebo	Difference	*P* Value
With thermal "hyposensitivity" (n = 11)				
SPID (NRS)	−0.7 (−4.0 to 2.6)	−0.2 (−3.0 to 2.7)	−0.5 (−3.8 to 2.7)	0.71
SPID percentage	−4.8 (−19.2 to 9.5)	−0.4 (−16.6 to 15.8)	−4.4 (−20.6 to 11.7)	0.55
Without thermal "hyposensitivity" (n = 10)				
SPID (NRS)	6.9 (0.5–13.3)	1.7 (−1.8 to 5.2)	5.2 (−1.5 to 11.9)	0.11
SPID percentage	19.2 (2.1–36.2)	1.4 (−9.4 to 12.1)	17.8 (−2.6 to 38.2)	0.08
All patients (n = 21)				
SPID (NRS)	2.9 (−0.7 to 6.5)	0.7 (−1.4 to 2.8)	2.2 (−1.3 to 5.7)	0.21
SPID percentage	6.6 (−4.9 to 18.1)	0.4 (−8.6 to 9.5)	6.2 (−6.6 to 18.9)	0.33

Values are mean (95% CI). Positive values of SPID indicate pain reduction after treatment. *P* values indicate paired comparisons of SPID (lidocaine *vs*. placebo [paired *t* test]).

NRS = Numerical Rating Scale; SPID = summed pain intensity difference.

Statistical Analysis

Pain intensities during the three standardized conditions (at rest, movement, and pressure evoked) were assessed twice-daily during the last 3 days before and during the last 3 days of each treatment period. The median value of the three standardized pain assessments was used to calculate the summed pain intensity (SPI) values (comprising six median values [assessments twice-daily for 3 days]). The SPI differences (SPID) were calculated as the differences in SPI values before and after each patch treatment period. The primary outcome was the difference in SPID between lidocaine patch and placebo patch treatments calculated for all patients (n = 21). In addition, the difference in SPID between lidocaine patch and placebo patch treatments was calculated for patients in the two subgroups: patients with thermal "hyposensitivity" (n = 11) and patients without thermal "hyposensitivity" (n = 10).

Relevant variability data from previous studies were not available and the power analysis in this superiority trial therefore was based on the authors' best estimates for the PIPP population. With an estimated within-patient SD for the SPI assessments of 3.1 (NRS), a minimal relevant difference for the six SPI assessments of 6 (NRS), a significance level of 0.01 and a power of 0.8, the estimated number of patients needed were calculated to be 10 in each subgroup (20 in total).

For secondary outcomes, including QST parameters, sensory mapping areas, and questionnaire scores (Daily Sleep Interference Scale, Hospital Anxiety and Depression Scale, Pain Catastrophizing Scale, and S-LANSS), differences between before and after each treatment (Δ values = posttreatment − pretreatment value) were used to compare changes between lidocaine and placebo patch treatments. Data were assessed for normality with Kolmogorov–Smirnov tests and visually by relevant plots. Paired data were analyzed with a *t* test (normally distributed data) or Wilcoxon signed-rank test (nonnormally distributed data). Two-tailed tests were used. Values are presented as mean (95% CI or SD) for normally distributed data and median (95% CI or interquartile range) for nonnormally distributed data. Analyses were performed using statistical software (SPSS 20.0, Chicago, IL). Calculations of nonparametric 95% CI were performed with MedCalc Software (12.3.0.0; Mariakerke, Belgium). To reduce the likelihood of a type I error, due to multiple comparisons, the significance level was set at a *P* value less than 0.01.

Results

Twenty-one patients were randomized. All patients completed the study and were included in the data analyses (fig. 2). Baseline demographics of patients are presented in table 1. Data from the three pain ratings (at rest, during movement, and pressure evoked) are included in the table, Supplemental Digital Content 1, http://links.lww.com/ALN/A964.

Pain

Calculations of changes in pain intensity (SPID) in all patients (n = 21) did not show any differences between lidocaine and placebo patch treatments (table 2 and fig. 3). The mean difference in SPID percentage was (6.2% [95% CI = −6.6 to 18.9%]; *P* = 0.33). Similarly, there was no statistically significant difference between lidocaine and placebo patch treatment in the two subgroups with (n = 11) or without (n = 10) thermal "hyposensitivity." In patients without thermal "hyposensitivity," the mean difference in SPID percentage was (17.8% [95% CI = −2.6 to 38.2%]; *P* = 0.08).

S-LANSS, Psychological Factors, and Sleep Quality

Sixteen of 21 patients (76%) reported an S-LANSS score of 12 or more at baseline suggesting pain components of neuropathic origin.[16] The median (95% CI) S-LANSS score at baseline was 18 (16–18). Analyses of changes in S-LANSS score during treatment demonstrated no differences between lidocaine and placebo patch treatments. In addition, Pain

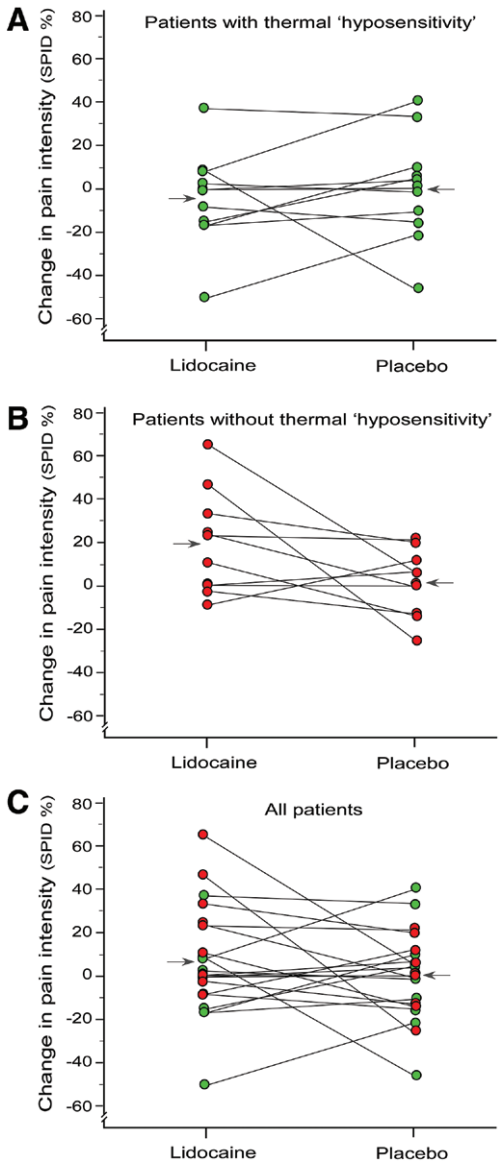

Fig. 3. Summed pain intensity differences (SPIDs) for lidocaine and placebo patch treatments. (*A*) Patients with thermal "hyposensitivity" (n = 11). (*B*) Patients without thermal "hyposensitivity" (n = 10). (*C*) All patients (n = 21). The mean SPIDs are indicated by *arrows*.

Catastrophizing Scale, Hospital Anxiety and Depression Scale scores, and sleep quality (Daily Sleep Interference Scale) did not differ between lidocaine and placebo patch treatments (one patient did not complete all questions from the Hospital Anxiety and Depression Scale questionnaire and was not included in the analysis).

Sensory Mapping

Baseline sensory mapping with a metal cool roller demonstrated sensory abnormalities in the groin area with pain in the majority of patients (fig. 4). All 11 patients with thermal "hyposensitivity" had an area of cool hypoesthesia in the groin. Among the 10 patients without thermal "hyposensitivity," 1 patient had an area with cool hyperesthesia, 5 patients had an area with cool hypoesthesia, and in 4 patients no sensory mapping abnormalities in the groin were observed. Mapping areas did not change between lidocaine and placebo treatments ($P > 0.35$; paired t test).

QST

The pressure pain threshold increased after lidocaine patch treatment compared with placebo in all patients (n = 21), mean difference (33.2 kPa [95% CI = 10.1–56.3]; $P = 0.007$), and in the subgroup of patients with thermal "hyposensitivity" (table 3). Changes in thermal thresholds and suprathreshold heat pain perception did not differ between lidocaine and placebo patch treatments (table 3).

IENFD

Assessment of punch biopsies in the 21 patients with pain revealed a decreased IENFD on the pain side compared with the nonpain side, mean difference (–3.8 fibers per millimeter [95% CI = –6.1 to –1.4]; $P = 0.003$; table 4).

Patients Experience of Pain Relief

Patients were asked whether they experienced pain relief from the treatment. In the "hyposensitivity" subgroup (n = 11), three patients experienced pain relief from the lidocaine patch, one patient from the placebo patch, and seven patients did not experience pain relief from any of the patches. Among patients without thermal "hyposensitivity" (n = 10), five patients experienced pain relief from the lidocaine patch, one patient from the placebo patch, and four patients did not experience pain relief from any of the patches.

Sequence Effect

To investigate a potential sequence effect, the total pain reduction in patients receiving lidocaine patches in the first treatment period was compared with the total pain reduction in patients receiving lidocaine patches in the second treatment period.[21] The analysis (n = 21) demonstrated no sequence effect, mean difference (NRS): –1.5 (95% CI = –11.3 to 8.4); $P = 0.76$ (unpaired t test).

Adverse Events

One patient developed mild erythema in the groin area during treatment with lidocaine and placebo patches. The erythema resolved shortly after treatment completion. No other adverse events or complications were seen.

Discussion

This randomized, double-blind, placebo-controlled study is the first study to evaluate the analgesic and sensory effects of lidocaine patches in a homogenous patient group, with persistent postsurgical pain after well-defined surgical procedures. A neuropathic pain component in PIPP[4,5] is corroborated in the current study by baseline S-LANSS scores suggesting pain of predominantly neuropathic origin in 76%

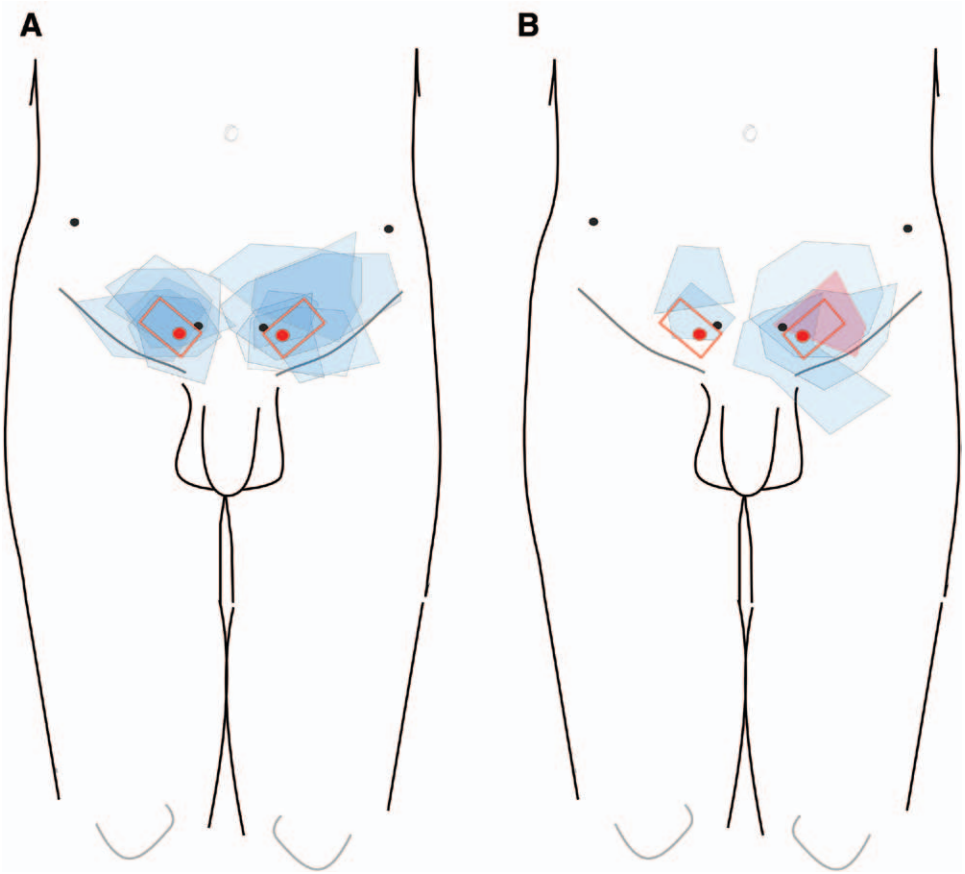

Fig. 4. Sensory mapping at baseline tested with metal cool roller. Areas from each patient were transposed to the drawing. *Small black circles* indicate the superior anterior iliac spine and the pubic tubercle. The *red circles* indicate the approximate site for maximum palpatory pain (on the pain side), and the *red rectangles* indicate the outline of the assessment thermode. *Blue-shaded polygons* indicate individual cool *hypo*esthesia area. *Red-shaded area* indicates cool *hyper*esthesia. (*A*) Patients with thermal "hyposensitivity" (n = 11). (*B*) Patients without thermal "hyposensitivity" (n = 10).

of patients. The study did not show significant differences between lidocaine and placebo patches, for the primary outcome parameter, pain relief. In addition, sensory mapping and QST assessments did not demonstrate cutaneous sensory changes after lidocaine patch treatment; however, a statistically significant effect of lidocaine patches on pressure pain thresholds was observed. Thermal thresholds did not change after lidocaine patch treatment. This finding is in accordance with observations from a randomized controlled trial where the sensory function after lidocaine patch application was assessed in healthy volunteers using QST.[22] In this study, thermal thresholds remained largely unchanged after lidocaine patch application.

IENFD

Skin punch biopsies showed a reduction in IENFD on the pain side compared with the nonpain side. This study is, to our knowledge, the first attempt to quantify nerve fiber density in patients with postsurgical pain, and the finding of reduced IENFD on the painful side corroborates the neuropathic component of the pain. Perioperative injury to one or more of the three inguinal nerves (*i.e.*, the ilioinguinal, iliohypogastric, or genitofemoral nerves) may underlie this reduction in skin innervation.[23]

Treatment Efficacy in Sensory Subgroups

A number of clinical trials in patients with neuropathic pain have reported higher treatment efficacy in certain subgroups based on sensory profiles.[13,24–26] Thus, Wasner *et al.*[14] demonstrated a statistically significant pain relief of lidocaine patches in postherpetic neuralgia patients with impaired nociceptor function (heat hypoalgesia), but not in patients with preserved/sensitized nociceptor function. Results from the current study on the contrary suggest a possible analgesic effect of lidocaine patches in the subgroup of patients with preserved nociceptors (without thermal "hyposensitivity"), although statistical significance was not achieved. In a lidocaine patch study in patients with distal painful neuropathies, no association between sensory profiles and lidocaine patch treatment response was observed.[27] Thus, in the few available studies, no consistent association between sensory profiles and treatment efficacy of lidocaine patches has been observed. Furthermore, the specific pain-relieving mechanisms of lidocaine patches in patients with neuropathic pain remain to be clarified.[28,29]

Table 3. Differences in Quantitative Sensory Assessments before and after Treatment

Δ Values	Lidocaine	Placebo	*P* Value
With thermal "hyposensitivity" (n = 11)			
ΔWDT, (°C)	−0.43 (−2.21 to 1.36)	0.18 (−2.39 to 2.76)	0.71
ΔCDT (°C)	−2.05 (−7.56 to 3.45)	−2.45 (−6.87 to 1.96)	0.91
ΔHPT (°C)	0.36 (−0.85 to 1.58)	1.17 (0.17–2.18)	0.32
ΔPPT (kPa)	33.0 (5.42–60.58)	−12.0 (−33.7 to 9.65)	0.008
ΔSTH (NRS)*‡	0.00 (−1.00 to 1.18)	0.00 (−1.18 to 1.18)	0.76†
Without thermal "hyposensitivity" (n = 10)			
ΔWDT (°C)	0.55 (−2.10 to 3.20)	−0.10 (−2.25 to 2.05)	0.64
ΔCDT (°C)	−2.75 (−7.80 to 2.30)	−0.20 (−1.55 to 1.15)	0.29
ΔHPT (°C)	1.02 (−0.86 to 2.90)	−0.18 (−1.95 to 1.59)	0.13
ΔPPT (kPa)	30.5 (5.08–55.9)	10.2 (−11.6 to 31.2)	0.28
ΔSTH (NRS)*	0.00 (0.00–0.00)	0.00 (−1.58 to 1.53)	0.83†
All patients (n = 21)			
ΔWDT (°C)	0.04 (−1.40 to 1.47)	0.05 (−1.49 to 1.59)	0.99
ΔCDT (°C)	−2.39 (−5.80 to 1.03)	−1.38 (−3.64 to 0.87)	0.63
ΔHPT (°C)	0.68 (−0.33 to 1.68)	0.53 (−0.42 to 1.48)	0.80
ΔPPT (kPa)	31.8 (14.7–48.9)	−1.43 (−16.3 to 13.4)	0.007
ΔSTH (NRS)*	0.00 (0.00–0.00)	0.00 (−0.44 to 1.00)	0.65†

Values are mean (95% CI). Δ value is posttreatment minus pretreatment value. *P* values indicate paired comparisons of Δ values (lidocaine *vs*. placebo [paired *t* test]). Positive differences for WDT, HPT, and PPT, and negative differences for CDT, indicate increased thresholds after treatment.

* Median (95% CI). † Wilcoxon signed-rank test. ‡ The suprathreshold heat pain perception was rated as 0 in one patient.

CDT = cool detection threshold; HPT = heat pain threshold; NRS = Numerical Rating Scale; PPT = pressure pain threshold; STH = suprathreshold heat pain perception; WDT = warmth detection threshold.

Deep Inflammatory Pain

In a subgroup of PIPP patients, a continued inflammatory response to the implanted mesh may contribute to the persistent pain state.[23] The presence of deep inflammatory pain may contribute to the lack of pain-relieving effect observed because lidocaine patches are assumed to exert their action on cutaneous afferents. However, the increased pressure pain thresholds observed in the current study after lidocaine patch treatment may indicate an effect of lidocaine on deep tissue sensitivity, although not translating to an overall pain-relieving effect in this patient group.

Central Sensitization

Central sensitization is considered to play an important role in development and maintenance of neuropathic pain[23,30] and may explain the lack of pain-relieving effect observed in this study. Thus, it may be speculated that the treatment period of 2 weeks used may be an insufficient period to attenuate central sensitization. Nevertheless, in patients with various focal peripheral neuropathic pain syndromes, a statistically significant pain relief with lidocaine patches compared with placebo was observed in a study with a treatment period of 7 days.[31] In addition, in patients with postherpetic neuralgia, a statistically significant pain reduction with lidocaine patches compared with placebo was observed after only 4 h of patch application,[32] and recently, a treatment trial duration of 2–3 weeks have been recommended for lidocaine patches.[6,33]

Limitations and Advantages

One limitation of the current study is the multiple comparisons made, increasing the likelihood of type I errors due to mass significance. We attempted to reduce this risk by using

Table 4. Assessments of IENFD on the Pain Side and Nonpain Side

	Pain Side (IENFD/mm)	Nonpain Side (IENFD/mm)	*P* Value
With thermal "hyposensitivity" (n = 11)	2.0 (0.2–3.8)	6.8 (4.0–9.6)	0.02
Without thermal "hyposensitivity" (n = 10)	4.8 (2.6–7.1)	7.5 (5.7–9.4)	0.08
All patients (n = 21)	3.3 (1.9–4.8)	7.1 (5.6–8.7)	0.003

Values are mean (95% CI). *P* values indicate paired comparisons of IENFD (pain side *vs*. nonpain side [paired *t* test]).
IENFD = intraepidermal nerve fiber density.

a significance level of 0.01. An advantage of the study is the meticulous study design with baseline sensory, psychological, and morphological characterization of patients and detailed follow-up with repeated QST and no drop-outs.

Conclusions

In conclusion, lidocaine patch treatment did not reduce combined resting and dynamic pain ratings, compared with placebo, in patients with severe PIPP. Furthermore, we did not find any significant sensory profile-dependent differences in analgesic efficacy of the lidocaine patch. Additional studies are needed to clarify treatment indications and mechanisms of action of lidocaine patches in patients with persistent postsurgical pain.

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