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ORIGINAL ARTICLE

A randomised controlled trial of injection therapy versus neurectomy for post-herniorrhaphy inguinal neuralgia: rationale and study design

M. J. A. Loos · T. Verhagen · M. R. M. Scheltinga · R. M. H. Roumen

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Abstract
Background Chronic inguinal neuralgia is considered to be an important complication after hernia repair. As a high-level evidence-based treatment regime is currently lacking, these patients usually receive a random combination of pain medication, local nerve blocks or an occasional surgical neurectomy. A controlled trial ('GroinPain Trial') was constructed to identify the optimal treatment modality in this population. The aim and rationale of the trial are presented in this paper.
Patients and methods Adult patients with chronic post-herniorrhaphy inguinal pain (>3 months) caused by inguinal nerve entrapment having a temporary pain reduction after a lidocain nerve block are eligible for randomisation. They received either repetitive nerve blocks with lidocain, corticosteroids and hyaluronic acid, or a 'tailored' surgical neurectomy.
Results Patient enrollment started in February 2006 and is expected to end in June 2010. The initial results will be available at the end of 2010.
Conclusions This trial is the first randomised controlled effort comparing two invasive treatment modalities for peripheral inguinal nerve entrapment. As awareness and knowledge on chronic neuropathic pain after inguinal herniorrhaphy in the near future is expected to increase, the findings of this trial will aid in optimising care in this patient population.

M. J. A. Loos (✉) · T. Verhagen · M. R. M. Scheltinga · R. M. H. Roumen
Department of General Surgery, Máxima Medical Centre, P.O. Box 7777, De Run 4600, 5500 MB Veldhoven, The Netherlands
e-mail: loosmaarten@hotmail.com

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Introduction

Hernia recurrence rates have plummeted ever since the introduction of mesh. Research interest has, therefore, shifted towards studying the characteristics of chronic pain following the routine implantation of mesh [1]. Approximately 11% of all operated hernia patients are troubled by chronic inguinal pain [2–4]. About half suffer from neuropathic pain caused by entrapment or damage to one (or more) of the inguinal nerves (Ilioinguinal, Iliohypogastric or/and genital branch of the genitofemoral nerve). The other half experience nociceptive pain, including periostitis, recurrent hernia, folded mesh ('meshoma'), fibrotic tissue or funiculodynia [5].

Published studies on the treatment regimes for post-herniorrhaphy inguinal pain syndromes are scarce. Examples of non-operative treatment options include nerve blocks with local anaesthetics and corticosteroids [6], transcutaneous electrical nerve stimulation (TENS) or pulsed radiofrequency (PRF) [7]. Neuropathic pain caused by nerve entrapment can also be treated by an open nerve removal (neurectomy), as this technique effectively decreased pain in 60–80% of the patients [8–13]. Peripheral nerve blocks likely aid in discriminating between pain types. However, it is important to realise that, to our knowledge, no validation studies on the sensitivity and specificity of nerve blocks in discriminating neuropathic from nociceptive pain have been conducted.

In order to evaluate which therapeutic regime serves best for neuropathic post-herniorrhaphy pain syndromes, a randomised controlled trial was constructed comparing two

frequently used treatment modalities; nerve blocks and neurectomy of the inguinal nerves. Characteristics of this randomised controlled trial will be discussed in the present article.

Methods

Study design

The GroinPain Trial is a randomised, non-blinded, monocentre study. The protocol was approved by the Regional Ethics Committee of the Máxima Medical Centre, Veldhoven, The Netherlands (no. 0543). The objective is to evaluate long-term pain reduction in patients with chronic postherniorrhaphy groin neuralgia following two different treatment modalities. Clinical results of nerve blocks with lidocain, corticosteroids and hyaluronic acid are compared with a surgical neurectomy of the Ilioinguinal, Iliohypogastric or/and genital branch of the genitofemoral nerve(s). Patient enrollment started in February 2006. The study protocol has been registered at http://www.clinicaltrial.gov (ClinicalTrials.gov identifier: NCT00306839).

Study population

All adult patients (18 years or older) with chronic neuropathic pain after routine inguinal hernia repair (open or laparoscopic) are considered for inclusion. A pain-free interval (hours to days/weeks) after a diagnostic nerve block using 10 cc 1% lidocain injected into the trigger point is a prerequisite for inclusion. Patients with less than 50% pain reduction do not qualify for the study. A nerve block administered at the outpatient department is part of our standard diagnostic pathway. In some patients, a diagnostic nerve block results in a persistent pain reduction. These patients are excluded from further participation but are registered and monitored over time. To assure that the international definition for the study of chronic pain (pain persisting beyond the normal healing period of 3 months) was applicable to all patients, a minimal follow-up period of 3 months was chosen. Patients were excluded if an adequate follow-up was impossible, omitting all patients with severely compromised physical or mental health. Patients with a recurrent inguinal hernia, harbouring signs of local inflammation or having an American Society of Anaesthesiologists (ASA) classification of 3 or more are also excluded.

Randomisation

After a thorough explanation regarding rationale and important characteristics of the trial, verbal and written informed consent is obtained at the outpatient department.

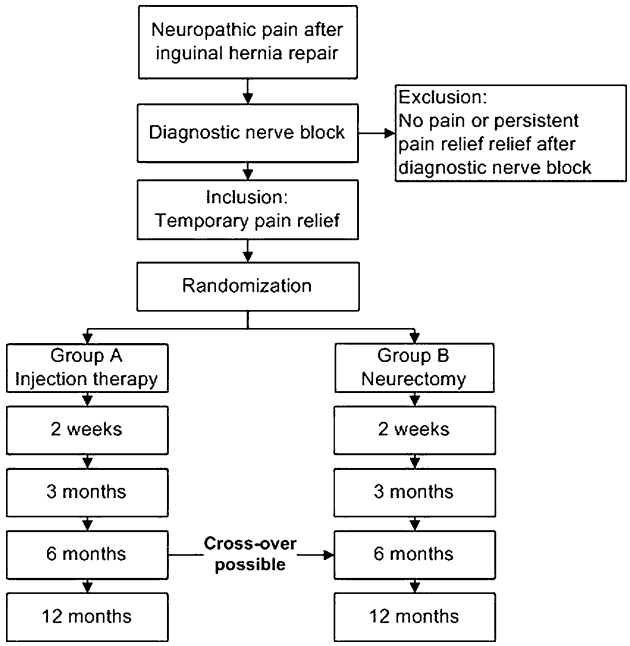

Fig. 1 Study design

Patients are subsequently randomised to repetitive nerve blocks using lidocain, corticosteroids and hyaluronic acid (group A) or a neurectomy (group B, Fig. 1). Blocks of eight-randomisation principle without prestratification are applied by a computer.

Interventions

Nerve blocks (Group A, Fig. 2): this group receives an injection with 2 cc 1% Lidocain, 40 mg corticosteroids (Depo-Medrol®) and 75 IE hyaluronic acid (Hyason®) at the surgical outpatient department. These blocks are placed in the pain trigger point. In case of additional genital branch neuralgia, a separate nerve block placed at the internal

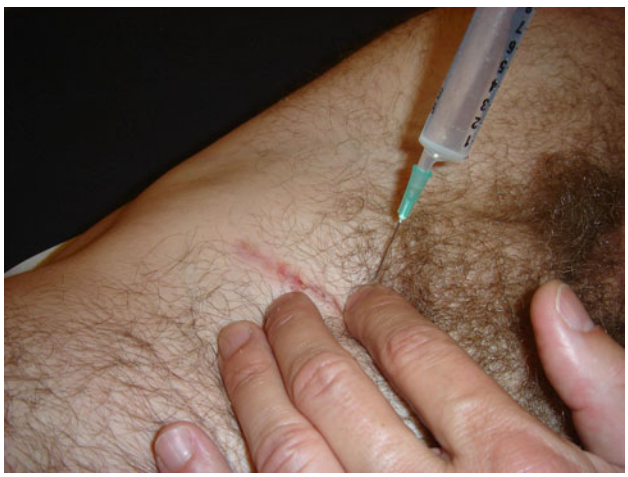

Fig. 2 Diagnostic nerve block in a left groin

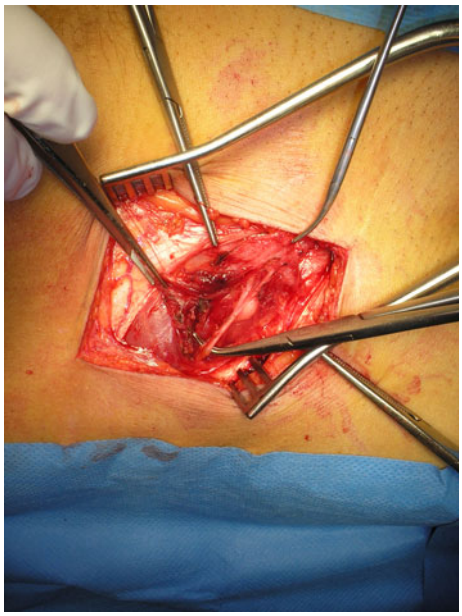

Fig. 3 Neurectomy of the right Ilioinguinal nerve. Neuroma at the lateral border of the mesh (= turned over medially)

inguinal ring is often mandatory. If pain reduction is temporary, injections are repeated at 2-week intervals. A maximal number of three blocks is used over a 6-week period. All injections are administered by the principal investigators (M.L. or T.V.).

Neurectomy (Group B, Fig. 3): patients are offered surgery using spinal or general anaesthesia in a day-care setting. All operations are performed by the senior authors M.S. and R.R., both of whom are experienced in performing this procedure. Patients receive 2,500 IU of low molecular heparin (Fragmin®) subcutaneously 2 h prior to the procedure. By extending the inguinal incision several centimetres laterally, access is gained to an unaffected area in most cases. The iliohypogastric and/or ilioinguinal nerves penetrating the internal oblique muscles are identified and followed as proximal as possible. The prosthetic material is usually opened and dissected for additional exposure. If indicated, the genital branch of the genitofemoral nerve is identified just underneath the spermatic cord. The genital branch can also be affected at the level of the internal ring, making an anterior approach difficult or less effective. Therefore, an additional retroperitoneal approach can be chosen in case of a suspected genital branch neuropathy. Occasionally, the genital branch is absent or not found due to previous procedures. Nerves are excised if fibrotic encasement or possible neuroma formation is observed. After peripheral division including the intramuscular segment, proximal nerve ends are cauterised, occasionally ligated under traction and allowed to retract into the internal oblique muscle to prevent a relapse of fibrotic encasement. If nerves are thought to be 'entrapped' by preperitoneal mesh placement, the preperitoneal space is opened by dividing the internal oblique and transversus abdominis layers. In case of displaced bulky mesh material, parts of the mesh are removed. In case of mesh removal, it is always accompanied by a neurectomy.

The sequence of surgical steps is dictated by the perioperative findings. A decision concerning nerve resection and (partial) mesh removal is, thus, guided by the individual situation, the 'tailored approach', which has been published recently by our group of investigators [11]. All resected specimens are histopathologically examined.

Collection of data and clinical follow-up

Five assessments are planned for each patient by the principal investigators. Baseline details and a standard questionnaire assessment are collected at inclusion (visit 1). In case of randomisation for nerve blocks, patients return 2 weeks after the first nerve block to the outpatient department for clinical examination and a second questionnaire assessment (visit 2). If pain reduction after nerve bocks is only temporary, a cross-over to the neurectomy group is offered 6 months post-inclusion (Fig. 1).

If randomised to neurectomy, the surgeon tabulates all operative details, including all surgical steps, in a standard report. Two weeks after the operation, patients are assessed at the outpatient department as well (visit 2). Cross-over from the neurectomy to the nerve block group does not seem to be beneficial and is not included in the protocol.

All patients receive a questionnaire by mail 3 and 6 months post-operatively. One year post-intervention, all participants are invited for the final questionnaire assessment and a physical examination at the surgical outpatient department (visit 3). Each patient will complete surgical pain scales [14], McGill Pain Questionnaire—Dutch Language Version [15] and SF-36 version II quality of life questionnaire at each follow-up moment [16]. At the outpatient department visits (baseline, after 2 weeks, 12 months), the LANNS Pain Scale, the Leeds Assessment of Neuropathic Symptoms and Signs, is completed [17]. Complications and change in employment status is noted at each post-intervention evaluation moment.

Study endpoints

The primary endpoint is the number of successfully treated patients with respect to pain reduction. Successful pain reduction is defined as a >50% pain reduction during resting conditions measured with the surgical pain scales after 6 months. In case of a necessity to cross over from the nerve block group to the neurectomy group or if additional treatment like chronic pain medication remains necessary, this is considered to be a treatment failure.

Secondary endpoints are quality of life (SF-36 version II), alterations in inguinal neurophysiological status (LANNS Pain Scale), complications (self-completed questionnaire) and change in employment status (self-completed questionnaire).

Sample size

A successful intervention is defined as a 50% reduction (visual analogue scale) in rest pain (surgical pain scales) after 6 months of follow-up. After a thorough study of the available literature, success rates of a nerve block appeared to be unknown. After a consultation of several of our anaesthesiologists specialised in the treatment of chronic pain, the success rate of a nerve block is set at 25%. Based on retrospective cohort studies, the success percentage following a surgical neurectomy approximates 75%. Using a type I error of 0.05 and a type II error of 0.10, a sample size is calculated of 54 patients (two groups of 27 patients).

Statistical analysis

Intention-to-treat analysis will be applied on the primary endpoint of pain reduction. Since we expect a significant cross-over from the nerve block group towards the neurectomy group, an 'as treated analysis' will be made as well. Endpoints will be analysed per group and at each evaluation time. The Chi-square test is used for the comparison of categorical variables. Quantitative variables will be compared by the Mann–Whitney *U*-test. The results will be considered to be significant if $P \leq 0.05$.

Discussion

In recent years, a number of studies has stressed the importance of chronic pain as an important complication after inguinal hernia repair [1–4]. However, to date, only a few studies on treatment options such as operative neurectomy or therapeutic nerve blocks have been published. There is a definite need for more evidence-based treatment regimes in these populations. The present trial will be the first randomised study comparing two frequently used treatment modalities for chronic neuralgia after inguinal hernia repair.

Populations with post-herniorrhaphy pain syndromes are notoriously heterogeneous. Therefore, only patients with presumed peripheral inguinal nerve entrapment are included. In contrast, individuals with non-neuropathic pain ('nociceptive'), including periostitis or folded or migrated fibrotic mesh material, are not eligible, as their pain is probably unresponsive to an exclusive neurectomy [8]. Patients that will probably also not respond to a tailored neurectomy are the 'long-term neuropathic pain sufferers' as they may have developed sensitisation of the central nervous system. Permanent sensitisation on the cerebral level is thought to render peripheral interventions such as a neurectomy insufficient [18]. Although these patients typically report symptomatology associated with neuropathic pain, peripheral nerve blocks will probably not induce pain reduction. Therefore, a substantial temporary pain reduction after inguinal nerve block with lidocain serves as an important prerequisite for inclusion in the present trial.

There is little evidence on the beneficial effects of an injection of a cocktail of agents for the treatment of chronic inguinal neuropathic pain. The choice for a combination of lidocain, corticosteroids and hyaluronic acid was made after the consultation of several anaesthesiologists/pain specialists [19]. One study suggested that corticosteroids act by the suppression of ectopic neural discharges from the injured nerve endings [6]. Moreover, hyaluronic acid may soften scar tissue and may aid in the local infiltration of the anaesthetic and corticosteroids [20]. It was hypothesized that the combination of these two substances acted synergistically and facilitated and potentiated the analgesic effects of lidocain.

Although the sequence of steps in the surgical neurectomy is standardised as much as possible, experience with past cases indicated that each patient requires individualisation. Therefore, pre- and perioperative findings guided us on the handling of the affected nerves, 'the tailored approach' [12]. In contrast, a single specialist centre advocates a standard 'triple neurectomy' for this pain syndrome, removing all three inguinal nerves during one procedure [9], achieving success rates of up to 85%. However, slightly lower success rates for this difficult chronic pain issue are probably more realistic, which we have demonstrated in a recently published retrospective review on the 'tailored approach.' The latter patient cohort exhibited a more heterogeneous pain pattern (e.g. also non-neuropathic) and had often received surgical interventions in other clinics as well. The patients in the GroinPain Trial will be more homogeneous, hopefully resulting in higher success rates. Moreover, a potential disadvantage of a classic triple procedure is neuroma formation in previously unaffected nerves with a possible onset of deafferentation pain.

This study also evaluates secondary endpoints such as quality of life and impact on occupational disability. Any improvement in quality of life will further underline the need for standardised treatment protocols. We are currently under the impression that an operative neurectomy may serve as the backbone of such treatment regimes. However, the present randomised study may find that nerve blocks can also serve as an important tool in the treatment of this growing patient population.

Acknowledgments This study was unfunded.

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