The role of peripheral afferents in persistent inguinal postherniorrhaphy pain: a randomized, double-blind, placebo-controlled, crossover trial of ultrasound-guided tender point blockade

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Abstract

Background: Severe, persistent inguinal postherniorrhaphy pain (PIPP) is a debilitating condition that develops in 2–5% of patients. PIPP may be neuropathic in nature, yet the lesion in the peripheral nervous system has not been located. Most PIPP-patients demonstrate a tender point (TP) in the medial aspect of the inguinal region that triggers pain upon minimal pressure. As TPs may play a role in the pathophysiology of PIPP, the aim of this trial was to investigate the analgesic effects of local anaesthetic TP-blockade.

Methods: A randomized, double-blind, placebo-controlled, crossover trial was performed in 14 PIPP-patients and six healthy volunteers. All participated in two sessions, seven days apart, receiving 10 ml of 0.25% bupivacaine or normal saline via an ultrasound-guided fascial plane block at the TP. The TP-area was used for pain assessments (at rest, on movement, with 100 kPa pressure-algometry) and quantitative sensory testing (pressure pain thresholds, thermal detection/pain thresholds, supra-threshold heat perception), before and after the TP-blockade.

Results: The median (95% CI) reduction in pain was 63% (44.1 to 73.6%) after bupivacaine compared with 36% (11.6 to 49.7%; *P* =0.003) after placebo. Significant increases in cool detection (*P* =0.01) and pressure pain thresholds (*P* =0.009) with decreases in supra-threshold heat pain perception (*P* =0.003) were seen after bupivacaine only. In four out of six volunteers, increased thermal and evoked-pain thresholds after bupivacaine compared with placebo, was demonstrated.

Conclusions: This trial demonstrates that peripheral afferent input from the TP-area is important for maintenance of spontaneous and evoked pain in PIPP.

Clinical trial registration: NCT02065219.

Key words: bupivacaine; chronic pain; herniorrhaphy; inguinal hernia; nerve blockade; randomized controlled trial

Debilitating post-surgical pain develops in 2–5% of patients after inguinal herniorrhaphy1 and it has been suggested that it is predominantly of neuropathic origin, because of its clinical characteristics and findings from neurophysiological examinations.2 3 Persistent inguinal postherniorrhaphy pain (PIPP) may result from nerve damage either incurred at the time of surgery or as a delayed consequence of a continuous inflammation induced by the implanted mesh, leading to nerve entrapment and...
neuroma formation. However, some patients continue to experience PIPP despite mesh removal and selective neurectomies of the iliohypogastric and ilioinguinal nerves.45 The trial was conducted on healthy volunteers and PIPP-patients from October 2013 until June 2014 at the Multidisciplinary Pain Center, Rigshospitalet, Copenhagen University, Denmark.

Healthy volunteers were included to assess the feasibility of the fascial plane block (tender point block) as this block has never been evaluated in the literature. Healthy volunteers were recruited through advertising on a website for medical research test subjects (www.forsoegspersoner.dk) and were all male, aged ≥18 yr with no known medical problems or previous inguinal surgery.

Subjects

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Patients were recruited from the Multidisciplinary Pain Center and inclusion criteria were: males; aged ≥18 yr; inguinal pain > six months duration after open inguinal herniorrhaphy; surgery performed >12 months earlier; and pain score ≥5/10 on numerical rating scale (NRS: zero=no pain and 10=worst imaginable pain; criteria added after trial commencement to achieve a homogenous group).13 Exclusion criteria for the trial were: known allergy to local anaesthetics; known recurrent inguinal hernia; work-related inguinal hernia; other operations in the inguinal or genital area; impaired cognitive function; inability to understand written or spoken Danish; known central or peripheral nerve diseases; alcohol or drug abuse; and inability to cooperate with participation requirements.

Trial design

The design was randomized, double-blind, placebo-controlled, crossover trial. Each trial participant was to undergo two sessions (Fig. 1) at least seven days apart, where the participants underwent a pain assessment, QST measurements, followed by an ultrasound-guided tender point blockade with local anaesthetic or placebo. Thirty min after the injection the pain assessment and QST assessments were repeated. Only the patients completed pain diaries before and after each injection (Fig. 1).

Randomization and blinding

A Rigshospitalet employee (not involved in the trial) randomized the participants to receive placebo/bupivacaine or bupivacaine/placebo using www.random.org. The session sequence for each participant was duplicated so that there was one for each session and placed in separate, non-transparent envelopes, numbered for the participant and session accordingly. The envelopes were kept in a locked drawer accessible only by the research nurse (not involved in the trial). For each session, the research nurse opened the specific envelope for that trial participant and session, then prepared the solution for injection. The solution was placed at a separate, secure location so that the investigators and nurse did not meet.

Pain assessment

At each session a summed pain intensity (SPI) score was taken, before and after injection (Fig. 1), by combining three pain scores using the NRS. Thus, SPI = NRSR + NRSRSP + NRSRSP, where NRSR is pain at rest (supine), NRSRSP is pain on movement (transferring from supine to standing) and NRSRSP is pain on application of 100 kPa by pressure algometry (1 cm² felt-tipped probe; Somedic AB, Hörrby, Sweden) centered on the maximum point of pain (P), i.e. the tender point in patients and the superficial inguinal ring in volunteers. From the SPIs the summed pain difference (SPID), i.e. SPI before vs SPI after injection, was calculated for each session (cf. paragraph on statistics).

Editor’s key points

- Better understanding of the underlying mechanisms of persistent post herniorrhaphy pain may improve management.
- The effects of fascial plane block on sensory processing in patients and volunteers were studied.
- Bupivacaine resulted in sensory changes indicative of a strong peripheral component maintaining post herniorrhaphy pain.
- These findings need to be explored further, to help direct future treatment strategies appropriately.
Quantitative sensory testing

Sensory mapping was performed in the inguinal area with a cool metal roller (25°C; width 3.2 cm; Somedic AB, Sweden) at a rate of 1–2 cm s\(^{-1}\), delineating areas with cool hypo-/hyper-aesthesia or allodynia, as previously described.\(^7\) The areas were marked with a felt tipped pen on the skin, traced onto a transparent sheet and scanned. The area of each sensory map was calculated from the scans using graphical software (Canvas 8.0.3 Deneba, ACD Systems International, Victoria, Canada) Table 1.

Thermal thresholds were determined using a computerized thermode (active surface: 2.5×5.0 cm\(^2\); MSA, Somedic AB, Sweden) placed in the inguinal region with its centre over the PT. The thermo-neutral baseline temperature was 32°C, ramp rate was plus or minus 1°C s\(^{-1}\) and cut-off values were 50°C for heat stimuli and 5°C for cold stimuli. The participant pressed a response button terminating the stimulus when warmth detection threshold (WDT), cool detection threshold (CDT) and heat pain threshold (HPT) were perceived. All thresholds were obtained in triplicate with random intervals (4–6 s) between each stimulus, and the thermode returned to baseline temperature between each measurement. The values generated during thermal threshold testing were the differences between the thermo-neutral temperature (32°C) and the threshold temperature achieved. Supra-threshold heat pain perception (SHT) was obtained by a short tonic heat stimulus (47°C, 5 s) and subsequent pain score. Pressure pain thresholds (PPT) were determined using a pressure algometer applied perpendicularly to the skin at a rate of 20–30 kPa s\(^{-1}\) with a 350 kPa limit. The participant pressed a button (terminating the stimulus) when the PPT was reached. The differences for QST-values were calculated: \(\Delta\)value=(post-block - pre-block) value.

Ultrasound-guided tender point blockade

All blocks were performed by an anaesthetist (N.W.) using an ultrasound unit (Venue 40, GE Healthcare, Waukesha, WI, U.S. A) equipped with a 12L-SC, broadband, linear probe. The inguinal area was cleaned and a sterile drape with access to the inguinal area was placed over the skin. The P\(_T\) was marked on the skin and the middle of the ultrasound probe was lined up with this mark. Colour Doppler ultrasonography was used to identify blood vessels in order to avoid intravascular injection. A pointer on the ultrasound screen represented the middle of the probe (Fig. 2A). A 22G block needle was used and its tip was aimed at this pointer using an in-plane technique. The solution was injected at this point in the fascial plane just above the spermatic cord. Confirmation of spread of the solution was seen on the ultrasound screen (Fig. 2B).

Pain and sleep diaries

The patients completed diaries for seven days before the first session to establish baseline pain behaviour. After each injection, the patients were asked to complete another identical pain diary for seven days. Patients were asked to indicate pain scores using the NRS twice a day in three predetermined states: at rest (supine), on movement (supine to standing) and with manual pressure on P\(_T\). Sleep quality was also assessed in the diary using a NRS (0=pain had no effect on sleep, 10=pain totally affected sleep).\(^14\)

Statistics

Sample size

The volunteers’ sample size calculation used CDT-data from a previous trial with a mean (intra-subject sd) of 30.4 (0.68°C) and a minimal relevant difference (MIREDF) of 5.0°C (http://hedwig. mgh.harvard.edu)\(^7\). For this crossover trial using a 0.01 (α...
significance level and a power of 0.90 ($\beta=0.10$), it was calculated that 4 subjects were needed. In order to compensate for dropouts, the number of volunteers was set to six. For the patients’ sample size calculation, a mean (intra-subject SD) baseline SPI of 12.7 (2.2) NRS units, and a minimal relevant difference of 6.4 NRS units were used. For this crossover trial, with an expected ratio of bupivacaine responders to non-responders and placebo-responders of 0.5, a significance level ($\alpha$) of 0.01 and a power of 0.90 ($\beta=0.10$), the number needed to demonstrate a significant outcome (i.e. responders) was 14 subjects. Responders were defined as patients who had a SPID-value of >50% after bupivacaine blockade and a SPID-value <25% after placebo blockade. Non-responders were defined as patients who had a SPID-value of <50% after bupivacaine blockade with a SPID-value <25% after placebo blockade. Patients who had an SPID value of >25% after placebo blockade were defined as placebo responders.

Statistical analyses
Data were assessed for normal distribution using the Shapiro-Wilk test. The primary outcome was summed pain intensity difference (SPID) after bupivacaine and placebo, where SPID (%) = ($\text{SPI}_{\text{pre-injection}} - \text{SPI}_{\text{post-injection}})/\text{SPI}_{\text{pre-injection}} \times 100$. The summation measure SPID was used to avoid mass significance in repeated measurements as a result of multiple comparisons (i.e. to avoid a type I error). The secondary outcomes were AQST-values. The pain and sleep quality scores from the diaries were tertiary outcomes, where paired analysis was performed comparing placebo to bupivacaine for each equivalent day after the injection. Wilcoxon tests were performed comparing bupivacaine- with placebo-sessions. All data are presented as median (95% CI) except for patient characteristic statistical data, where data are presented as mean (SD) and median (IQR), depending on the distribution. All analyses were performed using statistical software (MedCalc 14.8.1, MedCalc Software bvba, Ostend, Belgium). A significance level of $P<0.01$ was used.

Results
All six volunteers completed the trial with full datasets. Fourteen patients completed the trial (Fig. 3: CONSORT diagram). There were missing data from the pain diaries only, which were excluded from analysis. All other data sets were complete. The only adverse event experienced during the trial was a small self-limiting haematoma in patient number 13.

Patient and volunteer characteristics
Volunteers
The mean (range) age of the volunteers was 28 (21–41) yr and the mean (SD) BMI was 23.2 (2.1) kg m$^{-2}$.

Patients
Mean age was 53 (24 to 83) yr and the mean (SD) BMI was 25.3 (2.5) kg m$^{-2}$. The median (IQR) duration of pain was 35.0 (21.0 to 48.0) mo and median baseline SPI scores were 21.5 (18.0 to 23.5) NRS units.

Pain intensity
Volunteers
The volunteers SPI scores were 0, before and after, either injection. Administration of the blockade was not associated with significant discomfort or pain.

Patients
The median SPID was 63% (44.1 to 73.6%) after bupivacaine compared with 36.2% (11.6 to 49.7%; $P=0.003$) after placebo injection (Fig. 4). The individual pain score differences (NRS-units) demonstrated: a numerical reduction in pain at rest after bupivacaine 1.75 (0.5 to 6.0) compared with placebo 0.75 (0.0 to 2.1; $P=0.03$); no difference in movement-related pain, 3.0 (0.0 to 7.0) after bupivacaine compared with 2.0 (0.9 to 3.1; $P=0.34$) after placebo; and a significant reduction in pressure-evoked pain after bupivacaine 5.3 (4.0 to 7.6) compared with placebo, 2.8 (1.0 to 4.0; $P=0.002$).

Sensory mapping
Volunteers
All six volunteers developed a cool hypoesthesia area after the bupivacaine injection compared with three volunteers after placebo. Median areas: 42.4 cm$^2$ (16.7 to 53.8 cm$^2$) vs 7.8 cm$^2$ (0.0 to 57.0 cm$^2$; $P=0.31$), respectively.
Patients

All had a pre-existing cool hypoesthesia area which did not change after either injection: the difference in area size was $-4.5 \text{ cm}^2 (-11.8 \text{ to } 6.6 \text{ cm}^2)$ after bupivacaine compared with $-1.6 \text{ cm}^2 (-8.6 \text{ to } 5.9 \text{ cm}^2; P=0.76)$ after placebo.

**Sensory thresholds**

**Volunteers**

Increases in thermal thresholds after bupivacaine compared with placebo were seen: $\Delta WDT: 9.6^\circ C \text{ vs. } 0.4^\circ C (P=0.03, \text{ Fig. } 5A)$; $\Delta CDT: 15.0^\circ C \text{ vs. } -0.2^\circ C (P=0.09, \text{ Fig. } 5B)$; and $\Delta HPT: 4.7^\circ C \text{ vs. } -0.2^\circ C (P=0.16; \text{ Fig. } 5C)$. Heat pain perception (NRS-units) was numerically reduced: $\Delta STH -3.5 (-4.1 \text{ to } -0.5) \text{ after bupivacaine compared with } 0.0 (-0.8 \text{ to } 0.0; P=0.06)$ after placebo (Fig. 5D). Numerical increases in $\Delta PPT$ were seen after bupivacaine: $80 \text{ kPa (3.1 \text{ to } 91.0 \text{ kPa}) compared with } -22.5 \text{ kPa (-62.0 \text{ to } 55.6 \text{ kPa}; P=0.13}$ after placebo (Fig. 5E).

**Patients**

There were no significant changes in $\Delta WDT (P=0.15, \text{ Fig. } 5A)$ after bupivacaine injection compared with placebo; however, an increase in $\Delta CDT$ after bupivacaine $4.1^\circ C (1.8 \text{ to } 6.3^\circ C) \text{ compared with placebo 0.3^\circ C (-0.8 \text{ to } 0.8^\circ C; P=0.01; \text{ Fig. } 5B)$, was observed. There were no significant changes in $\Delta HPT (P=0.30, \text{ Fig. } 5C)$. Heat pain perception (NRS-units) was reduced after bupivacaine injection: $\Delta STH -3.5 (-4.1 \text{ to } -0.5)$ compared with $0.0 (-1.0 \text{ to } 0.6; P=0.003)$, after placebo (Fig. 5D). PPT-values were increased: $\Delta PPT$ was $101 \text{ kPa (49.9 \text{ to } 138.9 \text{ kPa}) after bupivacaine compared with 14.5 \text{ kPa (-16.4 \text{ to } 46.2.0 \text{ kPa}; P=0.009}$ after placebo (Fig. 5E).
Fig 5 QST results for all participants. All Δ values are post-injection – pre-injection values. WDT, warmth detection threshold; CDT, cool detection threshold; HPT, heat pain threshold; STH, suprathreshold heat pain perception; PPT, pressure pain threshold. For calculation of WDT, CDT, HPT, STH and PPT see Methods.
potential, peripheral site involved in the pain-signaling pathway for
be because of placebo and/or dry needling effects.
is impeded by the lack of controls as the observed effects could
as a treatment on its own.21 However, signi
the sensory effects of the local anaesthetic block, as demon-
assessments (Fig.5). The heterogeneity of the sensory data indi-
needling, was good. However, the blockade evaluated by QST-
volunteers (patients)
Paired analyses of the daily SPIs and sleep quality scores showed no statistical difference after the bupivacaine injection compared with placebo (Table 2).

Discussion
In this randomized, double-blind, placebo-controlled, crossover trial, ultrasound-guided tender point blockade with bupivacaine had a greater analgesic effect compared with placebo in patients with PIPP. To our knowledge this is the first trial to identify a po-
tential, peripheral site involved in the pain-signaling pathway for
IPP. Furthermore the validity of our finding was corroborated by the sensory effects of the local anesthetic block, as demon-
strated by significant decreases in pain pressure thresholds and
attenuation of suprathreshold heat pain responses.

Volunteers
The feasibility of the procedure, regarding the ease of performing the fascial plane block and the comfort of the subject during needling, was good. However, the blockade evaluated by QST-
variables did not result in consistent changes in the sensory assess-
ments (Fig.5). The heterogeneity of the sensory data in-
cates that our sample size estimate was incorrect. However, a cautious post hoc sample size estimate of CDT from our data (P=0.01; power=0.90; intra-subject SD=0.71°C; MREDIF=5.0°C
[http://hedwig.mgh.harvard.edu]) confirms that four subjects
would be needed to reject the null hypothesis. This obvious dis-
crepancy probably originates from non-normal data distribution.
Nevertheless, a general trend in the QST-variables seems to support LA-induced changes in the volunteers (Fig. 5).

Nerve blockade
Our trial is in line with two other tender point block studies in persistent postsurgical pain, with respect to the analgesic effect of LA in patients with post-thoracotomy pain17 and persistent pain after breast cancer surgery.18 However, neither of these studies were placebo-controlled or used neurophysiological tests to validate the findings, making the results difficult to inter-
pret. Other non-controlled nerve block studies in PIPP-patients have also shown analgesic responses with LA and have been used for identifying patients for neurectomy,19 neurolysis20 or as a treatment on its own.21 However, significant interpretation is impeded by the lack of controls as the observed effects could be because of placebo and/or dry needling effects.

As previously stated, we are only aware of two other studies utilizing a randomized, double-blind, controlled paradigm com-
paring LA peripheral nerve blockade with placebo.17,21 Our trial is in agreement with the tender point study on anterior cutaneous nerve entrapment syndrome (ACNES), which demonstrated analgesia of ≥50% with LA (13 out of 24 patients) compared with pla-
cebo (four out of 24 patients).1 In the present trial, two patients were block-responders, nine were placebo-responders and two were non-responders according to our own a priori set criteria for block- vs placebo-responders. However, on closer inspection 10 out of 14 patients had a ≥50% reduction in pain after LA injec-
tion compared with three out of 14 patients after placebo. Our trial added a further advantage because of its crossover design, thus yielding more information about block behaviour. For ex-
ample, the two patients experiencing a ≥50% reduction in pain to placebo had a better response to LA, and the neurophysiologic-
al effects were significantly greater after LA compared with pla-
cebo. The present trial highlights the magnitude of the placebo response, yet despite this we have demonstrated more effica-
cious response to LA.

The other PIPP-trial was identical to our trial except for the lo-
cation of the injection and the LA-drug injected.17 This trial used ultrasound-guided injection of lidocaine around the iliohypoga-
stric and ilioinguinal nerves and found only one out of 12 patients to be a LA-responder compared with five out of 12 placebo-respon-
ders. The authors suggested that the genital branch of the genito-
femoral nerve might have a greater role in pain transmission than iliohypogastric and ilioinguinal nerves in PIPP, as an expla-
nation to the failed analgesic response. Our injection near the spermatic cord may have targeted the genital branch of the genitofemoral nerve, but specific sensory (and/or motor) assessments would be needed to confirm this. Also, it is unlikely that the analgesic effect is as a result of genitofemoral nerve block alone, and a more likely explanation is that the LA blocks fibers from all three nerves. An-
other consideration is the contribution of peripheral sympathetic fibers to PIPP, but again, this was not assessed.

Neurophysiological effects
Interestingly, there were no significant differences across treat-
ments with regard to WDT (1.8°C LA vs 0.7°C placebo) and HPT (1.6°C LA vs 0.6°C placebo), yet a significant difference for CDT was observed (4.1°C LA vs 0.3°C placebo). Clinically, this is no sur-
prise as many clinicians will be familiar with the reliability of using cold stimuli to delineate the block area in patients. What is more interesting is that despite the lack of change in WDT or HPT, there was a highly significant difference in the STH-pain

Table 2 Pain and sleep diaries. Data from pain and sleep diaries Day one to six after administration of bupivacaine and placebo. Summed pain intensity (SPI) scores are the sum of three daily pain scores using the numerical rating scale (NRS 0–10); pain at rest, pain on movement and pain on application of manual pressure to the maximum point of pain in the groin (i.e. maximum score 30 NRS-units). Sleep quality is a
NRS from 0–10 where 0=pain has had no effect on sleep, 10=pain totally affected sleep. Wilcoxon tests were applied, comparing bupivacaine and placebo for each day. All numbers shown are median (95% CI). A significance level of P<0.01 was used

<table>
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<tr>
<th>Day</th>
<th>Summed Pain Intensity (NRS)</th>
<th>Sleep Quality (NRS)</th>
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<td></td>
<td>Bupivacaine</td>
<td>Placebo</td>
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<tr>
<td>1</td>
<td>12.8 (10.7 to 19.8)</td>
<td>16.3 (9.8 to 21.6)</td>
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<td>2</td>
<td>11.0 (9.9 to 18.8)</td>
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<td>17.5 (8.5 to 21.6)</td>
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response (~3.5 vs. 0 NRS units; P=0.003). All patients had pre-existing sensory deficits as evidenced by higher WDT and CDT in the operated inguinal area compared with the control areas (forearm and opposite inguinal area), therefore we did not expect to see an effect on these long-term sensory deficits. However, the STH-response demonstrated that the patients experienced heat pain as less painful after LA compared with placebo. This could be attributable to differences in nerve fiber activation, as significant reductions in intra-epidermal nerve fiber density in the surgical site compared with the non-surgical site have been demonstrated, explaining the sensory deficits seen in PIPP-patients. Therefore the more intense supra-thermal heat stimulus may activate the sub-epidermal nerve fibers and thus the major effects of LA may also occur here.

**Peripheral afferent input**

In a non-controlled trial using LA blockade in patients with reflex sympathetic dystrophy of the arm, the same phenomenon was seen: LA block attenuated spontaneous pain and cold and mechanical allodynia, whilst preserving tactile and thermal function. The authors suggested that peripheral afferent input is necessary to maintain this altered central processing, that leads to neuropathic pain. This was further corroborated in another non-controlled trial, examining LA blockade for diabetic and traumatic peripheral neuropathy, where patients experienced 100% analgesia after peripheral nerve blockade. The present trial did not replicate these findings, but demonstrated a reduction in pressure pain stimuli, with an increase in PPT after bupivacaine injection compared with placebo, supporting our results that LA attenuates evoked pain responses. Thus, infiltration with LA dampens pain signaling in thermal and mechanical pain modalities from the periphery, therefore it is highly likely that primary afferent input is necessary for maintaining PIPP.

**Limitations of the trial**

The main limitation of our trial is that in some subjects the absolute sensory threshold values could not be obtained because of partial or complete deafferentation of the examined areas. Therefore cut-off limits were necessary in order to avoid inadvertent tissue injury in PIPP-patients with severe sensory deficits. However, the cut-off limits were exceeded in four patients only. Therefore cut-off limits were necessary in order to avoid inadvertent tissue injury in PIPP-patients with severe sensory deficits. However, the cut-off limits were exceeded in four patients only. Also, we didn’t target a specific nerve or a group of nerves, but instead infiltrated tissues adjacent to the spermatic cord based on patients’ maximal pain locations. Thus, ultrasound was used to avoid intravascular and spermatic cord injection, and to confirm the spread of LA in the fascial plane. Another limitation is that we didn’t assess the patients’ range of lower limb movement, that could possibly give us more information about the actions of the block. The time period between the two visits was seven days and this may have been too short to rule out a sequence effect. Thus, modification in trial design would be needed in future studies. Our sample size calculation yielded a small number of patients for this trial. However, patients acted as their own controls and we were meticulous about creating a homogenous group as possible. Therefore, our conclusions are valid for this specific group of patients only. If a more homogenous group were to be studied, then the sample size would, obviously, need to be considerably larger.

**Further studies**

Further studies should include a more detailed look at the LA responders to evaluate possible long-term effects of the block. Furthermore, examining a standardized number of repeat-blocks over consistent time periods, could reveal the therapeutic potential of LA tender point blockade. A possible future trial could be to assess the ability of the blockade as a predictive tool, estimating the outcomes of neuromodulatory stimulation methods or selective neuroectomies.

**Conclusion**

Ultrasound-guided tender point blockade with bupivacaine had a greater analgesic effect and reduced evoked pain responses compared with placebo, in patients with persistent inguinal postheriorrhaphy pain, supporting the role of peripheral afferents in maintaining the persistent postsurgical pain state.

**Authors’ contributions**


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**Declaration of interest**

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