BJA

British Journal of Anaesthesia, 116 (6): 829–37 (2016)

doi: 10.1093/bja/aew071
Pain

PAIN

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

N. Wijayasinghe[1,*], T. K. Ringsted[2], J. M. Bischoff[2], H. Kehlet[1] and M. U. Werner[2]

[1]Section for Surgical Pathophysiology, and [2]Multidisciplinary Pain Center, Rigshospitalet, Copenhagen University Hospitals, Blegdamsvej 9, DK-2100 Copenhagen, Denmark

*Corresponding author. E-mail: nelunwij@gmail.com

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 herniorrhaphy[1] 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 postherniorrhapy 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

Accepted: March 2, 2016

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.

neuroma formation. However, some patients continue to experience PIPP despite mesh removal and selective neurectomies of the iliohypogastric, the ilioinguinal or (rarely) the genital branch of the genitofemoral nerve.[4 5]

Our research group has observed that PIPP-patients consistently demonstrate a 'tender point', a demarcated area of deep hyperalgesia at the spermatic cord near the superficial inguinal ring, where application of minimal pressure elicits severe pain.[2 6 7] This tender point may be involved in generation or modification of the nociceptive signal. However, a randomized, placebo-controlled trial of ultrasound-guided local anaesthetic (LA) blockade of the iliohypogastric and ilioinguinal nerves at the level of the anterior superior iliac spine, in PIPP-patients, failed to demonstrate an analgesic effect.[7] This trial is the only available controlled trial with LA carried out in PIPP-patients, and interestingly the placebo response was far greater than anticipated.[7] In addition, a control group of healthy subjects was included that demonstrated evidence of a block through changes in quantitative sensory testing (QST) variables after LA blockade. In another randomized placebo-controlled trial in patients with tender points as a result of anterior cutaneous nerve entrapment syndrome (ACNES), pain relief was significantly better with LA, suggesting involvement of the peripheral nervous system,[8] but without neurophysiological tests, such as QST, this cannot be substantiated. More recently, in an uncontrolled trial of patients with distal mono- and polyneuropathies complete pain relief was achieved after a peripheral LA block, suggesting that primary afferent input is necessary for the maintenance of pain.[9]

Local anaesthetic peripheral nerve blockade has been used by pain clinicians for the diagnosis and treatment of neuralgias.[10 11] However, the evidence for this practice is vague and not robust enough to establish a consensus of how to manage patients with neuropathic pain,[11] despite initial promising results from LA injection around peripheral nerves in patients with neuralgias.[12]

The aims of the present trial were *first*, to ascertain the feasibility of a tender point blockade in healthy volunteers and *second*, to investigate the role of primary afferent input in the maintenance of PIPP-patients. Therefore, we performed a randomized, double-blind, placebo-controlled crossover trial examining analgesic and sensory effects of ultrasound-guided tender point injections of LA, in a control-group of healthy volunteers and in a group of PIPP-patients.

Methods

Approvals

The trial was approved by the Committee on Health Research Ethics for the Capital Region of Denmark and registered on www.ClinicalTrials.gov. Written informed consent was obtained from all participants.

Subjects

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.

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 ≥five 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 a 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, $SPI=NRS_R+NRS_M+NRS_P$, where NRS_R is pain at rest (supine), NRS_M is pain on movement (transferring from supine to standing) and NRS_P is pain on application of 100 kPa by pressure algometry (1 cm^2 felt-tipped probe; Somedic AB, Hörby, Sweden) centered on the maximum point of pain (P_T), (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).