Surgical Management of Painful Neuromas

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Surgical Management of Painful Neuromas

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To my parents

Contents

Chapter 1:

Introduction

The impact of chronic neuropathic pain

Chronic pain can be severely disabling and represents a greatly underestimated public health problem. "Pain can kill. It can kill the spirit, vitality and the will to live," said Joel Saper, MD and president of the American Headache Society, in response to law the US Congress passed into provision in late 2000, declaring the following decade (January 1st 2001 – 2011) as the Decade of Pain Control and Research.[1] A critical goal of the Decade of Pain initiative was to maximize the public and professional understanding of pain and pain management.

Approximately 20% of adult Europeans suffer from chronic pain of moderate to severe intensity, seriously affecting the quality of their social and working lives.[2] Neuropathic pain is thought to be a particularly distressing chronic pain condition that is often under-diagnosed and under-treated.[3] Neuropathic pain has been defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system,[4] and is often therapy resistant for reasons largely unknown.[5] Pain intensity and duration are reported to be higher in comparison to chronic pain without neuropathic characteristics.[6] Recently published studies involving epidemiological surveys in Europe suggested neuropathic pain to have a prevalence of 7–8% in the general population.[6,7]

Approximately 3-5% of all patients involved in peripheral nerve injury develop a symptomatic neuroma.[8,9] In the Netherlands, there are approximately 3.5/100,000 or 580 new cases of neuropathic pain caused by traumatic or iatrogenic nerve injury every year.[10]

Symptomatic neuromas cause intense spontaneous burning, shooting or electric pain as well as lowered thresholds for pain (hyperalgesia) and pain at touch (allodynia) or mild cold (cold intolerance).[11] Nerve injuries most frequently involve the upper extremity.[12] Blue collar workers in factories operating various kinds of machinery are especially prone to upper extremity trauma. Since hand function is one of the most important bodily functions,[13] a painful neuroma in the upper extremity results in great disability, especially when the dominant side is affected. In the Guide to the Evaluation of Permanent Impairment' of the American Medical Association (AMA-5), loss of function of one hand was estimated as a physical disability of 30-60%.[14] The social disability compensation can add up to €19,500 per patient annually, based on the Dutch standard income.

Neuroma pain brings tremendous direct and indirect costs to patients and their families in terms of pain and suffering, quality of life and health care expenditures, as well as costs to society in health-insurance claims, lost productivity and occupational disability.[2,3,5,15,16]

Clinical case

The following case illustrates the impact of painful neuromas in clinical practice. It describes a true neuroma pain patient who presented at the outpatient clinic of the Department of Plastic and Reconstructive Surgery of the Erasmus Medical Center in August 2008.

Mr. Dolor is a 32 year old right-handed plastic processor. He is married, has 2 young children and likes to play computer games. He has no relevant medical history, and is a smoker. In March 2007 he sustained an occupational injury when his right hand got caught in a milling machine (Dutch: freesmachine). There was an injury to the thumb base, treated with a full thickness skin graft in a secondary care hospital.

In August 2008 he was referred to the Erasmus Medical Center for complaints of neuropathic pain and dysesthesias. The clinical exam showed areas of numbness, hyperalgesia, allodynia and cold intolerance in the thenar region and there was a positive Tinel's sign over the superficial branch of the radial nerve (SBRN). There were no signs of complex regional pain syndrome (CRPS) and motor function was intact.

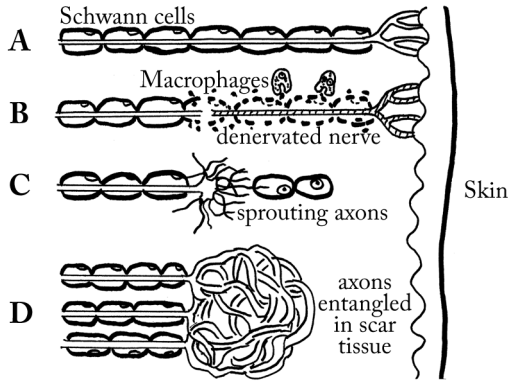
Mr. Dolor was diagnosed with a painful neuroma of the SBRN and treated with EMLA cream and iontophoresis for several months, without substantial effect. In January 2009, he sustained surgical relocation of the SBRN into the thenar musculature. When visiting the outpatient clinic in July 2009, he still experienced extreme neuropathic pain, especially in cold weather. The adjuvant pain medication he was prescribed made him drowsy. He remained restricted in his activities of daily living (ADL), including lifting with his right hand, writing, work and leisure activities, and performing his family role. He was now unemployed, received social disability compensation (WIA), and was involved in a litigation process against his employer. He indicated he would like to receive help from a psychologist, since he had lost all hope to ever become pain-free.

Peripheral nerve injury and regeneration

The incidence of peripheral nerve injury is estimated at 1.6 - 2.8% in patients with upper- or lower extremity trauma.[12,17] The majority of patients is between 18 and 35 years of age and peripheral nerve injuries occur more frequently in males than females. The leading causes are motor vehicle accidents, occupational injuries or aggression.[12,18] Type of injury can be categorized as being sharp (i.e. glass, knives, surgical procedures) crush (i.e. falls, heavy machinery) or avulsion (i.e. deglovement, milling accidents). Although sharp injuries are more common, crush injuries have the highest chance of peripheral nerve injury.[17]

Peripheral nerve injury leads to a series of cellular responses. Axons distal to the injury site degenerate and local Schwann cells and macrophages clear the distal endoneurial tubes of apoptotic debris. This is called Wallerian degeneration. The severed axon end begins to sprout within 24 hours after injury, and individual axons may produce more than one sprout.[19] Neurotrophic factors (i.e. BDNF, NGF), released by macrophages and Schwann cells, direct the regenerating axons and induce axon maturation and elongation into the endoneural sheaths.[19,20] The rate of axonal outgrowth is 1-5 mm/day, and, therefore, may take several months for regenerating axons to reinnervate their distal targets.[9] Large gaps, i.e. gaps over 15-30 mm, usually cannot be bridged by axons. Proliferating fibroblasts and newly formed scar tissue can form a physical blockade. When a blockade between the proximal and distal stump is present, or the distal stump is lost e.g. in case of amputation, nerve proliferation continues with a high chance of neuroma formation.[21]

Figure 1. Wallerian degeneration



A: cutaneous nerve

B: nerve damage and Wallerian degeneration of the distal nerve end. Macrophages remove debris

C: axon sprouting and Schwann cell proliferation (desired situation)

D: neuroma formation (undesired situation)

History, definition and pathogenesis of painful neuromas

Painful neuromas have first been described by Ambroise Paré, a 16th century military surgeon, who published a detailed description of what we now call causalgia following a nerve injury inflicted on King Charles IX of France. He also observed that patients who underwent a surgical amputation continued to experience pain long after the procedure. The first scientific description of neuroma formation appeared in 1811 by Odier, who described the bulbous nerve swellings which develop at the distal end of the proximal peripheral nerve stumps after partial or complete division. In 1863 an initial histologic analysis and classification system for neuromas was established by Virchow.[22,23]

A neuroma is formed by simultaneous regeneration of neural fibers and excessive fibrous tissue proliferation, which results in contraction of nerve fibers within the scar tissue.[21] It consists of tangled axons, Schwann cells, endoneurial cells, and perineurial cells in a dense collagenous matrix with surrounding fibroblasts.[24]

Approximately 3-5% of all patients involved in peripheral nerve injury develop a symptomatic neuroma,[8] and asymptomatic neuromas often remain unnoticed. Although it is a topic of great interest for neuroma research, there is no consensus on why some neuromas become painful and others do not.

In symptomatic neuromas, there is sensitization of nociceptive nerve fibers due to an up-regulation of sodium channels, adrenergic and nicotinic cholinergic receptors.[25-29] In addition, ephaptic conduction or "cross-talk" between adjacent nerve fibers can take place leading to abnormal sensitivity and spontaneous activity of axons in the neuroma.[30] As ectopic peripheral nerve input continues, changes in neural structures involved in pain perception, i.e. the dorsal root ganglion, the dorsal horn of the spinal cord, thalamus and sensory cortex, start to take place: There is increased excitability of neurons in adjacent spinal segments and cortical areas, also called 'central sensitization'.[30,31]

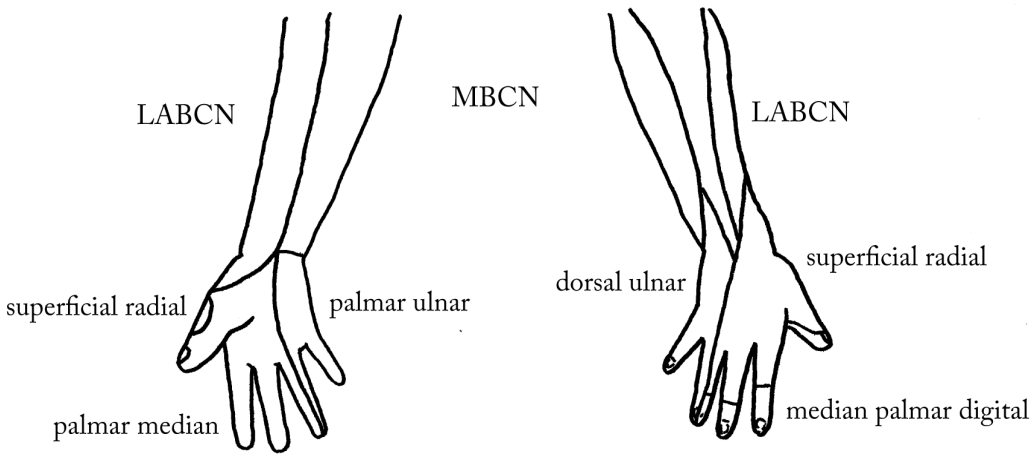
Furthermore, there is increasing evidence that mechanical and thermal hyperalgesia and allodynia are independent of spontaneous pain originating in the peripheral neuroma.[32-35] This suggests recruitment of axons from adjacent nerves,[32,36] changes in the processing of stimuli from intact neighboring nerve fibers,[34] or direct injury to surrounding nerve branches.[37,38]

Diagnosis, treatment and prognosis

The diagnosis of neuroma-specific neuropathic pain is primarily based on clinical judgment. Patients usually present with a history of nerve injury to the upper extremity, followed by symptoms of a painful neuroma. These include negative (hypoesthesia) and positive sensory signs (pinprick hyperalgesia, dynamic mechanical allodynia, pressure hyperalgesia, cold intolerance and spontaneous pain) in the distribution of a peripheral sensory nerve. When tapping the injured nerve, patients typically show a shooting electrical pain in the distribution of the nerve (positive Tinel's test). This test can be used to locate the ends of transected and regenerating axons.[39] Using quantitative sensory testing (Von Frey monofilaments) and 2-point discrimination (2PD), the exact areas of hypoesthesia corresponding to the injured nerve branches can be mapped out.[30]

In most cases, a temporary diagnostic nerve block with 1% lidocaine is performed at the outpatient clinic, to confirm involvement of the suspected peripheral nerve in the painful sensation.[38] The outcome of this test is often decisive for the treatment plan: insufficient pain relief following a diagnostic block is often considered a contraindication to surgery.[40] Unfortunately, the exact predictive value of this test is currently unknown and statistical evidence seems to be lacking.[41]

Figure 2. Innervation of the distal upper extremity



LABCN: lateral anterbrachial cutaneous nerve;
MBCN: medial antebrachial cuteneous nerve

If there is remaining doubt concerning the diagnosis following the clinical examination, the patient can be sent for nerve conduction studies to evaluate the location and extent of the possible nerve injury.[30] Although studies have been performed in visualizing neuromas of major peripheral nerves using ultrasonography,[42,43] it is not yet commonly used in the diagnosis, localization or follow up of neuroma pain. This is because of previously inadequate scanning frequencies for detailed visualization e.g. of small cutaneous nerve branches. When the nerve involved in the painful neuroma is identified, treatment starts with at least 6 months of non-operative therapy including scar massage, local application of lidocaine cream, iontophoresis (transdermal application of local anesthetic using electrical current) and desensitization with vibrations or light sandpaper. More invasive techniques, such as injections of the nerve stump with various chemical agents, spinal cord stimulation, transcutaneous electrical nerve stimulation (TENS) and repeated nerve blocks have also been applied, with limited success.[31] Neuroma pain patients are often prescribed adjuvant pain medication like antidepressants and anticonvulsants.[44]

As opposed to the life-long use of analgesic medication or medical devices, surgical neuroma treatment, if successful, can provide a permanent effect on pain relief. When the target organ or distal nerve end is present, reinnervation should be attempted by reconstruction of the injured nerve. There should be minimal tension on the repaired nerve, and in case of a nerve gap a nerve graft or neurotube can be used to guide axonal regeneration. In case of a painful neuroma in continuity preserving functional sensitivity should be attempted. In this case a muscle flap can be used to reduce symptoms from mechanical stimulation of the neuroma.[29 273]

When the distal nerve end is not available for reconstruction, as in amputation injuries, the proximal nerve end is usually relocated into an environment away from the original injury site, for example into bone, muscle or vein, where it is protected from mechanical or thermal stimulation and excessive concentrations of neural growth factors.[21,45] Mackinnon et al.[24] showed that neuromas that are formed after relocation of the nerve end into innervated and well vascularized muscle show significantly less scar tissue with a decreased density of less well myelinated nerve fibers. Other techniques proposed in literature include simple ligation, sealing or capping of the nerve and end-to-side anastomoses or nerve loops.[45,46]

Since treatment failure is common, accurate patient selection for surgical neuroma treatment is essential. Patient-specific prognostic factors, predicting insufficient pain relief after surgical neuroma treatment, can help clinicians in the process of patient selection and informing, treatment and care. They may also provide new surgical treatment strategies for patients that would otherwise have an unfavorable chance for adequate pain relief. Furthermore, there are many important determinants of patient satisfaction in chronic pain treatment, which are currently under-studied

and undertreated. These include disability, quality of life, psycho-social problems and cold intolerance.

Unfortunately, most studies that have been performed evaluating surgical management of the painful neuroma have had a retrospective design [47-49], or comprised case series with minimal patient numbers.[50-58] Other studies used ill defined or non validated outcome measures for pain [40,49,59-62], or did not assess other important aspects in the treatment of chronic pain, like upper extremity disability or quality of life.[52,53,62-65]. This is probably due to the reasonably low incidence of painful neuromas making large study populations are hard to obtain in a prospective setting. However, well-designed, clinical epidemiological studies may provide a step forward in the surgical management of painful neuromas.

Figure 3. Neuroma of the superficial branch of the radial nerve

Photo: AVD Erasmus MC. Printed with patient's permission

Objective and research questions

The purpose of this thesis was to explore why a large number of patients with neuroma pain still have insufficient pain relief following surgical neuroma treatment, and to explore the optimal strategies for surgical treatment and chronic pain prevention of individual patients.

To achieve the objective of this thesis, we need the answer to the following research questions:

- Which are important prognostic factors for insufficient pain relief?
- Can we use ultrasonography for diagnosis and localization of neuromas in the upper extremity?
- Is the diagnostic nerve block a predictive diagnostic tool?
- Can hyperalgesia be sustained by pain conduction via adjacent nerves; and how can we treat this hyperalgesia?
- Which are the most important outcome measures for peripheral neuropathic pain research?
- What is the most effective treatment strategy for neuroma pain patients?

These questions will be addressed in chapters 2-7 of this thesis.

Outline of the thesis

Chapter 2 is a review of the literature concerning prognostic factors for insufficient pain relief following surgical neuroma treatment. It also focuses on the process of central sensitization that occurs in neuroma pain patients.

In **Chapter 3** we explored the potential of high-resolution ultrasonography for the visualization of the small cutaneous nerve branches in the hand and wrist that are often involved in neuroma formation.

In **Chapter 4** we studied the prevalence of cold intolerance or thermal hyperalgesia in neuroma pain patients, and the improvement of these symptoms following surgical denervation.

Chapter 5 is a retrospective study on the surgical treatment of SBRN neuralgia. We looked at etiology and compared different treatment methods, including neurectomies of adjacent nerves.

In **Chapter 6** we evaluated the importance of several major outcome measures for patient satisfaction following surgical neuroma treatment. We determined cut-off scores for reliable and clinically significant change in these outcomes.

Chapter 7 presents the results from our prospective prognostic cohort study. In this study we evaluated the effect of surgical neuroma treatment on important outcome measures evaluated in chapter 6. Possible prognostic factors were investigated and the predictive value of the commonly used diagnostic nerve block was determined.

In **Chapter 8** the results from the previous chapters and their implications are discussed. The research questions will be answered and the main objective evaluated. The conclusions and recommendations of this thesis are presented, as well as possibilities for future research.

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Chapter 2:

Insufficient pain relief after surgical neuroma treatment

Insufficient pain relief after surgical neuroma treatment: prognostic factors and central sensitization. Stokvis A, Coert JH, Van Neck JW. J Plast Reconstr Aesthet Surg. In press, published online. 2009; doi:10.1016/j.bjps.2009.05.036

Abstract

Background:

Treatment of patients with neuromatous pain is difficult. Numerous treatment methods have been described, but none has been completely effective in providing sufficient pain relief. Patient specific prognostic factors, predicting pain after surgical neuroma treatment, can help clinicians in the process of patient treatment and care.

Methods:

A computerized bibliographical database (PubMed Medline) was searched for articles concerning prognostic factors predicting the outcome of surgical neuroma treatment, and all reference lists were checked.

Results:

Evidence for predicting the outcome was found for neuromas of the radial sensory branch and digital nerves, discrete nerve syndrome, workers compensation, employment status, litigation involvement, duration of pain, and number of previous operations. Psychosocial problems are often found in neuroma patients. In chronic neuropathic pain patients, changes in the central nervous system at the spinal cord level and in the somatosensory cortex can be found.

Conclusions:

Neuromas of the radial sensory branch and digital nerves, discrete nerve syndrome, workers compensation, employment status, litigation involvement, duration of pain and number of previous operations appear to predict the amount of pain after neuroma surgery. However, in a minority of patients the bad outcome cannot be explained by these factors; in these patients central sensitization and psychosocial factors may play a role in maintaining pain. Research focusing on prognostic factors and the central changes induced by painful peripheral injury can lead to new and improved clinical treatment algorithms for the relief and prevention of chronic neuropathic pain.

Introduction

When a peripheral nerve is damaged, it will try to regenerate itself toward the distal nerve end or target organ.[1] If a distal target is not found, axon sprouts grow into the surrounding scar tissue forming a neuroma.[2-4] Some of these neuromas cause intense pain, cold intolerance, altered sensation and hypersensitivity in the distribution of the injured nerve.[5] This causes loss of function and has a great impact on the daily life of patients. Neuropathic pain can be psychologically and physically disabling.[6] In a retrospective study of patients with digital amputations, Fisher and Boswick[7] found the painful neuroma to have an incidence of less than 4%. However, according to Koch et al.[8] as many as 30% of all neuromas are painful.

Neuropathic pain is very difficult to treat and often evolves into a chronic pain disorder.[9] The key to neuroma management is prevention by directly repairing damaged nerves and restoring functionality. Once the neuroma has formed, the best results are usually obtained from surgical intervention.[5,10] Vernadakis et al.[5], Whipple and Unsell[11] have formulated surgical treatment algorithms that describe the basic principles of surgical management of neuromas throughout the body; usually by relocation of the nerve end into muscle or bone.

Despite numerous treatment methods and careful patient selection, it appears that 0 to 67% of neuroma patients do not benefit from surgical intervention.[5,12-21]

Patient-specific prognostic factors, predicting insufficient pain relief after surgical neuroma treatment, can help clinicians in the process of patient selection, treatment and care. In the literature concerning prognostic factors of surgical neuroma treatment, the focus has mainly been on demographic and physical determinants.

In some patients there is no visible cause related to the peripheral nerve to explain persistent pain after surgery.[12,13,20,22]. Central sensitization and psychosocial factors may play a role in maintaining pain in these patients.[7,13,18,21]

The focus of this review is the literature concerning the prediction of outcome in surgically-treated neuroma patients. Besides the often-described prognostic factors, also the relatively new area of psychosocial factors and central centralization is addressed, as are possibilities for future research and treatment.

Methods

A computerised bibliographical database (PubMed Medline) was searched for citations concerning neuromas of peripheral nerves. Criteria included research in humans, publications in the English language only and case reports or series were excluded. The titles of citation printouts were reviewed, abstracts identified as being potentially

related to our topic were retrieved, and reference lists were checked for their relevance to our study. Prospective or retrospective cohort studies on the surgical treatment of painful neuromas of the extremities of at least five patients were included.

Results and discussion

The initial Medline search yielded 114 results, of which 51 titles matched our search criteria. After scrutinizing the references 61 articles were retrieved. We found 14 articles that mention possible prognostic factors or try to give an explanation for the observed surgical results[7,12,13,15,16,18,19,21,23-28]. Major prognostic factors were found to be similar among the studies (Table 1).

The factors that seem to predict the amount of postoperative pain in surgically-treated neuroma patients are: neuromas of the radial sensory branch (RSB) and digital nerves, discrete nerve syndrome, workers compensation, employment status, litigation involvement, duration of pain, and number of previous operations. These prognostic factors are discussed separately below.

Radial sensory branch neuromas

The apparent susceptibility of the RSB to form painful neuromas has been well documented.[15,16,19,23] An anatomical mechanism causing the predisposition of the RSB to develop painful neuromas has been proposed.[23] The RSB is located in close proximity to the wrist joint, is subject to substantial traction and lies relatively superficial in the skin, exposing it to repetitive mechanical/stretch trauma. Proximal tethering of this nerve as it exits from the deep fascia increases nerve tension. This could increase scar formation and, therefore, promote neuroma formation. Dorsoradial wrist neuromas remain the most difficult for which to achieve satisfactory pain relief.[27]

Treatment failure can be caused by placing the RSB into a muscle with significant excursion. For instance, placing the nerve end in the thenar muscle group can lead to significant pain with movement of the thumb, also limiting hand function. Dellon and Mackinnon[13] reported that all four patients who underwent this procedure had to be reoperated with subsequent placement of the nerve in the brachioradialis muscle. The brachioradialis muscle has little excursion and, therefore, contraction does not induce substantial traction on the nerve. This makes the brachioradialis muscle very suitable for RSB implantation.[18,29]

Another cause for treatment failure in patients with a RSB neuroma is misdiagnosis of an overlapping sensory pattern of the lateral antebrachial cutaneous nerve (LABCN) with the RSB.[13,27] Mackinnon and Dellon[27] found concomitant injury to

the RSB and the LABCN in 38 of all 52 patients with persistent dorsoradial wrist pain related to a neuroma of the RSB. Misdiagnosis may be avoided by the use of local diagnostic nerve blocks to confirm the exact source of the pain.[27]

Digital nerves

Patients with neuromas of digital nerves seem prone to persistent pain after surgery. Novak et al.[18] found that neuromas of the digital nerves were strongly related to poor subjective outcome; improvement was seen in only 12 of 22 digital nerve neuromas. Dellon and Mackinnon[13] treated seven patients with digital neuromas with poor results: 86% of these patients also remained little improved or unchanged. None of the patients achieved excellent relief of pain. The difference in outcome between neuromas located in the digital nerve and other nerve locations was significant at $p < 0.0005$.

The high failure rate of these operations was probably due to placement of the nerve endings in the intrinsic muscles of the hand. These intrinsic muscles are small and display relatively large excursions, causing pain at movement or contact.[13,15] Hazari and Elliot[25] investigated multiple methods for relocation of digital nerve neuromas. They observed the poorest results in therapeutical ray amputations and concluded that treatment of digital neuromas should be based on the relocation of the nerve ends into a more proximal and deeper site, distant from the scar area and locations subject to repeated minor trauma.[15,28] Relocation into the phalangeal or metacarpal bones seems to be the most effective treatment in patients with digital neuromas.[6,14,25,28]

Discrete nerve syndrome

Burchiel et al.[12] described the concept of a discrete nerve syndrome. This is a collective term for physical findings associated with complex regional pain syndrome, mechanical or thermal hyperalgesia and the presence of Tinel's sign. It is a condition in which a single nerve can account for both the neurological findings and the distribution of neuropathic pain. As expected, poorly localized, ill-defined signs and symptoms predict bad outcome. Discrete nerve syndrome, as a combined variable, demonstrated a moderate correlation with pain improvement ($p = 0.08$).

Workers compensation

Workers compensation is often mentioned as predictive of continued pain and loss of function.[7,13,18,30-33] Dellon and Mackinnon[13] found a significant difference in the percentage of excellent pain relief between patients with and without workers compensa-

tion ($p < 0.01$). Of all patients receiving workers compensation, 35% had an excellent outcome, while this was 75% for the patients without workers compensation.

Using a telephone survey to evaluate long-term subjective outcome, Novak et al.[18] also found workers compensation to be significantly related to poor subjective outcome ($p < 0.03$). Patients whose pain is job related may be difficult to evaluate postoperatively in terms of impairment and job restrictions,[24] as patients involved in workers compensation may have an interest in reporting poor outcome.[7]

The issue of compensation can also have a great impact on patient's lives. A condition called compensation neurosis might explain the bad results in patients receiving workers compensation. In this condition, psychological symptoms occur after an injury in which a compensation claim is possible or pending and symptoms are maintained by the patient's wish for monetary compensation.[30-33]

Burchiel et al.[12] found that patients who were receiving workers compensation did no worse than the group as a whole. Mackinnon and Dellon[27] argued that workers compensation cannot be seen separately from their employment status.

Employment status

Dworkin et al.[32] stated that the effect of workers compensation on outcome is not caused by compensation or litigation, but by actual employment status. In their study the poor prognostic effect of workers compensation disappeared when controlled for employment status; they argued it would be valuable to focus on activity and employment instead of the deteriorating effects of compensation neurosis in the treatment and rehabilitation of chronic pain patients. When Mackinnon and Dellon[27] looked at the employment status of patients receiving workers compensation, it was evident that patients who were employed and working achieved better results than those who were unemployed ($p < 0.01$), supporting Dworkin's theory. Furthermore, Novak et al.[18] found a significant difference in length of time off work preoperatively between patients who returned to work and those who did not ($p < 0.05$).

In a more recent paper, Suter[30] suggests that, in chronic pain patients, employment may lead to lower physical and emotional distress, particularly for those patients receiving workers compensation or involved in litigation.

Litigation involvement

There has been inconsistent evidence regarding the relationship between litigation status and chronic pain. Dworkin et al.[32] found that litigation involvement did not predict long-term outcome, only employment did.

However, Suter[30] demonstrated that involvement in litigation was associated with

increased pain, depression and disability in patients with chronic pain. This effect was independent of their employment status. Patients seem to benefit less from treatment when continued disability may be important for their pending litigation.[7] Burchiel et al.[12] showed near statistical significance for litigation as a predictive factor.

Duration of pain

Mackinnon and Dellon[27] compared the duration of pain prior to surgery in a group of patients with poor pain relief to the patients with good or excellent pain relief following surgery. The group with poor pain relief had a median duration of pain of 48 months, compared to 24 months in the other group ($p < 0.01$).

Changes in pain processing in the central nervous system (CNS) can occur during the chronic phase of neuropathic pain and sustain patients' pain.[13,18,20,22,34,35] These changes start to develop within hours after the initial nerve injury and take place over a year or more.[34] Therefore, the time passed before surgical treatment of neuropathic pain might influence the progression of central changes and, thus, outcome.[35]

If the central pain mechanism disturbances are absent, patients with neuroma pain of many years duration may still be improved.[18,36]

Previous operative procedures

Vernadakis et al.[5] reported that if pain relief after the initial surgery is absent, it is unlikely that subsequent surgeries will be successful. Dellon and Mackinnon[13] found a significantly worse outcome for pain in patients with three or more previous operations, compared to those treated for the first time ($p < 0.01$). The same result was found in patients with a neuroma of the RSB at a significance level of $p < 0.05$.[27]

The lower success rate in patients who had previous operations for pain may be partly explained by the CNS disturbances that can occur under chronic pain. Because these central changes cannot be easily reversed by manipulation of the peripheral nerve, it will be difficult to decrease pain through surgery in these patients.[13]

Unexplained insuffi cient pain relief

Many studies acknowledge that there is a group of patients that do not benefit from any form of surgical neuroma treatment. Central sensitization and psychosocial factors may also play a role in maintaining pain in these patients.[7,13,18,21]

Psychosocial factors

Psychosocial factors are seen to be an integral part of pain processing.[34] Some of the

Table 1. Major prognostic factors of pain following surgical neuroma treatment: evidence and impact on prognosis.

Prognostic factor	Studies providing p-values for factor	Possible mediator(s)	Prognostic value
Radial sensory branch neuroma	Dellon 1984[23] Dellon 1986[13]	Incorrect relocation into small muscle with great excursions. High tension. Overlap with LABCN.	Predicts bad outcome. Placement into m. brachioradialis has best chance of success.
Digital neuroma	Dellon 1986[13] Novak 1995[18]	Placement into small intrinsic muscles with great excursions. Superficial location.	Highly significant bad results caused by inefficient relocation. Best results by relocation into bone.
Discrete nerve syndrome	Burchiel 1993[12]	If single nerve can account for patients symptoms, likely to be neuromatous pain.	Predicts good outcome. Combined variable, only described by Burchiel et al.
Workers compensation	Dellon 1986[13] Dellon 1996[24] Mackinnon 1987[27] Novak 1995[18]	Difficult to evaluate outcome. Compensation neurosis. Effect due to employment status.	Significantly predictive of bad outcome. Conflicting results. Employment might be mediator.
Employment	Mackinnon 1987[27] Burchiel 1993[12]	Employment may lead to lower distress and redirects attention away from the pain.	Significantly predictive of good outcome. Valuable to focus on activity and employment.
Litigation involvement	Burchiel 1993[12]	Patients benefit less from treatment when disability is important for the pending litigation.	Predicts bad outcome, although not significant. Inconsistent evidence about mechanism: employment might be a mediator.
Number of previous operations ≥ 3	Dellon 1986[13] Mackinnon 1987[27]	Partly explained by CNS changes that occur over time.	Significantly predictive of bad outcome.
Duration of pain ≥ 24 months	Mackinnon 1987[27]	Partly explained by CNS changes that occur over time.	Predictive of outcome. Patients may be improved if CNS changes are absent.

LABCN: lateral antebrachial cutaneous nerve; CNS: central nervous system

factors associated with poor results, for example duration of pain and unemployment, may initiate secondary psychosocial situations like depression.[21,27]

However, if exacerbated and maintained the psychological symptoms can become the most prominent feature.[7,33] Preoperative evaluation by a psychologist is recommended to identify patients with major psychopathology or functional overlay, as in these patients surgery is contraindicated.[5,12,27]

Central nervous system changes

Although neuroma formation following injury to a peripheral nerve can cause extreme pain and abnormal sensitivity in the distribution of the injured nerve, not all neuromas are painful.[4,8,11,17] The difference between asymptomatic and painful neuromas may either be due to the abnormal signals produced at the peripheral site or the central perception of these signals in the brain.[11,37]

Several mechanisms are described in the literature to explain neuropathic pain after nerve injury. The sensory nerve endings are exposed to mechanical stimuli because of adherence of the neuroma to surrounding tissue or compression of the nerve endings.[2,38,39] There is abnormal sensitivity and spontaneous activity of axons within the neuroma.[37] Reduced blood supply to the neuroma leads to painful hypoxia of the nerve endings.[2,39,40] Erratic discharges in the nerve fibers cause spontaneous pain. Abnormal connections between A- and C-fibers are made, causing cross-talk of nociceptive and non-nociceptive nerve fibers, resulting in pain at touch.[5,37,41]

In addition to these changes at the distal site of injury, loss of normal sensory input may lead to a reduction of inhibitory input from afferent fibers, creating a state of central sensitization of neural structures involved in pain perception. With continued abnormal afferent input from the neuroma, there are alterations at the spinal cord level and in the somatosensory cortex in the processing of non-painful stimuli. Sensitization of spinal dorsal horn neurons and relative hypoperfusion of the thalamus with subsequent development of disinhibition-induced hyperexcitability can be found in chronic neuropathic pain patients.[9,35,41-43] Chronic pain leads to an expansion of the cortical representation zone related to the nociceptive input.[35] CNS changes can increase pain responses and will perpetuate the pain process even if the initiating peripheral injury is treated successfully.[7,18,20,22,34,35]

Secondary spinal and cortical changes can be visualized using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) scans. Using these functional imaging techniques, it is possible to examine the regional cerebral blood flow (rCBF) associated with the regional activity in the brain. A common finding in patients with chronic peripheral neuropathic pain, is a decrease in rCBF in the thalamus contralateral to the affected limb.[43,44] Decreased thalamic activity may be a clinical feature common to a wide variety of chronic pain disorders.[9,43,45]

Another finding in the study of chronic neuropathic pain has been the observa-

tion that children react differently to painful nerve damage. Peripheral nerve injuries and even limb amputations appear not to lead to chronic pain syndromes in young children under the age of three years.[46] Consistent results have been found in young rats after selectively administered nerve damage.[47] The lack of long-term chronic pain syndromes after nerve damage in neonates and young children is likely to be the result of CNS plasticity.[46]

Conclusions

By reviewing the literature, we found 14 cohort studies that mention possible prognostic factors predicting insufficient pain relief after surgical neuroma treatment.[7,12,13,15,16,18,19,21,23-28] Major prognostic factors were found to be similar among these studies. The factors that seem to predict the amount of postoperative pain are: neuromas of the radial sensory branch (RSB) and digital nerves, discrete nerve syndrome, workers compensation, employment status, litigation involvement, duration of pain, and number of previous operations. Knowing the mechanism behind these prognostic factors, raises possibilities for improved treatment strategies.

Although none of the neuroma treatment methods described in literature provide excellent pain relief,[12-21] the application of appropriate treatment algorithms can lead to a satisfactory result in the majority of patients.[5,11] If neuromatous pain is relieved by a diagnostic nerve block, surgical treatment should be performed without undue delay.[12,34] Neuromas of the RSB and digital nerves should be placed into bone or large muscles without large excursions during movements.[15,18,28,29] Patients receiving workers compensation or involved in litigation should be stimulated to redirect their attention away from their disability and focus on improving their performance.[7,32] Methods like transcutaneous electrical nerve stimulation (TENS), topical lidocaine treatment and adjuvant pain medication like antidepressants and anticonvulsants can have a role in neuropathic pain management.[48,49]

Patients suffering from painful neuroma can have an acceptable outcome after surgery; however, central pain disturbances can maintain pain in some patients.[12,13] These CNS changes seem to be related to the duration of pain and number of previous operations.[13,35] As the CNS effects of chronic pain are profound in some patients, their relevance to painful nerve injuries cannot be ignored.[7,12] For patients with central sensitization, rehabilitation programs of postoperative desensitization should be directed toward the re-education of non-painful stimuli. Appropriate input into the somatosensory cortex may alter the abnormal cortical processing.[18,34,35]

Pain-related cortical reorganization should be modifiable by operant and classical conditioning processes and re-direction of attention, such as feedback-based

interventions.[35] Mirror therapy, as described by Ramachandran and Hirstein[50] has a potential role in sensory re-education.[51] This technique has been used for the treatment of hyperesthesia and pain after hand injuries in cases in which the injured hand cannot be touched because of excessive hypersensitivity.[46,52] When touching the unaffected hand, application of a mirror gives a visual illusion of touching the injured hand without inducing pain. Repeated training sessions seem to result in a central desensitization effect with reduced hypersensitivity.

The treatment of patients suffering from neuromatous pain remains a challenge. Patient specific factors influencing prognosis after surgery should be taken into account. Research focusing on these prognostic factors and the central changes induced by painful peripheral injury can lead to new and improved clinical treatment algorithms for the relief and prevention of chronic neuropathic pain.[9,34,43]

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Chapter 3:

Diagnostic ultrasonography of cutaneous nerve branches

High-resolution ultrasonography of the cutaneous nerve branches in the hand and wrist. Stokvis A, Van Neck JW, Van Dijke CF, Van Wamel A, Coert JH. The Journal of Hand Surgery (European Volume) 2009; 34: 766-771.

Abstract

Ultrasonography can be used in the diagnosis of various neuropathies, including nerve injury. Nerves that are often involved in traumatic and iatrogenic injury are small cutaneous nerve branches in the hand and wrist, which cannot be observed in detail using current clinical US devices. This validation study was conducted to explore the potential of high-resolution ultrasonography in visualizing these nerve branches in the human. The VisualSonics Vevo 770 system (15-82.5 MHz) was compared to a commonly used clinical US device (7-15 MHz). The accuracy was validated by ultrasound guided dye injection into cadaver nerves, with subsequent anatomical dissection and verification. Results were confirmed in two healthy volunteers. The Vevo 770 system was able to accurately identify the small cutaneous nerves. Furthermore it could depict the median nerve and its fascicles in greater detail. Our findings may be useful for clinical diagnosis, localization and follow-up of various neuropathies and nerve injuries.

Introduction

Ultrasonography (US) can be used to identify peripheral nerves. It is a non-invasive, cost-effective and easy to use technique. Major peripheral nerves in the extremities, such as the median, ulnar and radial, sciatic, common peroneal and posterior tibial nerves, can be visualized using conventional US performed with 7-15 MHz probes.

US can diagnose various neuropathies, such as nerve compression in carpal tunnel syndrome,[1,2] cubital tunnel syndrome,[3,4] nerve tumours,[5] and traumatic nerve lesions.[6,7] US can be used to determine the location, extent and type of lesion, nerve swelling and inflammation, to identify compressive structures like calcifications and scar tissue surrounding the nerve and to evaluate nerves following surgery.[8-11] For surgically treated problems, such as injured nerves or Morton's neuroma, it is important to know the exact site of the nerve lesion, before surgery. In these cases, imaging helps surgical excision or injection of steroids or phenol.[12-15]

Nerves that are often involved in traumatic and iatrogenic nerve injury are the superficial cutaneous branches of the median, ulnar and radial nerves in the hand and wrist, and the digital nerves.[16-18] These sensory nerve branches are located superficial to the fascia just underneath the skin, making them prone to nerve damage, sometimes resulting in extreme pain and major disability. A painful neuroma is the most severe outcome of peripheral nerve injury.[9]

The resolution of the current clinical US equipment, with frequencies of 5-20 MHz, does not allow adequate visualization of the small cutaneous branches of peripheral nerves. Therefore, this equipment may not be able to diagnose the cause of many nerve disorders in small subcutaneous nerve branches. By increasing the insonation frequency with high-resolution imaging transducers the imaging resolution improves. Recent advances in US imaging techniques have permitted frequencies over 80 MHz, with a spatial resolution down to 30 microns. These instruments can allow the imaging of small superficial structures. We report the use of such high resolution imaging in visualizing the small cutaneous nerve branches in human cadavers and volunteers.

Methods

A validation study was performed on two fresh cadaver arms, free of skin lacerations and without a known history of peripheral nerve pathology. The median nerve and its palmar branch, the sensory branch of the radial nerve, the dorsal branch of the ulnar nerve, and the digital nerves of the middle finger were studied. These nerves were also identified in vivo on the upper extremities of two healthy volunteers (approval by the institutional medical ethical review board, number MEC-2007-092).

Sonographic examinations were performed using two different US devices: the HDI 5000 system (Philips, Amsterdam, The Netherlands) equipped with broadband linear array transducers and the Vevo 770 system (VisualSonics Inc., Toronto, Canada) equipped with broadband mechanical scanning single element transducers. The HDI 5000 was equipped with two electronic real-time linear-array transducers (C12-7, C10-5) with a total range of 5-12 MHz. The Vevo 770 is a commercially available high-resolution US system designed for small animal research. It offers spatial resolution down to 30 microns, the highest real-time resolution currently available. The system was equipped with three RMV (real-time micro visualization) scanheads ranging from 15-82.5 MHz, with a field of view of up to 20 mm. The scanning depth ranged from 0 to 15 mm, depending on scanning frequency. The three scanheads used were no. 703, with a range of 15-49 MHz, scanning depth 4-15 mm; no. 704: 20-60 MHz, depth 1-10 mm; and no. 708: 27.5-82.5 MHz, maximum depth 11 mm.

All US examinations were performed by a senior staff radiologist (CFvD), with over eight years experience in US of the musculoskeletal system. Dissection of the cadaver arm was performed under loupe magnification by an assistant professor in reconstructive surgery, with over 15 years of experience in hand surgery (JHC). Care was taken to maintain the US beam perpendicular to the skin surface. A generous amount of US transmission gel, with air bubbles expelled, was applied to the skin to minimize the pressure of the transducer on the skin and to ensure a satisfactory scan. Nerves were located using known anatomical landmarks and were followed along their course distally. Scans were performed in both the transverse and longitudinal plane.

To subjectively evaluate the results of the difference in spatial resolution between the HDI 5000 system and the Vevo 770 system, images of the median nerve in the wrist crease were acquired with both systems. The images were compared subjectively on visualization and diameter measurements of (small) peripheral nerves and their fascicles, visualization of superficial structures and nerve sheaths and the ease of following the anatomical course of the nerve.

To validate the efficiency of the Vevo 770 equipment in seeing cutaneous nerve branches, a cadaver study was undertaken. With real-time high-resolution US guidance, the tip of a 23-gauge fine needle was advanced toward the echogenic structures that were thought to represent the median nerve and its palmar branch, the dorsal branch of the ulnar nerve, the sensory branch of the radial nerve at the wrist of the cadaver forearm and the digital nerves. Subsequently, coloured cyanoacrylate (basic blue colorant dissolved in superglue) was injected through this needle into the nerves. The area was dissected and studied macroscopically (by JHC) to confirm the injection site.

Results

Both the HDI 5000 en de Vevo 770 systems could visualize the distal median nerve at the distal wrist crease as a hyperechoic structure with an internal hypoechoic fascicular pattern (Fig. 1 & 2). However, due to the higher spatial resolution provided by the 15-49 MHz probe of the Vevo 770 system, the median nerve could be depicted in considerably more detail (Fig 2), making it easier to measure the size of the nerve and study its internal structure, the fascicles. However, because of the great magnification and the relatively small field of view, it was more difficult to evaluate the position of the nerve in relation to its surrounding structures using the high-resolution US device (Table 1).

Table 1: Comparison of a standard and high-end US device in the visualization of peripheral nerves in the human.

	Standard US device	High-end US device
Visualization of major peripheral nerves	++	++
Diameter measurements of large peripheral nerves	++	++
Visualization and measurements of fascicles	+	++
Visualization of small peripheral nerves	0/+	++
Diameter measurements of small peripheral nerves	0/+	++
Visualization of nerve sheaths	+	++
Following the anatomical course of the nerve	++	+
Visualization of superficial structures	+	++

US: ultrasound; ++: excellent visualization; +: good visualization; 0: poor visualization

Also the palmar cutaneous branch of the median, radial sensory, dorsal ulnar and digital nerves could be visualized using the 15-82.5 MHz probes of the Vevo 770 device. Validation has been performed by JHC after injecting coloured cyanoacrylate under US guidance (Fig 3) in the respective nerves and subsequent anatomical dissection to verify the structure seen. At macroscopic examination of the nerve structures in the cadaver arm, the injected dye was found in all studied nerves. This confirms the accuracy of our observations

Using the Vevo 770 system, all peripheral nerves under study were seen as echogenic oval to round structures with a honeycomb structure on transverse scans. A hyperechoic rim of connective tissue surrounded the nerves. Hypoechoic fascicles could be seen inside the nerve, ranging from only four fascicles in the smallest nerves, to around a dozen in the median nerve. On longitudinal scans the nerves were composed of multiple hypoechoic and parallel linear areas separated by hyperechoic bands.

Figure 1. 5–10 MHz US image of the median nerve

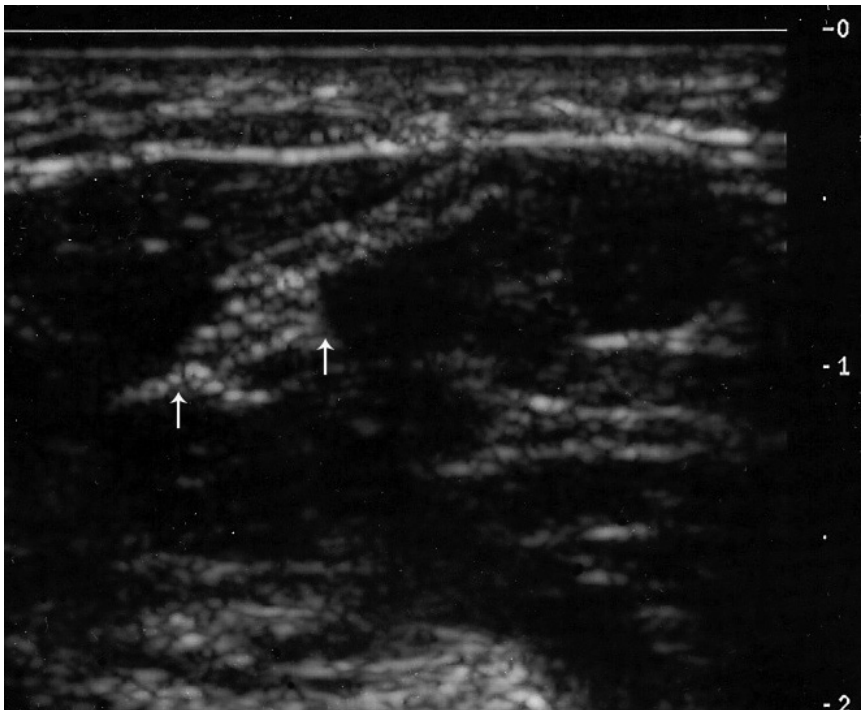
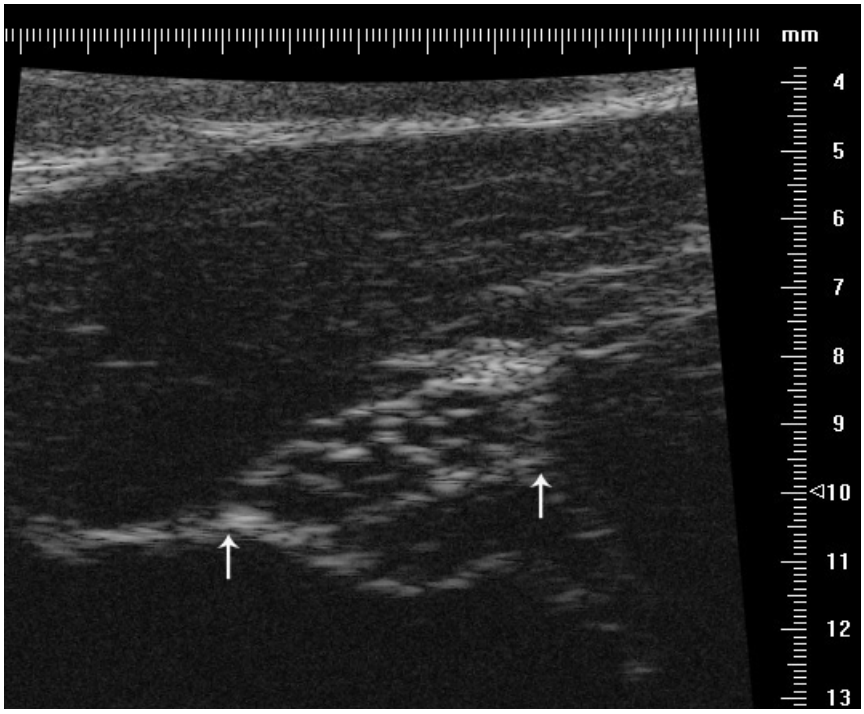


Figure 2. 15–49 MHz US image of the median nerve.
Both images made 8 cm proximal to the wrist crease



With the 5-12 MHz US larger nerves, i.e. median nerve, could be visualized well, however, smaller cutaneous nerves, i.e. dorsal branch of the ulnar nerve or palmar branch of the median nerve, could not be detected.

Applicability of the standard and high-end US devices in visualizing peripheral nerves was also confirmed in two healthy volunteers. By repeating our work without the dye injection and subsequent dissection, small nerve structures could only be observed in detail using high-end US (Fig 4 & 5). Overall, compared to the cadaver arms, the capture of nerve structures seemed easier in living subjects. This is probably due to the improved visualization of blood-vessels that often accompany the nerve.[6]

Figure 3. US guided injection of coloured cyanoacrylate into the median nerve. Left arrow indicates tip of the needle.

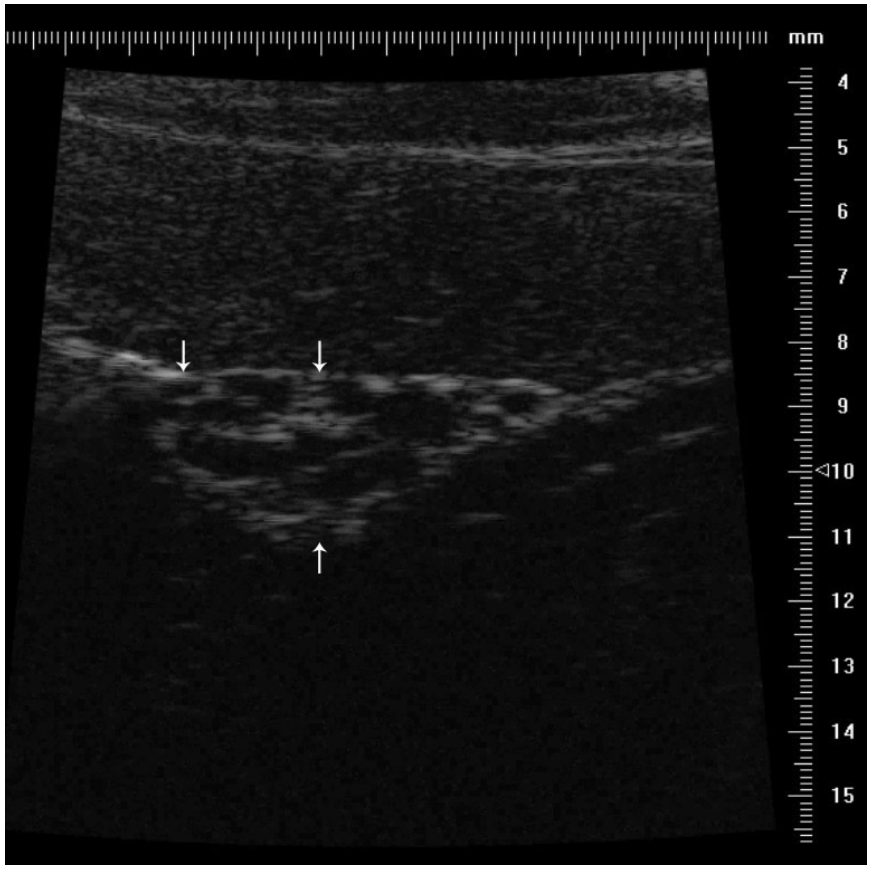


Figure 4. US image (5–10 MHz) of the middle finger palmar digital nerve (left arrow) and digital artery (right arrow).

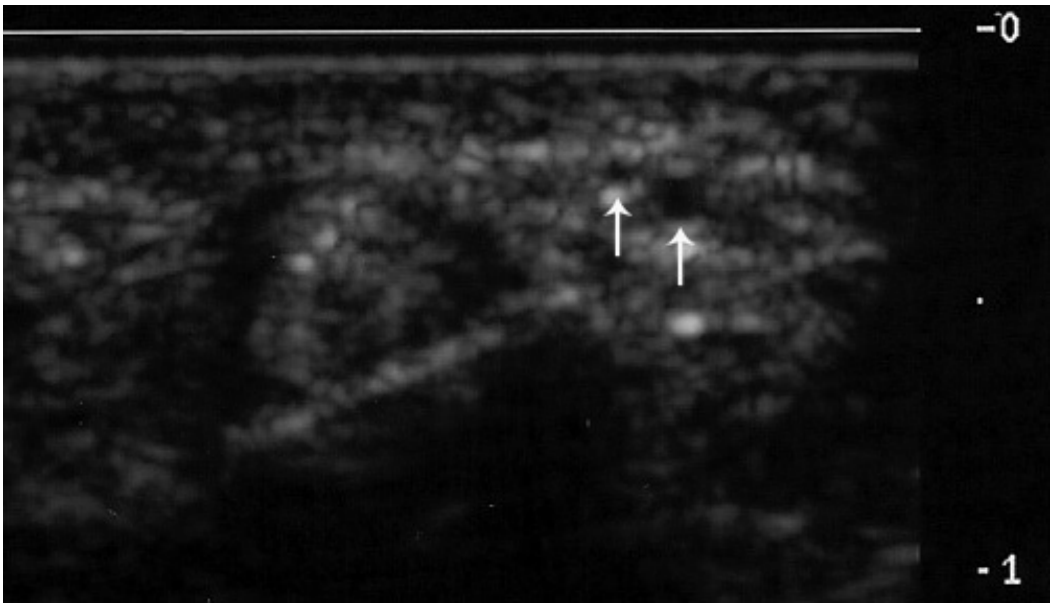
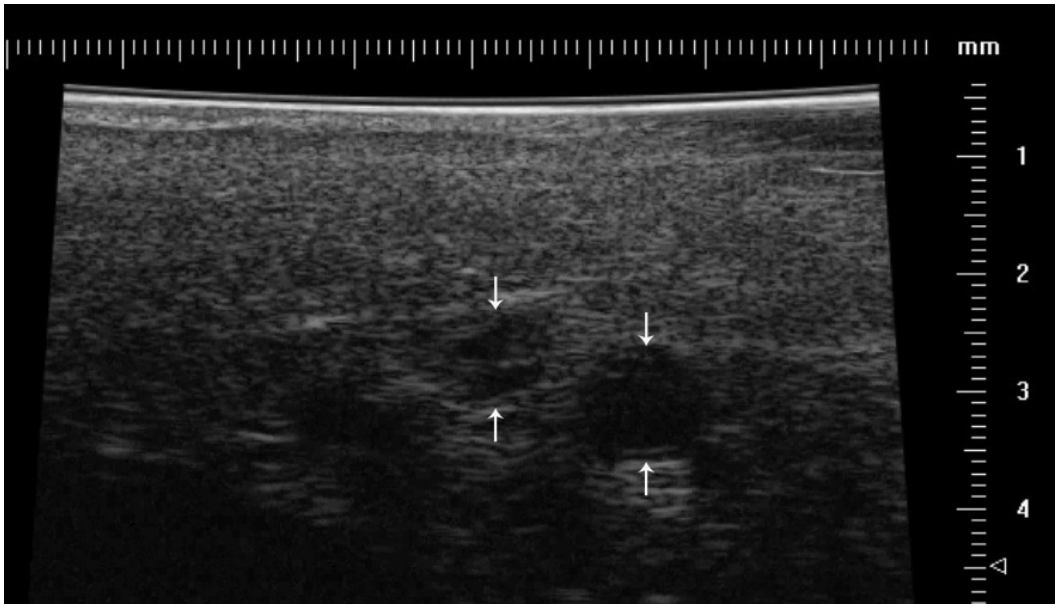


Figure 5. US image (20–60 MHz) of the middle finger palmar digital nerve (left arrows) and digital artery (right arrows).



Discussion

The present study was conducted to explore the use of a high-resolution US device (VisualSonics Vevo 770) in the imaging of small superficial peripheral nerves. All investigated nerves could be visualized using the high frequency probes of the device. Although US is used for major peripheral nerves,[1-4,9,11] US visualization of the smaller sensory branch of the radial nerve, palmar branch of the median nerve and dorsal branch of the ulnar nerve may be helpful in making a diagnosis, in finding the exact location and in grading the severity of entrapment, nerve injury and possibly neuropathic pain.[8,10,11,14,15,19] In traumatic or iatrogenic nerve injury, high-resolution US could discriminate between partial or full injury and help in surgical planning.[9] Also, it could be used to monitor nerves treated conservatively to assess regenerating nerves.

When following the anatomical course of a nerve, high-resolution US has some limitations due to its restricted field of focus. Different probes are needed to follow the course of a nerve especially when its anatomical localization becomes deeper. By increasing the frequency, the pulse length decreases, this makes the waves less capable of penetrating deeper tissues. US in clinical use has reached frequencies of 20 MHz at present and frequency and resolution are steadily increasing.

The US Vevo 770 equipment was developed for research in small animals where the drawback of the decreased penetration depth is of lesser importance. However, high frequency transducers have already been used for various clinical applications, such as dermatological and intravascular imaging.[20]

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Chapter 4:

Cold intolerance in surgically treated neuroma patients

Cold Intolerance in Surgically Treated Neuroma Patients: A Prospective Follow-Up Study. Stokvis A, Van Neck JW, Coert JH. The Journal of Hand Surgery (American Volume) 2009; 34A: 1689–1695.

Abstract

Purpose:

Cold intolerance imposes great changes on patients' life-style, work and leisure activities and is often severely disabling. This study aims to investigate the prevalence and severity of cold intolerance in patients with traumatic neuromas of the upper extremity and improvement of symptoms after surgical treatment. Furthermore, we try to find predictors for cold intolerance and correlations with other symptoms.

Methods:

Between January 2006 and February 2009, 34 consecutive patients with surgically treated neuroma specific neuropathic pain of the upper extremities, were sent a questionnaire composed of both general questions concerning epidemiologic determinants and several specific validated questionnaires, including the Visual Analogue Scale (VAS) for pain. To objectively estimate the prevalence of cold intolerance in neuroma patients, we used the validated CISS (Cold Intolerance Symptom Severity) questionnaire with a pre-specified cut-off point.

Results:

The CISS questionnaire was filled out by 33 patients before and 31 after surgery, with a mean follow up time of 24 months. We found a prevalence of cold intolerance of 91% before surgery, with a mean CISS score high above the cut-off point for abnormal cold intolerance and a prevalence of 77% after surgery. The mean CISS score decreased only mildly, while the mean VAS score decreased significantly after surgery ($p<0.01$). CISS scores were lower in patients with a sharp injury of the peripheral nerve ($p=0.02$). A higher VAS score correlated significantly with a higher CISS score ($p=0.01$).

Conclusions:

Cold intolerance is a difficult and persistent problem that has a high prevalence in patients with a painful traumatic neuroma. There seems to be a relation between severity of cold intolerance and spontaneous pain and type of injury. It is unlikely that cold intolerance disappears with time or surgical treatment.

Introduction

Cold intolerance is defined as abnormal pain of the hand and fingers after exposure to mild or moderate cold, with or without discoloration, numbness, weakness or stiffness. It is also known as thermal hyperalgesia or cold sensitivity and affects all work and leisure activities taking place outdoors or in moderate cold. Therefore, cold intolerance may seriously influence patients' daily life.[1,2] Cold intolerance is a common long-term sequel following upper extremity injury, with an estimated incidence of 42 - 100%.[3-6]

When a peripheral nerve is damaged, it will try to regenerate itself toward the distal nerve end or target organ.[7] If a distal target is not found, axon sprouts may grow into the surrounding scar tissue forming a neuroma.[8-10] Some of these neuromas cause intense pain and altered sensation in the distribution of the injured nerve.[11] Once a neuroma has formed, best results are usually obtained from surgical intervention, usually by relocation of the nerve end into muscle or bone.[11,12] A high incidence of cold intolerance is to be expected in neuroma patients. However, there is no data available on the prevalence of cold intolerance in patients with a painful traumatic neuroma. The extent of this problem is currently unknown.

Most studies focusing on peripheral nerve injuries have estimated the prevalence of cold intolerance using only subjective symptoms mentioned by patients.[3,13] They also did not specify the variable used to measure cold intolerance.[14] To objectively estimate the incidence of cold intolerance in neuroma patients, we used the validated CISS (Cold Intolerance Symptom Severity) questionnaire with a pre-specified cut-off point. In addition, we follow the surgically treated neuroma patients to see how their pain and cold intolerance symptoms change post-operatively and investigate the relationship between these two problems.

This study aims to investigate the prevalence and severity of cold intolerance in patients with traumatic neuromas of the upper extremity and improvement of symptoms after surgical neuroma treatment. Furthermore, we try to find predictors for cold intolerance and correlations with other symptoms.

Materials and methods

Study design

Between January 2006 and February 2009, we performed a prospective cohort study on surgically treated neuroma patients. Intake questionnaires were sent prior to surgery. This questionnaire contained both general questions concerning epidemiologic determinants and several specific validated questionnaires on pain, loss of upper

extremity function, symptoms of psychopathology and cold intolerance. Follow-up questionnaires concerning cold intolerance and pain were sent in February 2009, to all included patients with a follow-up period of at least 3 months.

Study population

Entry criteria were patients diagnosed with neuroma pain, planned for surgical neuroma treatment by author JHC in or institution. 34 consecutive patients, with neuroma specific neuropathic pain of the upper extremities, were asked to participate in our study.

The diagnosis neuroma specific neuropathic pain was made based on history and complaints, presence of Tinel's sign and reduction of pain after nerve blockade. The surgery entailed excision of the neuroma with relocation of the nerve end into muscle or bone. After obtaining their consent, the patients were sent an initial questionnaire when they were scheduled for surgery and another questionnaire at least 3 months post operatively. Non-responders were contacted by telephone and requested to return the questionnaire. This study was approved by the Medical Ethics Committee of our institution.

Scoring methods

The pre-operative questionnaire contained questions concerning patient specific factors such as age, gender, length, weight, smoking status, dominant hand affected, employment status, workers compensation, pending litigation, type of injury and number of previous operations.

The severity of post-traumatic cold intolerance was measured using the self-administered Blond McIndoe Cold Intolerance Symptom Severity (CISS) questionnaire, which has been validated in both a peripheral nerve injury group and a normative control group.[6,15]The CISS questionnaire is used to measure self-reported symptoms of CI and consists of 6 questions (table 1). The first question involves the occurrence of the following symptoms and signs: pain, numbness, stiffness, swelling and skin color change into white or blue. According to the official score guidelines, answers to this first question are not calculated towards the final CISS score. Questions two to six relate to the frequency, duration, severity and impact of cold intolerance symptoms on activities of daily live. Question 5 consists of the earlier McCabe Cold Sensitivity Test.[4,16,17] The CISS questionnaire was translated into Dutch, following the recommendations for the cross-cultural adaptation of health status measures, supported by the American Academy of Orthopaedic Surgeons (AAOS) and the Institute for Work & Health (IWH). The CISS questionnaire gives a minimum score of 4 and a maxi-

Table 1. The CISS Questionnaire, by Irwin et al.[6]

Question #	Score
1. Which of the following symptoms do you experience in your injured limb on exposure to cold?*	
Pain; numbness; stiffness; swelling; blue or white skin color change	-
2. How often do you experience these symptoms? (please tick)	
Continuously/ all the time	10
Several times a day	8
Once a day	6
Once a week	4
Once a month or less	2
3. When you develop cold induced symptoms, on your return to a warm environment are the symptoms relieved (please tick):	
Within a few minutes	2
Within 30 minutes	6
After more than 30 minutes	10
4. What do you do to ease or prevent your symptoms occurring? (please tick)	
Take no special action	0
Keep hand in pocket	2
Wear gloves in cold weather	4
Wear gloves all the time	6
Avoid cold weather/stay indoors	8
Other (please specify)	10
5. How much does cold bother your injured hand in the following situations (please score 0-10):	
Holding a glass of ice water**	10
Holding a frozen package from the freezer**	10
Washing in cold water**	10
When you get out of a hot bath/shower with air at room temperature**	10
During cold winter weather	10
6. Please state how each of the following activities have been affected as a consequence of cold induced symptoms in your injured hand and score each (please score 0-4):	
Domestic chores	4
Hobbies and interests	4
Dressing and undressing	4
Tying your shoe-laces	4
Your job	4

** The answers given in this question do not count towards the final CISS test-score.*

*** These are the questions from the McCabe Cold Sensitivity Test.*

mum score of 100.

The visual analogue scale (VAS) consists of a horizontal line of 10 cm, anchored with the words 'no pain at all' on the left side and 'unbearable pain' on the right. The patient has to place an x on the line representing the amount of pain felt. The VAS score ranges from 0 to 10. Additionally, four questions concerning the severity of different types of pain were asked. The types were: spontaneous pain, pain on pressure, pain on movement and painful hyperesthesia on light skin touch. The severity of the pain was scored as severe, moderate, mild or absent.

The disabilities of the arm, shoulder and hand (DASH) questionnaire is a self-administered outcome instrument developed as a measure of self-rated upper extremity disability and symptoms. It is the most widely used upper extremity-specific health-status measure.[18] The DASH consists mainly of a 30-item disability scale, scored 0 (no disability) to 100 (most severe disability). In this study we used the approved Dutch version of the DASH.[19]

Duration of pain was defined as time between the development of neuroma pain and surgery and follow-up as time since surgery in months.

Statistical methods

Patient and injury characteristics were tested for association with the pre-operative CISS score using Pearson's Correlation test for continuous variables. Analysis of variance (ANOVA) and (paired) t-tests were used to compare categorical variables. The z-test was used to compare proportions. All tests were two sided and a p-value of less than 0.05 was considered statistically significant. All data analyses were performed using Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA), version 16.0.

Results

Study population

Between January 2006 and February 2009, 34 patients returned the intake questionnaire, approximately 4 weeks before surgery. All 34 patients were operated with excision of the neuroma and relocation of the nerve end into muscle or bone. One patient filled out the pre-operative questionnaire incorrectly; she was excluded from our study. The follow up questionnaire was sent to 32 patients; excluding one patient from post-operative analyses, which had had surgery less than 3 months ago. The follow-up questionnaire was returned by 30 patients, 2 patients did not want to coop-

erate. Demographics of the 33 included neuroma patients are presented in table 2. The study population consists of 18 males and 15 females, with an average age of 43 years on the day of filling out the first questionnaire. The mean duration of pain was 42 months. In 76% of the cases the dominant hand was affected. Types of injury included 18 (54%) sharp lacerations, 9 (27%) crush injuries, 5 (15%) avulsion injuries and 1 (3%) had an unknown cause. Nine patients (27%) had a (partial) digital amputation. After surgical treatment, 12 patients required secondary procedures for their pain problem.

Outcome variables

Pain was the most frequent cold-induced symptom in neuroma patients, indicated by 85% of the participants before surgery (table 1, question 1). Numbness was present in 21% of the neuroma patients. Other signs were stiffness (42%), skin color change (21%) and swelling (6%). Six percent of patients reported no signs or symptoms of cold intolerance prior to surgery. Most of these signs and symptoms were mentioned less frequent after surgery (table 3). The mean total CISS score of questions 2 to

Table 2: Characteristics of responding neuroma patients (n=33)

Characteristic		
Age (years)	mean	43 (SD 14)
	range	17 - 75
Gender	male	18 (55%)
	female	15 (45%)
Injured nerve	digital	17 (52%)
	radial sensory branch	12 (36%)
	LABCN	3 (9%)
	ulnar	1 (3%)
Dominant hand affected	yes	25 (76%)
	no	8 (24%)
Lesion	sharp	18 (54%)
	crush	9 (27%)
	avulsion	5 (15%)
	unknown	1 (3%)
Duration (months)	mean	42 (SD 36)
	range	5 – 142
Follow-up (months) (n=31)	mean	24 (SD 13)
	range	3 – 47

SD: standard deviation; LABCN: lateral antebrachial cutaneous nerve

6 was 54 (SD 20) prior to surgery, with a minimum of 6 and a maximum of 84. Thirty patients (91%) exceeded the standardized cut-off point (CISS score of 30) for abnormal cold intolerance.[15] After an average of 24 months follow-up, the percentage of patients with cold intolerance was 77%, this decrease was not significant (z-test). 4 patients, who had significant symptoms of cold intolerance before surgery, did not have a significant score on the CISS questionnaire averagely 39 months after surgery. Overall, the mean CISS score decreased only mildly (52, SD 31). The mean VAS score decreased significantly from 6.6 to 4.5 after surgery (paired t-test, $p<0.01$).

Using ANOVA we found no statistical difference in CISS-scores between the different affected nerves. We found no significant correlation between CISS and duration of pain or follow-up time. Other non-significant predictors for CISS score were: age, gender, smoking status, dominant hand affected, employment status, workers compensation and pending litigation (data not shown). Number of previous operations was not correlated to CISS score, nor was the mean CISS score different for patients with or without secondary procedures.

VAS score was positively correlated ($p=0.01$) and to CISS score. The DASH score showed a significant positive correlation with CISS score, but controlled for VAS score, this correlation was no longer significant. Performing a t-test on type of injury, we found a statistically significant lower mean CISS score for sharp injuries compared to other types of injuries ($p=0.02$).

Discussion

The present study was conducted to evaluate the prevalence and severity of cold intolerance in patients with neuroma pain. Using the CISS questionnaire we found an pre-operative prevalence of 91%, with a mean CISS score high above the cut-off point of 30, for abnormal cold intolerance.[15] The mean CISS score and prevalence of cold intolerance did not significantly decrease after surgical neuroma treatment. Cold intolerance was lower in patients with a sharp injury of the peripheral nerve. A higher subjective pain score (VAS) correlated significantly with a higher CISS score.

To our knowledge, literature relating to cold intolerance in neuroma patients is sparse. Therefore, our data will be put into perspective using literature on peripheral nerve injury in general. A high incidence of post-traumatic cold intolerance in the upper extremity has been reported by several authors.[3-5,14,20-22] Most studies in this field describe the incidence of cold intolerance following peripheral nerve injury or amputation and after replantation of digits. Our study is the first to look at the prevalence of cold intolerance in patients that have been operated for painful nerves after an injury. The obtained mean CISS score of 54 in our study population is significantly

Table 3. Results of validated questionnaires

Variable	Pre-operative	Post-operative
CISS score	54 (SD 20)	52 (SD 31)
Pain	85%	67%
Numbness	21%	30%
Stiffness	42%	40%
Color changes	21%	30%
Swelling	6%	3%
No complaints	6%	13%
Patients with cold intolerance (CISS ≥ 30)	30 (91%)	23 (77%)
DASH score	50 (SD 22)	41 (SD 24)
VAS score	6.6 (SD 2.3)	4.5 (SD 3.2)**

SD: standard deviation; CISS: Cold Intolerance Severity Scale, range 4-100, where 100: most severe cold intolerance, cut-off point for abnormal cold intolerance is 30. DASH: Disability of Arm Shoulder and Hand, range 0-100, where 0: no disability and 100: most severe disability. VAS: Visual Analogue Scale, scale 0-10, where 0: no pain at all and 10: unbearable pain.
***: significant difference between pre- and post-operative value, with p<0.01.*

Table 4. Influence of continuous variables on CISS score (Pearson's correlation coefficient)

Variable	Correlation Coefficient (*r*)	p-value
VAS pre-operative	0.443	0.010**
BMI	-0.349	0.046*
DASH	0.438	0.011*
Controlled for VAS	0.258	0.155
Duration of pain (months)	0.033	0.856
Follow-up (months)	-0.260	0.165

VAS: Visual Analogue Scale. DASH: Disability of Arm Shoulder and Hand. BMI: Body Mass Index
** = p-value significant at the 0.05 level.*
*** = p-value significant at the 0.01 level*

higher than scores obtained in other types of nerve injury patients.[6,23] In a study by Ruijs et al.,[23] a mean CISS score of 38 was found for median and ulnar nerve injuries, with 59% of the 107 subjects being classified as having cold intolerance. Irwin et al.[6] found a mean CISS score of 41 in 398 patients with upper extremity nerve injuries.

The estimated prevalence of cold intolerance, as reported in literature, largely depends on the method of measuring and defining cold intolerance.[13,20] In literature, this classification ranges from subjective symptoms mentioned by patients,[3,13] to the use of a validated questionnaire.[6,23] Some articles do not even specify the variable used to measure cold intolerance,[14] or do not describe any cut-off point for abnormal intolerance of cold or validation of the method used.[24] In our study, we used the validated CISS questionnaire with a specified cut-off point. In contrast to VAS pain score, the mean CISS score and percentage of patients identified as experiencing above normal cold intolerance, did not significantly decrease after surgery. Similar results have been reported in literature: these studies tested patients multiple times and found that, despite an improvement of symptoms, cold intolerance did not disappear.[4,5,21,22] Our results are illustrative of the severe and persistent nature of post-traumatic cold intolerance and they show that little or no benefit can be gained from surgery.

There was no significant relationship between duration of pain or follow-up time and CISS score, which implies that cold intolerance is independent of time between injury or surgery, and the time that has elapsed after treatment. This is supported by other studies that found cold intolerance unlikely to disappear with time.[5,6,20,21,23,25-27]

Pain was the most frequent cold-induced symptom in our study population. This is a common finding in literature where pain is often mentioned as the most troublesome symptom of cold intolerance.[24,28] Although smoking is known to impair digital bloodflow and wound healing in the hand,[29,30] a relation between smoking and cold intolerance could was not observed.[4,26]

Our data showed a significantly lower CISS score in patients with a sharp injury, compared to other types of injuries. This finding is consistent with the finding of Irwin et al.,[6] demonstrating that sharp injuries are less likely to be associated with the severity cold intolerance. They may lead to a larger chance of a successful revascularization and replantation of amputated digits than do crush or avulsion type injuries.[6,21,31,32] An explanation for the higher CISS score in patients with an avulsion or crush injury may be the fact that adequate coaptation of the nerve ends is nearly impossible. This may cause several "micro-neuromas" at different levels. Another cause for the increased CISS score in these injuries is the greater extent of the zone of nerve injury.

Painful neuromas of the peripheral nerves may occur after (partial) nerve damage. Patients with a painful traumatic neuroma display intense pain, altered sensation, mechanical hyperalgesia and cold intolerance in the distribution of the injured nerve. Little is known about mechanisms of cold intolerance.[33] In normal situations, lower-

ing skin temperature evokes a painless cold sensation, which will ultimately become a cold and painful sensation after further cooling. In cold intolerant patients this process is disturbed.

Cold sensation is mediated by small myelinated A-delta fibers and cold induced pain by unmyelinated C-nociceptors. The combination of the two inputs results in the blended sensation of cold and usually aching pain. In a neuroma, abnormal connections between A- and C-fibers are made, causing "cross-talk" between nociceptive and non-nociceptive nerve fibers, resulting in mechanical and thermal hyperalgesia. There is abnormal sensitivity and spontaneous activity of injured axons, caused by sensitized C-nociceptors.[16,34-38] In addition, loss of afferent A-fiber input may lead to disinhibition, creating a state of central sensitization of neural structures involved in pain perception.[39-41]

These mechanisms possibly explain the significant correlation between cold intolerance and subjective pain experience in neuroma patients: sensitized nociceptive C afferents in neuroma patients display exaggerated and unmodulated signals of pain after mild exposure to cold. In addition they may also fire without this exposure, leading to spontaneous pain. The central nervous system changes do not seem to disappear in time or with surgical treatment, which may explain why CISS scores did not decrease in our study population.

This study was conducted to look at the prevalence of cold intolerance in patients with a neuroma of the upper extremity and improvement of symptoms after surgical treatment. Cold intolerance is a difficult problem that has a high prevalence in patients with a painful traumatic neuroma. Cold intolerance was observed to be less common after sharp injuries compared to other types of injury. We observed a relation between severity of cold intolerance and subjective spontaneous pain and it is unlikely that cold intolerance disappears with time or surgical treatment.

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Chapter 5:

The 'unforgiving' superficial branch of the radial nerve

The unforgiving nerve: treatment strategies for neuropathic pain caused by the superficial branch of the radial nerve. Stokvis A, Coert JH. Under review for The Journal of Hand Surgery (American Volume)

Abstract

Purpose:

Neuropathic pain in the upper extremity can cause extreme disability, often leading to workers compensation and high health care expenditures. The sensitivity of the superficial branch of the radial nerve (SBRN) for the development of neuropathic pain is well documented, and achieving satisfactory pain relief remains extremely difficult. This study was performed to evaluate different treatment strategies for neuralgias caused by direct injury to the SBRN on the dorsum of the wrist.

Methods:

Surgical records were searched for patients with SBRN neuralgia. Data were collected from medical files. The effect of a pre-operative diagnostic nerve block was determined. Study outcomes were patient satisfaction and pre- vs. post-operative pain decrease scored with the numerical rating scale (NRS). Patient satisfaction following neurolysis, nerve reconstruction, denervation and adjacent nerve neurectomies was evaluated, and different relocations of the SBRN end were compared. Forty-nine patients were included. Thirty-one patients underwent external neurolysis of the SBRN. In five patients the nerve was reconstructed and 38 patients underwent denervations of the SBRN. Eighteen patients underwent neurectomies of adjacent nerves, including the posterior interosseous nerve (PIN) and lateral antebrachial cutaneous nerve (LABCN).

Results:

In total, 29 patients achieved satisfactory results (59%). The median NRS pain score decreased from 7.5 to 2.5 ($p<0.001$). Operations relocating the SBRN into the brachioradial muscle achieved significantly higher patient satisfaction rates than relocation of the nerve end elsewhere ($p=0.04$). PIN and LABCN neurectomies also provided satisfactory pain relief. A lower NRS pain score decrease and lower satisfaction rates were found in patients with an unsuccessful diagnostic nerve block.

Conclusions:

When treating traumatic SBRN neuralgias, there are several effective treatment methods, depending on the continuity of the injured nerve and the involvement of adjacent nerves. In case of an end-neuroma of the SBRN, relocation of the nerve end into the brachioradial muscle should be performed.

Introduction

Neuropathic pain in the upper extremity following peripheral nerve injury is a serious problem, commonly involving relatively young patients.[1] The pain causes loss of function and productivity, changes patients' life-style, and can progress into a chronic pain syndrome that can be severely disabling.[2] This leads to high unemployment and workers compensation rates with considerable costs to society,[3] as well as high health care expenditures.[4]

Neuropathic pain caused by lesions or perineural adhesions of the superficial branch of the radial nerve (SBRN), remains one of the most difficult conditions for which to achieve satisfactory pain relief,[5,6] and provides a good example for the problematic treatment of peripheral neuropathic pain. The SBRN supplies sensation to the dorsolateral hand and the dorsal aspects of the first three fingers, and can easily be injured following trauma or surgical procedures, because of its superficial location.[7,8] After peripheral nerve damage, axon sprouts grow into the surrounding scar tissue forming a neuroma,[9] this often causes sensory deficits, areas of skin dysesthesia, and severe pain.[8,10]

Treatment options for this peripheral nerve problem are primarily surgical. Despite improving techniques for complete denervation of the SBRN, many patients suffer from recurrent pain and mechanical hyperalgesia in the operated area. There is increasing evidence that hyperalgesia is independent of spontaneous pain originating in the peripheral neuroma.[11-14] This suggests changes in neighboring intact nerve fibers,[13] recruitment of axons from adjacent nerves,[11,15] or direct injury to surrounding nerve branches.[16,17] Apart from surgical treatment, therapeutic options are largely limited to symptom control, including pharmacologic treatment, nerve stimulators or temporary nerve blocks.[4,14]

This study was conducted to evaluate patient satisfaction following different surgical treatment methods for SBRN neuralgia caused by lesions or adhesions of directly traumatized superficial branches of the radial nerve (SBRN), including neurolysis, nerve reconstruction, denervation and adjacent nerve neurectomies. Different relocations of the SBRN end were compared and the prognostic value of a pre-operative diagnostic nerve block and patient specific determinants was explored.

Materials and Methods

We performed a retrospective cohort study, to evaluate the different treatment strategies for SBRN neuralgia caused by direct injury to the superficial branch of the radial nerve. Surgical records were searched for procedures involving neuropathic pain

caused by the SBRN, performed or supervised by the senior author between March 2001 and May 2009. Patients with traumatic nerve lesions or perineural adhesions of the SBRN in the dorsoradial hand or wrist were included. Patients with SBRN entrapment between the tendons of the brachioradialis and extensor carpi radialis longus (Wartenberg syndrome), were excluded, as well as proximal entrapments of the radial nerve in the upper extremity.

We found 56 patients who underwent relevant surgical procedures of the SBRN. Seven patients were excluded. Four of these patients were treated for Wartenberg neuropathy, one had an injury of the radial nerve in the elbow, and two patients underwent nerve repair or neurolysis for loss of sensibility after injury, without complaints of pain or dysesthesia. Characteristics of the 49 included patients are presented in table 1. The study population consisted of 17 males and 32 females, with an average age of 40 years. The mean duration of pain was 30 months. Six patients had undergone previous operative procedures for their pain problem in other medical centers.

Types of injury included 44 (90%) sharp lacerations, two (4%) crush injuries, two (4%) avulsion injuries, and one (2%) unknown cause. An iatrogenic cause was present in 82% of patients, mainly concerning surgical De Quervain's release (table 2). Follow up time varied between three and 99 months, with an average of 41 months.

Table 1. Patient characteristics (n=49)

Characteristic		**N**
Sex	male	17
	female	32
Age (years)	mean	40 (SD 12)
	range	16–63
Injury	sharp	44
	crush	2
	avulsion	2
	unknown	1
Iatrogenic injury		40
Dominant side affected		30
Amputation		2
Duration of pain (months)	mean	30 (SD 41)
	range	2 – 222
Duration of pain	<12 months	17
	>12 months	32
Follow up (months)	mean	41 (SD 24)
	range	3 – 99

Table 2. Iatrogenic causes of neuralgia (n=40)

Surgical procedure	Number of patients	%
De Quervain's release	14	35%
Joint (arthrodesis, arthroplasty)	6	15%
Ganglion excision	4	10%
Ligament (SL, Eaton-Littler, UCL)	4	10%
CTS release	3	8%
Tendon, other (tenolysis, transfer)	3	8%
Bone (sequestrotomy, osteotomy)	3	8%
Flap (RFF, TE)	2	5%
Debridement	1	3%

SL: scaphoid–lunate; UCL: ulnar collateral ligament; CTS: carpal tunnel syndrome; RFF: radial forearm flap; TE: tissue expander.

Patients were diagnosed on the base of their symptoms, history, and clinical assessment. Symptoms suggestive of SBRN adhesions or injury consist of electric pain in the dorsoradial wrist or hand, with a history of with a past history of a skin laceration or incision in the dorsoradial wrist area.[8] Clinical assessment showed a positive Tinel's sign: shooting pain after percussion on the nerve. In most cases, a diagnostic nerve block with 1% lidocaine was performed to evaluate possible overlap of neighboring nerves contributing to the pain problem,[16] and to identify the presence of central sensitization processes or phantom limb pain.[8,16,22] It is assumed that if the pain diminishes, surgery will be effective in providing pain relief.[22] Absence of relief after anesthetic block can be interpreted as a contraindication to surgery[8] and patients without a decrease or even an increase of their symptoms are excluded from operation.

Information on treatment strategy and surgical techniques was collected from surgical reports. Patients suffering from SBRN neuralgia often undergo multiple surgical procedures in order to achieve satisfactory pain relief. Patients were treated using various techniques proposed in the literature.[5,9,10,16,23] A flow chart of the treatment strategy that was used is presented in figure 1. All procedures included in this study were performed or supervised by the same hand surgeon.

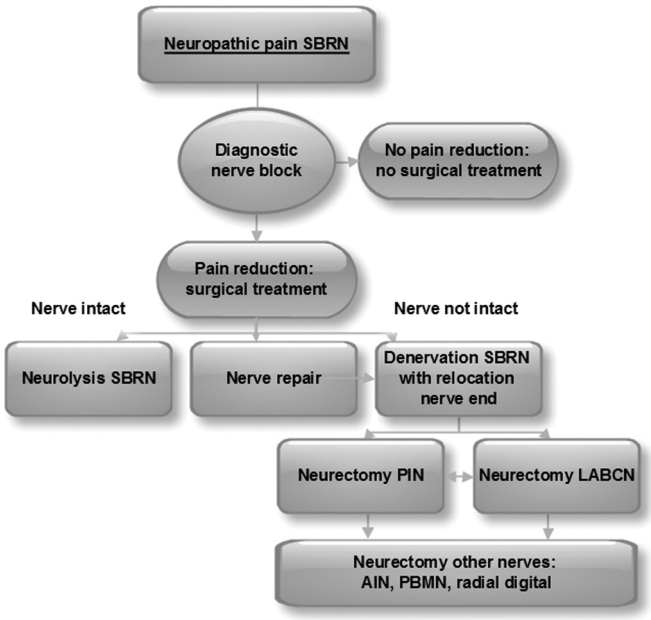
Thirty-one patients that presented with perineural adhesions of the SBRN were primarily treated by external neurolysis.[5] In case of a painful neuroma, the neuroma was excised and in five patients continuity could be restored, in some cases using a neurotube or nerve graft.[23] If nerve repair was not possible, denervation of the SBRN was performed with relocation of the nerve end into bone,[24] muscle,[8,16,23] a silicon

nerve sheath or an end-to-side nerve loop.[10] Twenty patients underwent denervation of the SBRN with relocation of the nerve end into the BR muscle (figures 2–4). In 18 patients the nerve end was relocated elsewhere.

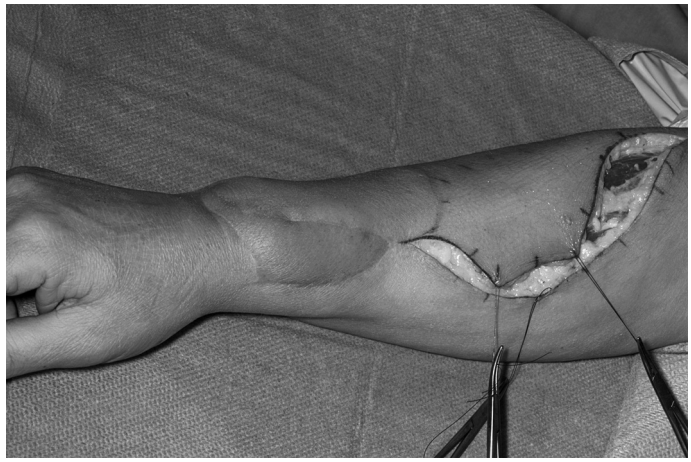
In case of recurrent or persistent pain following SBRN denervation, neurectomies of adjacent nerves suspected of transmitting pain signals were performed. Nerves that often lie in proximity to the SBRN injury site are the lateral antebrachial cutaneous nerve (LABCN), posterior interosseous nerve (PIN), palmar branch of the median nerve (PBMN), anterior interosseous nerve (AIN) and the radial digital nerve of the thumb. Eighteen patients underwent surgical procedures of neighboring nerves in the dorsoradial wrist area.

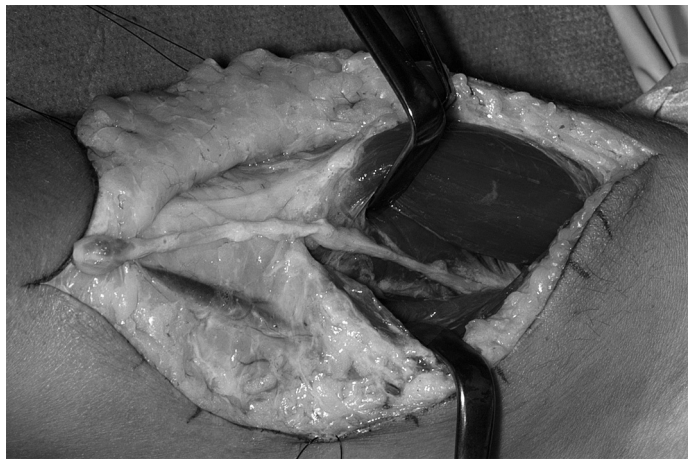
Patient follow up data were obtained from outpatient clinic records that were available for all included patients. The primary outcome was patient satisfaction was scored in four categories: excellent, satisfactory, unsatisfactory, and extremely unsatisfactory; as well as a total satisfaction rate. Patients were classified according to their pain reduction, dysesthesia relief, and the necessity of further (surgical or anesthetic) pain treatment judged by the attending hand surgeon at the outpatient clinic: 'Excellent': patient reported extreme satisfaction with treatment result; or all symptoms of pain and hyperalgesia had disappeared. 'Satisfactory': patient reported satisfaction; or pain and hyperalgesia decreased to a bearable level. 'Unsatisfactory':

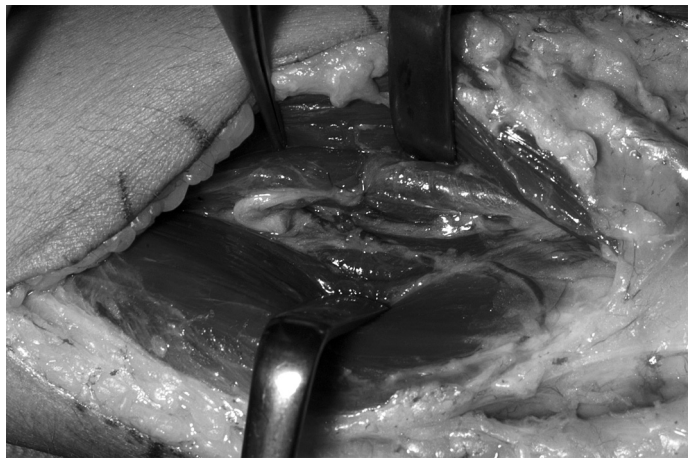
Figure 1. Flow chart of treatment strategy for neuropathic pain caused by the superficial branch of the radial nerve



Figures 2-4. Surgical denervation, with relocation of the superficial branch of the radial nerve into the brachioradial muscle







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patient reported to be dissatisfied; or minimal decrease in pain and/or hyperalgesia without indication for re-operation. 'Extremely unsatisfactory': patient reported to be extremely dissatisfied; or minimal/no decrease or increase in pain and hyperalgesia, indication for re-operation.

Pain (decrease) scored with the numerical rating scale (NRS), was a secondary outcome.[25] Patients were asked to rate their pain as any number between 0, 'no pain at all', and 10, 'unbearable pain' pre- and post-operatively. Pre- and post-operative NRS pain scores were available for respectively 21 and 41 patients. Information on demographic factors, etiology, type of lesion, duration of pain, and previous surgical procedures were collected from medical files.

In a secondary analysis including 28 patients, we studied the prognostic value of the pre-operative diagnostic SBRN block. The effect of the diagnostic nerve block was attained using pre- and block NRS pain scores, which were recorded at the outpatient clinic before surgery**.** We determined a cutoff value of at least 3.5 points pain reduction on the NRS for good nerve block effect.

The study has been approved by our institutional medical ethical review board (number MEC-2007-094).

Statistical methods

To evaluate different treatment strategies, we calculated satisfaction rates for all types of surgical procedures performed, analyzing only one surgical procedure per patient. For denervations of the SBRN, we compared patient satisfaction following primary surgical procedures, relocating the nerve the nerve end into the brachioradial muscle, or elsewhere. Post-operative satisfaction for these procedures was compared using the Kruskal-Wallis test. Possible confounders were tested on their distribution among treatment groups. Independent t-tests were used to compare continuous variables and paired t-tests for repeated measurements.

NRS pain score decrease and satisfaction rates were compared between patients with and without an effective diagnostic nerve block. We compared patient characteristics and outcomes (age, sex, duration of pain, number of previous operations, post-operative pain and satisfaction) among the groups with and without available nerve block outcomes. The Mann-Whitney U test was used to compare ordinal (NRS score decrease and patient satisfaction) data among groups, and the Wilcoxon signed-rank test for comparison of paired data ordinal data, including the pre- and post-operative NRS pain scores.

All tests were two sided and a p-value of less than 0.05 was considered statistically significant. All data analyses were performed using Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA), version 16.0.

Table 3. Patient outcomes (n=49)

Outcome	N	
Number of operations		
1	21	>1 operation: 57%
2	14	
≥3	14	
Patient satisfaction		
Extremely satisfied	20	
Satisfied	9	Satisfied: 59%
Unsatisfied	12	
Extremely unsatisfied	8	Unsatisfied: 41%
Median NRS pain score (range)		
Before surgical treatment	21	7.5 (2.5 – 9.0)
Following surgical treatment	41	2.5 (0.0 – 10)*

** Wilcoxon signed-rank test (n=21) for pre- and post-operative NRS pain score: p<0.001*

Results

Surgical results were excellent in 20 patients, satisfactory in nine, unsatisfactory in 12, and extremely unsatisfactory in eight patients (table 3). The median NRS pain score decreased from 7.5 to 2.5 after surgical treatment (Wilcoxon signed-rank test, p<0.001). Patient satisfaction varied between different treatment methods as presented in tables 4 and 5. Operations relocating the SBRN into the BR muscle achieved a satisfaction rate of 45%; this was 11% with relocation of the nerve end elsewhere. SBRN neurolyses showed a satisfaction rate of 39%. This was 55% and 50% for PIN and LABCN neurectomies respectively.

Satisfaction rates of primary surgical procedures for SBRN end-neuromas were compared; the results are displayed in table 6. Average duration of pain, number of patients with pain duration over 12 months, median pre-operative NRS pain score and number of previous surgeries were evenly distributed among the two treatment groups. Denervation with relocation of the nerve end into the BR muscle was significantly more effective in providing satisfactory pain relief than relocation elsewhere (p=0.03). None of the patients primarily operated by nerve repair or relocation of the SBRN elsewhere achieved satisfactory pain relief after surgery.

Patients with at least 12 months of symptoms prior to their primary surgical procedure, showed a lower decrease in NRS pain score than patients with a shorter duration of pain (median NRS decrease: 5.5 versus 4.0). The number of operations necessary for sufficient pain relief was significantly higher in the group with a longer duration of pain (median number of operations: 2 versus 1, Mann–Whitney U test p=0.02).

Table 4. Results of different surgical procedures

Procedure	Number of patients	Extremely satisfied	Satisfied	Unsatisfied	Extremely unsatisfied	% satisfaction
SBRN						
Neurolysis	31	8	4	14	5	39%
Nerve reconstruction	5	0	0	4	1	0%
Denervation, BR muscle	20	5	4	10	1	45%
Denervation, other*	18	1	1	10	6	11%
PIN neurectomy	11	3	3	2	3	55%
LABCN neurectomy	8	4	0	1	3	50%

*SBRN: superficial branch of the radial nerve; BR: brachioradial; PIN: posterior interosseous nerve; LABCN: lateral antebrachial cutaneous nerve; * see table 5*

Table 5. Results of different SBRN denervations (n=18)

Procedure: relocation into	Number of patients	Extremely satisfied	Satisfied	Unsatisfied	Extremely unsatisfied	% Satisfaction
Distal radius	6	1	1	2	2	33
Interosseous space	6	0	0	3	3	0
Small muscle	4	0	0	4	0	0
Other*	4	0	0	3	1	0

** silicone sheath, end-to-side, free flap*

Table 6. Primary surgical procedures for SBRN neuromas

Procedure	Number of patients	Extremely satisfied	Satisfied	Unsatisfied	Extremely unsatisfied	% satisfied
Nerve reconstruction	3	0	0	3	0	0%
Denervation, BR muscle*	10	2	1	7	0	30%
Denervation, other	16	0	1	9	6	6%

*Kruskal Wallis test for equality of medians among groups: p=0.03; * Mann-Whitney U test comparing denervations into BR muscle to nerve reconstructions and other denervations: p=0.04*

Table 7. Predictive value of diagnostic block

Block effect	N	Median post-operative NRS pain score (range)	% satisfaction
Good	24	4.3 (0.0 - 10)	46%
Poor	4	7.3 (6.0 - 8.0)	0%

Block effect: Good ≥ 3.5; Poor < 3.5 points decrease in NRS pain score;
Mann-Whitney U test for difference in post-operative pain score: p<0.25

Patient characteristics and primary outcomes were not significantly different between the groups with and without available nerve block outcomes. The median NRS pain score decrease was lower in patients with a poor diagnostic nerve block effect (table 7, p=0.11), and zero patients were satisfied with treatment results in this group. When considered continuous data, the difference was highly significant (t-test, p=0.005).

Discussion

This study was conducted to evaluate patient satisfaction following different surgical treatment methods for SBRN neuralgia caused by lesions or adhesions of directly traumatized superficial branches of the radial nerve (SBRN), including neurolysis, nerve reconstruction, denervation and adjacent nerve neurectomies. Different relocations of the SBRN end were compared and the prognostic value of a pre-operative diagnostic nerve block and patient specific determinants was explored

There have been previous studies evaluating the surgical treatment of SBRN neuralgia. However most of these studies comprised small patient numbers.[5,6,26,27] or did not compare surgical techniques.[18,16] None of these studies showed any statistical evidence for the superiority of one surgical technique for the SBRN over another.

This study was performed in a relatively homogeneous population, since all patients were involved in neuropathic pain caused by the SBRN, in the dorsoradial hand or wrist. There are some limitations to this study that should be discussed. The study design was a retrospective cohort study, which might induce the risk of information bias. We determined primary and secondary outcomes prior to our study, and since follow up data were available for all patients, information bias for patient satisfaction was limited. Unfortunately, pre- and post-operative NRS pain scores, as well as pain scores following diagnostic nerve blockade, were not available for all patients. Patient characteristics and primary outcomes were evenly distributed among patients with and without missing data.

Our study population existed of patients referred to a university medical center

for expertise in the field of neuropathic pain treatment, and there were a considerable number of patients with substantial treatment delays before referral to the study location. This might be reflected in the severe and therapy resistant nature of our patients' complaints and therefore negatively influence outcome compared to other medical centers and neuropathic pain disorders.

Most patients underwent multiple surgical procedures in the same extremity. It is statistically incorrect to analyze all procedures as independent measurements, since this leads to an underestimation of variability and inflates sample size.[28] This is why we separately calculated satisfaction rates for all types of surgical procedures, analyzing only one procedure per patient.

For neuropathic pain caused by perineural adhesions, external neurolysis provides a good primary surgical treatment option, not causing any area of skin anesthesia. Satisfaction rates of this procedure vary among literature.[5,6] In our study population, 12 out of 32 patients treated by external neurolysis were satisfied with surgical results.

The apparent susceptibility of the SBRN to form painful neuromas has been well documented,[7] and achieving satisfactory pain relief is difficult.[16] Treatment failure can be caused by incorrect relocation of the SBRN into an insufficiently protective environment from mechanical trauma, or into a muscle with large excursion, inducing repetitive tension on the nerve. We found that none of the patients with relocation of the nerve into the small muscles of the forearm, the interosseous space or silicone sheaths were satisfied. Nerve reconstruction was ineffective in relieving pain as well. Relocation of the nerve end into the distal radius was effective in two out of six patients, and might provide a reasonable treatment option.

Relocation of the nerve end into the BR muscle was significantly more successful in achieving satisfactory pain relief than relocation elsewhere. The BR muscle has little excursion and, therefore, contraction does not induce substantial traction or pressure on the nerve. Furthermore, the relatively large muscle belly protects the nerve end from mechanical trauma. Our results are supported by the sparse literature available.[6,16]

Remaining or recurrent pain after surgical treatment can also be explained by secondary displacement of the translocated neuroma, failure to identify the presence of more than one neuroma in the same patient,[8] or injury of neighboring nerve branches. Mackinnon and Dellon[16] found concomitant injury to the LABCN in 75% of patients with persistent dorsoradial wrist pain related to a neuroma of the SBRN. After complete neurectomy of the SBRN, adjacent nerves may start to transmit sensory signals from the denervated skin area.[29] This process is desirable for normal sensory recovery, but can lead to recurrent or sustained pain in surgically treated SBRN neuroma patients. Lluch and Beasley[15] reported unsatisfactory results due to an overlapping

pattern of the PIN with the SBRN. PIN neurectomy was effective in resolving dysesthesia without any functional impairment or complications.[8] In our study population, relatively high satisfaction rates for LABCN and PIN neurectomies were found. In case of persistent pain, alternative denervations were incidentally performed of the PBMN, the AIN and the radial digital nerve of the thumb.

There is increasing evidence that hyperalgesia is independent of input from injured afferents, suggesting that ectopic activity originating from a neuroma is not necessary for development of hyperalgesia.[11-13] Stokvis et al.[14] were the first to report this effect in humans. Patients surgically treated for a painful neuroma in the upper extremity showed a significant decrease in spontaneous pain after follow up. However, the intense symptoms of cold intolerance, also called thermal hyperalgesia, remained unchanged.

Li et al.[13] have proposed that interactions between intact and injured nerve fibers undergoing Wallerian degeneration may lead to changes in the intact fibers that play a critical role for both initiation and maintenance of mechanical hyperalgesia. However, Dorsi et al.[11] observed reinnervation of denervated skin following peripheral nerve injury using the tibial neuroma transposition (TNT) rat-model and did not find Wallerian degeneration in the distal nerve stump, indicating that repopulation of the distal nerve stump was not due to invasion by axons arising from the tibial nerve but rather to recruitment of axons from adjacent nerves from other nerves regenerated through the distal stump of the tibial nerve. These findings provide an explanation for the beneficial effect of adjacent nerve neurectomies performed in our study.

Misdiagnosis, or failure to identify the presence of distal reinnervation and central sensitization processes, may be avoided by the use of a local diagnostic nerve block to accurately identify and anesthetize the sensory nerves involved.[8,16,22] Although presented to be an effective diagnostic tool,[16,30] its ability to predict surgical outcome has, to our knowledge, never been reported before.

In our study, we found a lower median NRS pain score decrease in the group with an ineffective pre-operative nerve block (Mann-Whitney U test, $p=0.11$). At the outpatient clinic, patients were asked to rate their pain as any number between zero and ten. When viewed as continuous data, the group with an ineffective nerve block showed a highly significantly worse outcome compared to patients with an effective block (t-test, $p<0.01$), indicating that patients with no or little effect of diagnostic block, should not undergo surgical neuroma treatment. In these patients, attention should rather be focused at desensitization, cortical re-organization techniques, and pain management.[31,32] Another important conclusion we can draw from our results, is that high pain reduction after blockade is no absolute guarantee for good outcome after surgery, since still 54% of patients with a successful block were unsatisfied following surgical treatment. The use of a continuous Visual Analogue Scale should be

considered in future studies measuring pain relief.

Compared to patients treated without delay, we found a significantly higher number of operations required for sufficient pain relief, in patients treated with duration of pain of at least 12 months prior to their primary surgical procedure. These results might be explained by alterations at the level of the spinal cord and the somatosensory cortex in the processing of non-painful stimuli.[4,33] These changes start to develop within hours after the initial nerve injury, and may persist for years or decades.[34,35]

Adequate surgical treatment of peripheral neuropathic pain is challenging. We demonstrated the problems of achieving satisfactory pain relief in a population of patients surgically treated for neuropathic pain of the SBRN. However, these results can be used as an example for treatment strategies for neuropathic pain caused by various peripheral nerves. Treatment strategies should take into account the duration of symptoms, the possibility of sensory overlap between neighboring nerves, the effect of a diagnostic nerve block, and finally, the choice of an appropriate surgical technique with respect to local tissue and mechanical characteristics.

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Chapter 6

Determinants of patient satisfaction

Determinants of patient satisfaction after neuropathic pain treatment. Stokvis A, Van der Avoort DJJC, Van Neck JW, Coert JH. Submitted to The European Journal of Pain.

Abstract

To accurately study treatment methods for neuropathic pain, the use of appropriate outcome measures is essential. Core outcome domains for chronic pain research have been proposed in literature. The purpose of this study was to find the determinants that are most important for patient satisfaction after surgical treatment for neuropathic pain, caused by peripheral nerve injury.

Thirty-four patients surgically treated for upper extremity neuroma pain were prospectively followed. They returned validated questionnaires on the core outcome domains of chronic pain pre- and postoperatively, including the Visual Analogue Scale (VAS), McGill Pain Questionnaire (MPQ), Disability of the Arm, Shoulder and Hand (DASH), Short Form-36 (SF-36), Symptom CheckList-90 (SCL-90), Tampa Scale of Kinesiophobia (TSK) and the Cold Intolerance Severity Scale (CISS). Cut-off values for meaningful change were calculated using the reliable change index (RCI) and the clinical significant change (CSC) cut-off value. We compared satisfied and unsatisfied patient groups for all outcome domains.

The most important outcome domains were found to be 'pain', 'physical functioning' and 'other symptoms'; 'Emotional functioning' was not related to satisfactory outcome. The VAS for pain was most important for patient satisfaction, and a decrease of at least 30 mm or a score below 20 mm on the VAS were found to represent relevant changes in pain. The amount of pain indicated as bearable by patients, did not change after treatment. The VAS is easy-to-use in clinical practice, readily interpretable and should be considered as a primary outcome measure for future studies of neuropathic pain treatment.

Introduction

The importance of chronic pain in our society has become increasingly acknowledged over the last decade.[1] Peripheral neuropathic pain is a particularly distressing and often underestimated chronic pain problem, due to its intensity and little improvement over time.[2] Although etiologic theories have developed in recent years, truly effective treatment strategies are lacking, and patient satisfaction remains unacceptably low.[3]

Patients that have developed a painful neuroma in the upper extremity following peripheral nerve injury are an example of a chronic neuropathic pain group that suffers from severe physical, emotional, and social problems. Their pain is often accompanied by hyperalgesia, allodynia and cold intolerance.[4,5] These are often relatively young, otherwise healthy patients that can become severely disabled due to their pain problem, resulting in great loss in functionality and high unemployment rates with important economical consequences.[6-8] Hand function is considered one of the most important bodily functions,[9] it is vital for performing various work activities. Furthermore, painful neuromas in the hand are less protected from mechanical trauma compared to other locations, further deteriorating disability. Painful neuromas can be treated surgically, but unfortunately, many patients are not satisfied with treatment, and the cause of their remaining complaints is often unknown.

To accurately study treatment methods for neuropathic pain, the use of appropriate outcome measures is essential.[3] Most studies performed in the area of chronic pain focus on only one aspect of treatment outcome.[10] They overlook the broad scale of physical, emotional, and social problems that can occur in chronic neuropathic pain patients.[2] However, there is a growing demand to investigate the relationship between patient satisfaction and relevant clinical outcomes.[11,12] The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) proposed 6 core outcome domains that should be considered in chronic pain research,[13] and should be assessed using validated questionnaires with known psychometric aspects.

Global patient satisfaction ratings with treatment results can be used to investigate the clinical importance of changes in these outcome domains (Dworkin et al., 2005).[14] The development of patient-centred success criteria involves two main steps. Researchers must first indentify which outcome domains are most important to the particular patient population, and then establish how much change is required to achieve an acceptable outcome.[11,15] Since patients may 'recalibrate' their criteria for success after exposure to treatment, this should be assessed as well.[11]

This study was performed to find out which factors are most important for patient satisfaction after surgical treatment for peripheral neuropathic pain. Understanding the relationship between these outcome domains and patient satisfaction may result in more effective evaluation of therapeutic methods.

Methods

Study design

Between January 2006 and August 2009 we conducted a prospective cohort study in a University Medical Centre located in the Netherlands. Participants were sent validated questionnaires on the core outcome domains of chronic pain prior to surgery and after follow up.

Patients

Inclusion criteria were: surgical treatment for neuropathic pain of the upper extremity, caused by an injury-related neuroma. A painful neuroma can be formed after damage to peripheral nerve, with subsequent sprouting of axons into surrounding scar tissue.[16] Patients with a different cause of neuropathic pain, i.e. nerve adhesions or entrapments, were excluded, as well as patients who did not undergo surgery and patients who were unable to accurately fill out and return both questionnaires.

Surgical treatment consisted of excision of the neuroma, if possible followed by nerve repair using nerve grafts or neurotubes when necessary. If the distal nerve end was not available for repair, the proximal nerve stump was relocated away from the site of injury and buried into muscle or bone.[5]

Scoring methods

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommended 6 core outcome domains that should be considered in chronic pain research.[13] These 6 core outcome domains are (I) pain; (II) physical functioning; (III) emotional functioning; (IV) participant ratings of improvement and satisfaction with treatment; (V) other symptoms and adverse events during treatment; and (VI) patients disposition and characteristics data. These core domains were assessed using questionnaires and specific questions discussed below (table 1). All questionnaires are commonly used in pain research and were previously validated.

Patient Satisfaction

Patients were requested to rate their satisfaction as satisfied or unsatisfied. This data was used to investigate participants' judgments of the clinical importance of changes in other outcome measures, by comparing improvement in core outcome domains between satisfied and unsatisfied patients.

Table 1: Core outcome domains, defined by The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)

IMMPACT Outcome Domain	Question(naire)s
(I) Pain	Visual Analogue Scale McGill Pain Questionnaire
(II) Physical functioning	Disability of the Arm, Shoulder and Hand Short Form-36 Physical score
(III) Emotional functioning	Short Form-36 Mental score Symptom CheckList-90
(IV) Improvement and satisfaction with treatment	Patient satisfaction
(V) Other symptoms or adverse events	Tampa Scale of Kinesiophobia Cold Intolerance Severity Scale Treatment complications
(VI) Patient characteristics and disposition	Sex, age, duration of pain, dominant side affected, socio-economic status

Visual Analogue Scale

The visual analogue scale (VAS) for pain consists of an unmarked horizontal line of 100 mm, anchored with the words 'no pain at all' on the left side and 'unbearable pain' on the right. The patient has to place an x on the line representing the amount of pain felt. The VAS score ranges from 0 to 100. Although the VAS score represents data that lay between ordinal and interval (continuous) values, it is most appropriately analyzed using parametric techniques.[17] We applied a quadruple VAS, regarding current pain intensity (at this moment), pain intensity during the past week, minimal/maximal and bearable pain. These measures were used to compare patients' pain experience and cut off scores for bearable pain before and after treatment.[15] Current VAS pain intensity data was used for satisfaction analyses.

Disabilities of the Arm, Shoulder and Hand

The disabilities of the arm, shoulder and hand (DASH) questionnaire is a measure of self-rated upper extremity disability and symptoms. It is the most widely used upper extremity-specific health-status measure.[18] The DASH consists of a 30-item disability scale, scored 0 (no disability) to 100 (most severe disability). In addition, two optional modules on work and sport activities can be filled out, leading to separate scores. The Dutch version of the DASH has been validated by Veehof et al.[19].

McGill Pain Questionnaire

The McGill Pain Questionnaire (MPQ) was developed by Melzack et al.[20] and has

been described as the leading instrument to describe the diverse dimensions of pain.[21] The MPQ-Dutch language version (MPQ-DLV) was composed and validated by Van der Kloot et al.[22]. It consists of 78 pain descriptors classified into 20 categories of pain that can be scored to assess 3 major psychological dimensions of pain: sensory (PRI-s), affective (PRI-a) and evaluative (PRI-e) pain, as well as a total pain severity score (PRI-T) and the total number of words selected within each pain dimension (NWC).

Short Form-36

The short form-36 (SF-36) health survey developed by Ware and Sherbourne[23] is the most commonly used measure of health related quality of life.[14] It consists of 36 items that assess 8 health dimensions: limitations in physical activities because of health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities because of physical health problems; bodily pain; general mental health; limitations in usual role activities because of emotional problems; vitality and general health perceptions. The scores range between 0 (worst) and 100 (best) for each dimension. Two summary scores can be calculated from these dimensions: the physical and mental health components (PCS and MCS). Translation and validation of the Dutch language version of the SF-36 has been performed by Aaronson et al.[24]. They provided normative data to standardize each scale to the mean and standard deviation of the general Dutch population.

Symptom Checklist-90

The symptom checklist-90 (SCL-90) is used to measure self-reported symptoms of psychopathology.[25] It consists of 90 symptoms that are scored from 1 (never) to 5 (very often). The Dutch version of the Symptom Checklist-90 was validated by Arrindell and Ettema[26], and includes scores eight subscales, namely "Anxiety", "Agoraphobia", "Depression", "Somatic complaints", "Suspicion and interpersonal sensitivity", "Insufficient thinking and behaviour", "Sleeping problems" and "Anger-hostility". The SCL-90 total score for "psychoneuroticism" ranges between 90 and 450.

Tampa Scale of Kinesiophobia

The Tampa Scale of Kinesiophobia (TSK) assesses the participants' fear of (re)injury by physical movement or activity. 17 items are rated on a 4-point scale from "strongly disagree" to "strongly agree", higher scores indicating stronger fear of (re)injury. The TSK has shown to be a reliable assessment tool for chronic pain and recent studies have supported a two-factor solution with subscales for activity avoidance (AA) and somatic focus (SF).[27] A shortened version of the TSK, the 13 items without the reversed key items, was shown to be preferred over the original 17-item TSK by

Goubert et al.[28]. In our analysis, we used the 13 item TSK, providing a total score, as well as the AA and SF subscales.

Cold Intolerance Severity Score

The severity of posttraumatic cold intolerance was measured using the self-administered Blond McIndoe cold intolerance severity score (CISS) questionnaire, which has been validated in both a peripheral nerve injury group and a normative control group.[29,30] The CISS questionnaire consists of 6 questions relating to the frequency, duration, severity, and impact of cold intolerance symptoms on activities of daily life. The CISS questionnaire has a minimum score of 4 and a maximum score of 100.

Complications

Medical records were reviewed for any treatment reported complications, including post-operative pain, wound infection and haemorrhage.

Patient characteristics and disposition

The pre-operative questionnaire contained questions concerning patient specific factors such as age, gender, length, weight, dominant arm affected, education and income. Duration of pain was defined as time between the development of neuroma pain and surgery. Patients' socio-economic status was categorized into 3 groups, according to level of education and income.

Statistical methods

Patients were analyzed in two groups: satisfied and unsatisfied. Mean pain domain scores and pre- to post-operative change was compared between these groups. For all variables, a Kolmogorov-Smirnov (K-S) goodness-of-fit test for normal distribution was performed.

For all measures, cut-off values for meaningful change were determined using the reliable change index (RCI) and the clinical significant change (CSC) cut-off value, as described by Jacobson et al.[31]. The RCI is used to determine the minimal change necessary to identify true change between two measurements in a patient, which is not due to chance or the unreliability of the measurement. RCI values follow the normal distribution and a value of >1.96 is considered a reliable change. The RCI can be calculated using the reliability of a test (Cronbach's alpha or the test-retest reliability coefficient) and the standard deviation (SD) of the measure obtained from the clinical population.[25]

Aside from statistical reliable change, clinically significant change is important for clinical practice. The CSC provides a cut-off value for clinically meaningful

change. This cut-off point can be calculated using three different criteria proposed by Jacobson et al.[31] depending on the availability of normative data for the measure under study. Criterion (a) only requires the data obtained from the clinical population. CSC is defined as a value that falls outside the 2 SD range of the clinical population, in this case the pre-operative score. Criterion (b) defines CSC as a post-operative value that falls inside the 2 SD range of the normative population. Criterion (c) uses both the clinical and the normative data to establish a cut point that lies between the means of these populations. CSC is reached when the statistical probability of falling in the normative population is higher than falling in the clinical population. When normative data is available, and the two distributions overlap, criterion (c) is preferred over (b).[31] Reliability and normative data for all measures were obtained from published reports.

We combined the RCI-values and CSC cut points to identify patients who underwent a statistically reliable and clinically meaningful change in outcome measure. For all measures, the proportion of patients with a reliable and/or clinical significant change was calculated and compared among satisfaction groups using Fisher's exact test.

To assess whether patients recalibrate their criteria for success after exposure to treatment, we compared the bearable VAS scores as indicated by patients before and after treatment.

Furthermore, we compared the mean scores for continuous measures between satisfied and unsatisfied patients, using an independent t-test. All tests were two sided and a p-value of less than 0.05 was considered statistically significant. To correct for multiplicity of endpoints, the Bonferroni correction was also provided, defining a statistically significant difference as a p-value of less than α/K, where K is the number of endpoints tested. For this study the Bonferroni correction was 0.05 (α) divided by 16 secondary endpoints, resulting in a significant p-value of <0.0031, or <0.05 with $p+0.0469$. All data analyses were performed using Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA), version 16.0.

Results

45 patients were sent a questionnaire pre-operatively. Two patients did not want to cooperate. In 7 cases, no neuroma was found during surgery and only external neurolysis was performed. These patients were excluded from our study. One patient did not undergo surgery after all. Averagely 23 months (range 3 to 37) after surgical treatment, final follow up questionnaires were sent to 35 patients. The 34 patients surgically treated for a painful neuroma of the upper extremity who returned the

follow up questionnaire were included in our analyses. Patient characteristics are presented in table 2. The study population consisted of 18 males and 16 females, with an average age of 43. The average duration of pain was 44 months. In 25 out of 34 cases, the dominant hand was affected.

Table 2. Baseline characteristics (N=34)

Characteristic	
Age in years,: mean (SD)	42.8 (13.7)
Sex: male - female	18 - 16
Dominant arm affected	25
Duration of pain in months, mean (SD)	44.0 (40.1)
Social economic class:	
1 high	12
2 middle	18
3 low	4

For all measures, the K-S test p-values were above 0.05, indicating a normal distribution for all measures. Cronbach's alpha could be obtained from literature for all measures accept the VAS and CISS scores. For these measures, a test-retest reliability coefficient was used to calculate the value that equals RCI>1.96, the RCI-value. Normative data was available for the SF-36, SCL-90, DASH and CISS scores. For these measures, the CSC cut-off point could be calculated using Jacobson's criterion (c). For the MPQ, Tampa and VAS scores, no normative data was available and criterion (a) was used. The CSC cut-off points for all subscales of the MPQ were below zero, therefore these could not be used. All clinical and normative population means, reliability measures, RCI-values, CSC cut off scores and Jacobson's criteria used, are displayed in table 3.

The mean scores for most outcome domains differed significantly between the satisfied and unsatisfied patient groups (table 4). The outcome measures that were most significantly different between satisfaction groups were the VAS for pain, the MPQ_PRI-e and the CISS ($p<0.001$). The measures for the outcome domain 'pain' were highly significantly correlated with each other (VAS and PRI-e, $r=0.76$, $p<0.001$). Other measures that were significantly different between the satisfied and unsatisfied patient groups were the DASH and PRI-T scores ($p=0.001$), followed by the SF-36 PCS ($p=0.002$), the MPQ_PRI-s ($p=0.005$) and NWC ($p=0.004$) subscales, the DASH work score ($p=0.005$) and the TSK ($p=0.006$), including its AA ($p=0.017$) and SF ($p=0.01$) subscales. Most of the 8 health dimensions of the SF-36 were sig-

Table 3. Reliable and clinical significant change data

	Clinical population pre-operative score (SD)	Normative population score (SD)	Reliability coefficient	RCI-value	CSC cut point	Jacobson's criterion
VAS	66.2 (23.2)	NA	0.80	28.7	≤19.8	a
MPQ DLV						a
PRI-s	12.1 (7.1)	NA	0.61	12.3	Cut-off	
PRI-a	3.2 (3.4)		0.66	5.5	scores	
PRI-e	6.7 (2.8)		0.65	4.6	below zero	
PRIT	21.9 (12.0)		0.80	14.9		
NWC	11.3 (5.4)		0.82	6.4		
DASH	48.7 (21.3)	10.1 (14.7)	0.96	11.8	≤25.9	c
Sport	74.3 (32.2)	9.8 (22.7)		17.9	≤36.5	
Work	52.2 (30.7)	8.8 (18.4)		17.0	≤25.1	
SF-36						c
PCS	38.9 (6.6)	50 (10)	0.84	7.3	≥43.3	
MCS	60.0 (6.4)	50 (10)	0.84	7.1	≥56.1	
SCL-90						c
PSNEUR	121.9 (33.1)	118.3 (32.4)	0.97	15.9	≤120.1	
TSK	30.2 (7.8)	NA	0.80	9.7	≤14.6	a
AA	19.1 (5.8)		0.73	8.4	≤7.5	
SF	11.1 (3.2)		0.70	4.9	≤4.7	
CISS	53.0 (19.3)	12.9 (8.2)	0.90	16.9	≤24.8	c

Reliability coefficients and normative population scores taken from literature. Crohnbach's alpha was used for all questionnaires except the VAS and CISS scores. For the VAS and CISS scores the test-retest correlation coefficient was used.

RCI-value: Reliable Change Index value: change in pre- post-treatment score that equals RCI>1.96; CSC: Clinical Significant Change; Jacobson's criterion a: CSC outside the 2 SD range of the clinical population, b: CSC within 2 SD range of the normative population, c: CSC with higher statistical probability of falling into the normative population than the clinical population.

VAS: Visual Analogue Scale (pain, range 0-10)[35]; MPQ: McGill Pain Questionnaire (psychological dimensions of pain)[22], PRIT: Pain rating Intensity Total (range 0-63), NWC: Number of Words Chosen (range 0-20), PRI-s: Pain Rating Intensity sensory (range 0-36), PRI-a: Pain rating Intensity affective (range 0-15), PRI-e: Pain rating Intensity evaluative (range 0-12); DASH: Disability of the Arm, Shoulder and Hand (range 0-100)[19]; SF-36: Short Form 36 (quality of life)[24], PCS: Physical Component Summary score (range 0-100), MCS: Mental Component Summary score (range 0-100); SCL-90: Symptom Checklist 90 (symptoms of psychopathology)[26], PSNEUR: Psychoneuroticism score (range 90-450); TSK: Tampa Scale of Kinesiophobia (fear of re-injury)[28], AA: Activity Avoidance (range 8-32), SF: somatic focus (range 5-20); CISS: Cold Intolerance Severity Scale (range 4-100)[29,30].

Table 4. Outcomes compared among satisfaction groups

	Post-operative score (SD)		No. of patients with CSC / total		No. of patients with RC / total		No. of patients with RC & CSC / total	
	Satisfied	*Unsatisfied*	*Satisfied*	*Unsatisfied*	*Satisfied*	*Unsatisfied*	*Satisfied*	*Unsatisfied*
VAS	27.4 (23.7)	71.4 (23.6)[c]	9/19	1/15[a]	10/19	1/15[b]	7/19	0/15[a]
MPQ_DLV								
PRI-s	7.0 (5.8)	13.7 (7.0)[b]			2/18	0/14		
PRI-a	1.6 (2.5)	4.0 (4.5)			2/18	0/14		
PRI-e	3.6 (2.8)	7.9 (1.7)[c]	NA	NA	8/18	0/14[b]	NA	NA
PRIT	12.2 (10.4)	25.6 (11.5)[c]			7/18	0/14[a]		
NWC	7.6 (5.1)	13.1 (4.8)[b]			6/18	1/14		
DASH	29.7 (19.7)	55.8 (21.1)[c]	8/19	2/15	12/19	2/13[a]	6/19	0/13
Sport	37.5 (33.4)	85.4 (13.0)	3/5	0/3	2/4	0/2	6/9	2/4
work	57.6 (31.4)	24.6 (21.3)[b]	7/16	3/9	11/13	2/7[a]	0/8	0/5
SF-36								
PCS	44.4 (6.9)	36.2 (7.2)[c]	9/19	2/15	7/19	0/15[a]	6/19	0/15[a]
MCS	57.4 (6.2)	59.7 (8.4)	13/19	11/15	1/19	1/15	1/19	1/15
SCL-90								
PSNEUR	127.0 (48.4)	135.5 (48.3)	11/19	5/14	4/17	1/13	3/17	0/13
TSK	23.2 (6.9)	31.5 (9.6)[b]	2/19	0/15	6/18	0/15[a]	1/18	0/15
AA	14.7 (4.3)	20.0 (6.9)[a]	0/19	0/15	5/18	0/15[a]	0/18	0/15
SF	8.5 (3.1)	11.5 (3.3)[a]	0/19	0/15	5/18	1/15	0/18	0/15
CISS	36.7 (23.4)	70.5 (26.9)[c]	6/19	1/15	9/19	0/13[b]	5/19	0/13

CSC: clinical significant change; RC: reliable change; [a] Significant difference between satisfied and unsatisfied group with $p<0.05$; [b] Significant difference $p<0.01$; [c] Significant difference $p<0.0031$ ($p<0.05$ with Bonferroni correction of +0.0469).

nificantly different, the greatest difference was found in the 'bodily pain' dimension ($p<0.001$). Dimensions that were no different between both satisfaction groups were 'mental health', 'vitality' and 'general health perception'. For the SCL-90 and all its subscales no significant differences could be found. Other outcome measures that were not significantly different were the SF-36 MCS, the DASH sport score and the MPQ_PRI-a.

We calculated the proportion of patients with a reliable and/or clinically meaningful change in score after surgical treatment, and compared these proportions between the satisfied and unsatisfied patient group (table 4). The proportion of patients that reached a RCI of >1.96 was also different between both groups for most measures under study. The proportion of patients with a reliable change in MPQ_PRI-e score was 8 out of 18 in the satisfied group, compared to 0 out of 14 patients in the unsatisfied group ($p=0.004$). Other significant differences between the satisfaction groups were found for the VAS score for pain ($p=0.008$), the SF-36 PCS ($p=0.011$), the total DASH ($p=0.012$) and DASH work score ($p=0.022$), the MPQ_PRI-T ($p=0.01$), the total Tampa ($p=0.021$) and AA subscale ($p=0.049$), and the CISS score ($p=0.004$).

Patients with a clinically meaningful change were less common. This is represented in the small differences between the satisfied and unsatisfied patient groups. The only significant difference in number of clinically changed patients was found for the VAS score for pain: 9 out of 19 patients reached the CSC-cut point in the satisfied group, compared to 1 out of 15 patients in the unsatisfied group ($p=0.02$). When we compared the proportion of patients with a reliable and clinical significant change among satisfaction groups, we again found that only the VAS score for pain differed significantly (7/19 vs. 0/15, $p=0.011$).

Bearable pain, as indicated by patients on a VAS pre-operatively, did not change after surgery. The mean bearable VAS score was 40 (SD 28) before and 41 (SD 25) after surgery. Patients self-reported current VAS score was lower or equal to the self-reported bearable VAS score in 14 out of 19 satisfied patients, compared to 3 out of 15 unsatisfied patients ($p=0.005$).

For only one patient a complication was reported, this patient developed complex regional pain syndrome after surgical treatment.

Finally, we analyzed the differences in patient characteristics between satisfaction groups (table 5). The duration of pain in the unsatisfied group was approximately twice as long compared to the satisfied group (60.5 vs. 30.9 months, $p=0.05$). Age, sex, duration of pain, dominant arm affected and social-economic status were not related to a satisfactory outcome.

Table 5. Patient characteristics and satisfaction

Characteristic	Satisfied	Unsatisfied	p-value
Age: mean (SD)	42.8 (12.0)	42.8 (16.0)	0.99
Sex: male - female	11/18 - 8/16	7/18 - 8/16	0.73
Dominant arm affected	15/19	10/15	0.46
Duration of pain in months: mean (SD)	30.9 (22.7)	60.5 (51.1)	0.05
Social economic class:			
1 high	8	4	
2 middle	9	9	
3 low	2	2	0.65

Discussion and conclusions

This study was performed to determine which factors are most important for patient satisfaction following surgical treatment for upper extremity neuropathic pain. We compared post-operative scores between satisfied and unsatisfied patient groups for all important outcome domains for chronic pain. Furthermore, we compared the proportions of patients reliably and clinically significantly changed among these groups, using the method described by Jacobson et al.[31]. Absolute scores, as well as the proportion of patients with a statistically reliable improvement were significantly different between satisfied and unsatisfied patients in the core outcome domains 'pain', 'physical functioning' and 'other symptoms', but not in 'emotional functioning'. The proportion of patients with clinically significant improvement was significantly higher in the satisfied group only for VAS-score for pain; the other measures did not differ significantly. The amount of pain classified as bearable by patients, did not change after treatment.

Patient satisfaction can be influenced by many factors of which we measured the most important according to the IMMPACT recommendations.[13] However, there are some limitations to this study that we will now discuss. Hirsh et al.[12] showed a significant influence of patients' expectations and their satisfaction with care on overall patient satisfaction, however, these issues were not assessed in this study. Furthermore, we did not use a specific neuropathic pain measurement tool, like the Neuropathic Pain Questionnaire,[32] neither were patients' coping strategies assessed.

In contrast to the number of measures with a statistically reliable change, only one measure reached a clinically significant change following treatment: the VAS score. This could reflect an actual phenomenon or could indicate the use of criteria that are too stringent to calculate a CSC cut-off score.

The likelihood of obtaining statistically significant results by chance increases

with the number of analyses performed, however, the problem of multiplicity is reduced when the outcome measures are positively correlated.[33] We provided the Bonferroni correction to correct for multiplicity of secondary endpoints. The difference between satisfied and unsatisfied patient groups in achieving a reliable and clinically significant change did not reach significance following the Bonferroni correction of p+0.0469 for any measure.

There are some important strengths to this study. It was performed with a prospective follow-up design, thereby minimizing the risk of information bias. The response rate was very high, reducing possible selection bias. Patients with an injury-related neuroma of the upper extremity provide a homogeneous study population. This is preferred to studies that combine patient groups with differences in aetiology, symptoms and treatment,[2,10,34] which might result in biased conclusions.[3] Another advantage of this study population is that these are relatively young and otherwise healthy patients. Other studies focusing on chronic neuropathic pain often involve diabetes; this affliction often occurs at a higher age and is associated with much co-morbidity, which can obscure primary outcomes. Another often studied neuropathic pain disorder is post-herpetic neuropathy. Compared to this patient group, our study population is likely to be more severely affected by disability, because of the intense pain located in the upper extremity. To date, the treatment of diabetic and post-herpetic neuropathic pain focuses mainly on symptom alleviation, since curative treatments are not yet available. Furthermore, those treatment schemes are subject to non compliance. In our patient population, surgical treatment was performed in all patients, with a curative intention. All patients underwent approximately the same surgical procedure, so results were less affected by differences in treatment.

There has been increasing demand to investigate the relationship between patient satisfaction and symptom relief.[12] We provided new insights in the experience of chronic pain by determining the factors most important for satisfaction, in peripheral neuropathic pain patients. Only previously validated questionnaires, with sufficiently high reliability coefficients were used.

In a study defining success criteria for the treatment of chronic spine pain by Brown et al.[11], patients adjusted their criteria for success over time by becoming less stringent. In our study population, bearable pain reported by patients was similar before and after treatment (40/100 vs. 41/100). The different results might be explained by the fact that in the study by Brown et al. there was 21% loss to follow up, and those patients had significantly more stringent success criteria before treatment ($p<0.05$). Furthermore, the test-retest reliability of the Patient-Centred Outcomes Questionnaire they used to determine success criteria, was questionable (r=0.43-0.58). We used the VAS for pain with good test-retest reliability (r=0.80)[35] and there was only one patient lost to follow up, who was excluded from analysis.

The outcome domain 'pain intensity' was found to be most important for a satisfactory outcome. This is not surprising, since these were patients treated for chronic neuropathic pain. The VAS score and PRI-e were the measures most significantly important for patient satisfaction.

Clear and easy-to-use cut-off values were found for the VAS score for pain. When rounded off, a decrease of at least 30 mm or a score below 20 mm on the 100 mm scale were found to represent relevant changes in pain. These cut-off values are similar to values found in previous literature concerning the VAS. Although the MPQ-DLV is somewhat more time consuming to administer, the MPQ_PRI-e subscale regarding the overall intensity of the pain experience is composed of only 3 questions.[22]

Since both measures were significantly correlated with each other ($p<0.001$), it would be sufficient to use only one of both when assessing the outcome after peripheral neuropathic pain treatment. For everyday clinical practice, it is important to use outcome measures that are easy to use and are reliable.[36] The VAS meets both these criteria, and no other pain scale consistently demonstrates greater responsiveness in detecting improvements associated with pain treatment.[14]

From our results it seems that 'emotional functioning' does not play an important role in patients' self-reported satisfaction. The mean quality of life mental component score (SF-36 MCS) was high compared to the normative population, indicating a good mental health. Schmitz and Kruse[37] demonstrated that a co-morbid somatic condition may affect the performance of the scores; physical impairment may increase the SF-36 MCS because of a negative weighting, possibly explain the relatively high mean MCS score in our population. Self-reported symptoms of psychopathology, measured with the SCL-90 were also below average, indicating a good mental health. All subscales were similar among satisfaction groups. These findings are in contrast with the available pain literature stating that chronic pain is often accompanied by symptoms of psychological distress and psychiatric disorders, including depression, anxiety, anger and sleep disturbances.[3,14] This difference could results the actual mental state of peripheral neuropathic pain patients, however, it might also be due to patients in our study population emphasizing the physical aspects of their pain problem, and underreporting their emotional stress.

The other outcome domains, 'physical functioning' (DASH, SF-36 PCS), 'other symptoms and adverse events during treatment' (TSK, CISS) and 'patients disposition and characteristics' (duration of pain) were important for patient satisfaction, but to a lesser extent than 'pain intensity'. Therefore, the necessity to evaluate these domains in all patients treated for neuropathic pain is questionable.

In conclusion: In patients treated for chronic neuropathic pain of the upper extremity caused by peripheral nerve injury, the most important outcome domains were found to be 'pain', 'physical functioning' and 'other symptoms'. Emotional func-

tioning was not related to satisfactory outcome. The most important measure for patient satisfaction was the VAS score for pain. This measure is easy-to-use in clinical practice, readily interpretable and should be considered as a primary outcome measure for future studies of neuropathic pain treatment.

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Chapter 7:

Surgical treatment of neuroma pain

Surgical management of neuroma pain: a prospective follow-up study. Stokvis A, Van der Avoort DJJC, Van Nek JW, Hovius SER, Coert JH. Under revision for Pain.

Abstract

Painful neuromas can cause severe loss of function and have great impact on the daily life of patients. Surgical management remains challenging; despite improving techniques, success rates are low. To accurately study the success of surgical neuroma treatment and factors predictive of outcome, a prospective follow-up study was performed.

Between 2006 and 2009, pre- and post-operative questionnaires regarding pain (VAS, McGill), function (DASH), quality of life (SF-36), symptoms of psychopathology (SCL-90), epidemiologic determinants and other outcome factors were sent to patients surgically treated for upper extremity neuroma pain. Pain scores after diagnostic nerve blocks were documented at the outpatient clinic before surgery.

34 patients were included, with an average follow up time of 25 months. The mean VAS score decreased from 6.8 to 4.9 after surgery ($p<0.01$), 19 (56%) of patients were satisfied with surgical results. Upper extremity function improved significantly ($p=0.001$). Neuroma patients had a significantly lower quality of life compared to a normal population. Employment status was predictive of the outcome ($p<0.05$). VAS scores after diagnostic nerve block were predictive of post-operative VAS scores ($p=0.05$). Furthermore, smoking was significantly related to worse outcome (RR 2.06, $p<0.05$).

These results could lead to improved patient selection and treatment strategies. If a diagnostic nerve block is ineffective in relieving pain, patients will most likely not benefit from surgical treatment. Patients should be encouraged to focus on activity and employment instead of their symptoms. Smoking should be strongly discouraged in all patients who will undergo surgical neuroma treatment.

Introduction

Neuropathic pain caused by symptomatic neuromas is an important problem following peripheral nerve injury, seriously affecting patients' daily life. The incidence of symptomatic neuromas is estimated at approximately 3-5% of all patients involved in peripheral nerve injury.[1] The extreme spontaneous pain, allodynia, hyperalgesia and cold intolerance cause loss of function and productivity,[2] resulting in high unemployment and workers compensation rates as well as high health care expenditures.[3,4]

Neuromas are formed when nerve recovery towards the distal nerve end or target organ fails and axons sprout into the surrounding scar tissue. They consist of a deranged architecture of tangled axons, Schwann cells, endoneurial cells, and perineurial cells in a dense collagenous matrix with surrounding fibroblasts.[5] There is an up-regulation of sodium channels, adrenergic receptors, and nicotinic cholinergic leading to abnormal sensitivity and spontaneous activity of injured axons.[6] As ectopic peripheral nerve input continues, changes at the spinal cord and sensory cortex level start to take place, creating a state of central sensitization.[7]

Unfortunately, treatment of patients with neuroma pain is difficult. Many treatment methods have been proposed, such as, injections of the nerve stump with various chemical agents, transcutaneous electrical nerve stimulation (TENS), topical lidocaine, repeated nerve blocks, desensitization techniques and adjuvant pain medication like antidepressants and anticonvulsants.[8] The treatment of disabling neuropathic pain following nerve injury is a topic that is of timeless interest to plastic- and neurosurgeons, orthopedic and general Surgeons, as well as anesthesiologists and pain management teams, but an entirely effective treatment method has yet to be found.[9] Although not all pain specialist are aware of this option, peripheral nerve surgery can provide a permanent effect on pain relief, as opposed to the life-long use of analgesic medication or medical devices.

Best results are usually obtained with reconstruction of the nerve using nerve grafts or neurotubes, or relocation of the painful nerve into an environment away from the original injury site and protected from mechanical, thermal, or other injury of the nerve,[10] for example into bone, muscle or vein.[11] End-to-side anastomoses or nerve loops can also provide satisfactory results.[9] Despite the use of these techniques, remaining or recurrent pain is a common finding.[7]

For decision making processes and patient education, it is important to know the effect of surgical treatment on different outcome domains. Since treatment failure is common, it can be important to point out patient groups that will not likely benefit from surgical treatment. Patient-specific prognostic factors, predicting insufficient pain relief after surgical neuroma treatment, can help clinicians in the process of patient selection, treatment and care. The current study was performed to evaluate the

effect of surgical neuroma pain treatment on multiple important outcome domains and to find prognostic factors for insufficient pain relief, including the predictive value of commonly used diagnostic nerve blocks.

Methods

Between January 2006 and August 2009, we conducted a prospective follow-up study on surgically treated upper extremity neuroma pain patients. Included patients were diagnosed with neuroma specific neuropathic pain after presenting with a history of nerve injury to the upper extremity, followed by symptoms of a painful neuroma including spontaneous pain, electrical spikes or burning pain, allodynia and hyperalgesia to touch, pressure or movement.[12] Clinical examination typically showed a shooting electrical pain when tapping the injured nerve (positive Tinel's test). In most cases, a diagnostic nerve block with 1% lidocaine was performed at the outpatient clinic, to confirm involvement of the suspected nerve in the painful sensation.[13] The effect of this nerve block was registered by the hand surgeon on a 0-10 pain scale. Patients that were selected by the hand surgeon to sustain a surgical procedure were sent a questionnaire approximately 2 weeks prior to their operation. Follow-up questionnaires assessing primary and secondary outcomes were sent to all included patients with a follow-up period of at least 3 months.

Patients were operated under general anesthesia combined with a local block or under regional anesthesia**.** Pre-operatively the location of maximum pain was marked. After opening the skin, the nerve was neurolyzed from the surrounding scar tissue and the neuroma was excised. If a neuroma-in-continuity or a nerve transection with an available distal stump was present, continuity was restored. If the distal nerve was not available for repair, the proximal stump was buried into bone or muscle, preferably proximally to the site of injury. In some cases other techniques were applied such as a nerve loop or silicone sheath. Tension on the nerve was always avoided.

The lateral antebrachial cutaneous nerve (LABCN), posterior interosseous nerve (PIN), palmar branch of the median nerve (PBMN) and the anterior interosseous nerve (AIN) may have overlapping sensory innervation with SBRN. In case of recurrent or persistent pain, the suspected adjacent nerve involved was diagnostically blocked with 1% lidocaine and if the block showed a considerable pain reduction, a denervation was performed.

Primary outcomes were patient satisfaction (yes or no) and pain scored pre- and post-operatively on a 10 cm visual analogue scale (VAS), ranging from 0 'no pain at all', to 10 'unbearable pain'. Cut off scores for insufficient pain relief were defined as less than three points decrease on the VAS pain scale, or a final VAS score above 2,

using the reliable change index (RCI) and clinical significant change (CSC) (data not shown).[14-16]

We evaluated the effect of treatment on important secondary outcome domains, including pain, physical and emotional functioning and accompanying symptoms, as proposed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).[17] These secondary outcomes were assessed using validated questionnaires, including the McGill pain questionnaire (MPQ), which divides pain into sensory-discriminative, affective-motivational, and evaluative-cognitive pain[18]; the SF-36 for physical and emotional quality of life assessment[19]; the SCL-90 for assessment of psychological problems and psychopathology[20]; the Tampa scale for kinesiophobia (TSK)[21], which measures the patient's anxiety for being physically active; and the disability of arm, shoulder and hand (DASH) questionnaire, with its subscales for work and sport activities.[22] Pre- and post-operative scores were compared to each other and to normative population scores found in literature. Furthermore, we looked at different pain modalities, as described by Sood and Elliot[12], and their improvement following surgical treatment. These include ratings of spontaneous pain, pain on pressure or movement, and hypersensitivity.

Prognostic factors such as employment status, workers compensation and litigation involvement, number of previous operations and duration of pain,[7] as well as other patient characteristics such as sex, body mass index (BMI) and smoking status and socio-economic status were evaluated for their effect on primary outcome. We also compared the effect of all surgical procedures performed during our study and compared the outcome for the different nerves involved in the upper extremity. The predictive value of the diagnostic nerve block performed at the outpatient clinic was determined by comparing pain scores following the nerve block with those following surgical treatment. Pain medication usage, type and frequency, were recorded both pre-operatively and after follow-up.

Student's t-tests were used to compare two independent means and for comparing pre- and post-operative data the paired t-test was used. For paired ordinal data the Wilcoxon signed rank test was used. Chi square tests were performed for 2 by 2 contingency tables, when the minimum expected count per cell was at least 5. For 2 by 2 tables not meeting this criterion, Fisher's exact test was performed. For prognostic factors for the primary outcome, relative risks (RR) with 95% confidence intervals (95% CI) were calculated. Stratification was performed in case of possible confounding of results. The Mantel-Haenszel adjusted relative risk was used to provide a weighted average of the stratum-specific relative risks. To evaluate correlations between ordinal and continuous data, the non-parametric Spearman's rank correlation coefficient was used. Pearson's correlation coefficients were used for continuous data. Although multiple procedures and measurements were available for some patients, only the final

operation of patients was used to compare groups, to avoid an underestimation of variability and inflation of sample size.

This study was approved by the Medical Ethics Committee of our institution (MEC-2007-094).

Results

From January 2006 through August 2009, pre-operative questionnaires were sent to 45 patients. Two patients did not return the questionnaire. Seven patients were excluded as no neuroma was found during surgery and only external neurolysis was performed. One patient decided to refrain from further surgical treatment. The follow up questionnaire was sent to 35 patients and returned by 34 patients, 1 patient did not respond. Demographics of the 34 included neuroma patients are presented in table 1.

Table 1. Baseline characteristics

Characteristic		
Sex	male	18
	female	16
Age (years)	mean	42.8
	range	17-75
Duration of pain (months)	mean	44.0
	range	4-142
Dominant hand		25
Number of previous operations	0	15
	≥1	19
	median (range)	1 (0-5)
BMI	mean	26.4
	range	17-37
Social economic status	high	
	medium	12
	low	18
		4
Smoking status	current smokers	12
	past smokers	12
	never smoked	10
Employed		15
Workers compensation		18
Litigation involved		13

Table 2. Causes of injury

Injury	N
Trauma	*20*
Sharp	8
Crush	8
Avulsion	4
Iatrogenic (sharp)	*13*
Arthrodesis	3
De Quervain's release	2
Ganglion	2
Ligament (S-L, Eaton Littler)	2
CTS release	1
Fasciotomy	1
Bone (sequestrotomy)	1
Flap (tissue expander)	1
Unknown	1

The study population consisted of 18 males and 16 females with an average age of 42.8 years. The average duration of follow-up was 22 months (range 3-37). The causes of nerve injury are presented in table 2. There were 9 amputation injuries. There was no significant difference in outcome between traumatic and iatrogenic injuries or the type of injury (sharp, crush, avulsion).

Nineteen patients (56%) were satisfied with treatment results. The mean pre-operative VAS score was 6.6, and decreased to 4.8 after follow up ($p<0.0001$). In the satisfied patient group, the mean pain decrease was 3.0 (from 5.7 to 2.7) compared to 0.7 (from 7.8 to 7.1) in the unsatisfied group ($p=0.003$). Fourteen patients (41%) had a decrease of at least 3 points on the VAS for pain, or a score below 2.

Pre- and post-operative SF-36, TSK, CISS, SCL-90 and MPQ scores, as well as normative population scores, are presented in table 3. Neuroma pain patients had a significantly lower physical quality of life compared to the normative population ($p<0.01$). Upper extremity disability (DASH), and cold intolerance (CISS) scores were high ($p<0.01$). The mental quality of life (SF-36, MCS) was no different from a normal population and there was no increase in symptoms of psychopathology (SCL-90) compared to the normative population. After surgery, upper extremity function improved significantly ($p=0.003$). For the McGill pain score, only the evaluative dimension was significantly improved (PRI-e 6.8 vs. 5.4, $p<0.05$).

Different pain modalities and their improvement following surgical treatment are shown in table 4. Pain at pressure was most frequently rated as severe prior to surgery and significantly improved after follow up ($p<0.01$). Pain with movement

Table 3. Secondary outcomes

Measure	Pre-operative score (SD)	Score after follow up (SD)	Paired t-test , p-value	Normative population scores
DASH	48.7 (21.3)	40.0 (24.1)	0.003	10.1 (14.7)
Sport/Hobby	67.7 (37.3)	59.4 (36.8)		9.8 (22.7)
Work	52.2 (30.7)	30.3 (28.7)	0.005	8.8 (18.4)
MPQ_DLV				NA
PRI-s	12.4 (7.0)	9.9 (7.2)	0.07	
PRI-a	3.2 (3.4)	2.7 (3.7)		
PRI-e	6.8 (2.6)	5.4 (2.7)	0.03	
PRIT	21.9 (12.0)	18.0 (12.9)	0.07	
NWC	11.6 (5.3)	9.9 (5.7)		
SF36				
PCS	38.9 (6.6)	40.7 (8.0)		50 (10)
MCS	60.0 (6.4)	58.4 (7.2)		50 (10)
SCL90				
PSNEUR	121.7 (33.7)	131.0 (49.4)		118.3 (32.4)
TSK	30.2 (7.8)	27.3 (8.9)	0.05	NA
AA	19.1 (5.8)	17.3 (6.0)	0.07	
SF	11.1 (3.2)	10.0 (3.4)	0.07	
CISS	53.0 (19.3)	50.5 (29.9)		12.9 (8.2)

DASH: Disability of the Arm, Shoulder and Hand (range 0-100); MPQ: McGill Pain Questionnaire (psychological dimensions of pain), PRIT: Pain rating Intensity Total (range 0-63), NWC: Number of Words Chosen (range 0-20), PRI-s: Pain Rating Intensity sensory (range 0-36), PRI-a: Pain rating Intensity affective (range 0-15), PRI-e: Pain rating Intensity evaluative (range 0-12); SF-36: Short Form 36 (quality of life), PCS: Physical Component Summary score (range 0-100), MCS: Mental Component Summary score (range 0-100); SCL-90: Symptom Checklist 90 (symptoms of psychopathology), PSNEUR: Psychoneuroticism score (range 90-450); TSK: Tampa Scale of Kinesiophobia (fear of re-injury), AA: Activity Avoidance (range 8-32), SF: somatic focus (range 5-20); CISS: Cold Intolerance Severity Scale (range 4-100)

and hypersensitivity also improved (p0.03). However, the number of patients with no complaints of hypersensitivity did not decrease following surgical treatment.

For patients satisfied with the result of surgical treatment, the use of all types of pain medication had decreased (table 5). In the unsatisfied group, the use of most types of pain medication increased after follow-up. The frequency of pain medication usage showed the same pattern (table 6): in unsatisfied patients, the frequency of usage increased after follow up; while in satisfied patients, the frequency of pain medication usage clearly decreased following surgery (p=0.055). After follow-up, none of the patients with a good treatment result used pain medication on a daily basis, while 30% of unsatisfied patients did.

Data on pre-operative diagnostic nerve blocks was recorded for 18 patients at the outpatient clinic. There was no significant relationship between duration of pain and nerve block effect. The amount of remaining pain following diagnostic nerve block, was significantly correlated with the post-operative pain score on the VAS (figure 1; *Spearman's rho*=0.538, p<0.05). Patients with an effective diagnostic nerve block (pain score less than 3.5), had significantly less pain following surgery compared to patients with an ineffective nerve block (VAS score 3.8 vs. 8.2, p=0.001).

Success rates of the various surgical procedures performed during the study can be found in table 7. Neuromas of the superficial branch of the radial nerve (SBRN) led to the worst outcome, with only 33% of procedures providing satisfactory results. Post-operative satisfaction rates were not significantly different between the different affected nerves or performed surgical procedures.

There were several prognostic factors related to insufficient pain relief after surgical neuroma treatment; the relative risks are presented in table 8. Longer duration of pain was significantly correlated to a higher post-operative VAS score for pain (r=0.387, p=0.02) and the mean VAS score was higher after a duration of at least 48 months (VAS 6.1 vs. 4.1). The number of previous procedures did not influence primary outcome, neither did sex or socio-economic status. Before treatment, 19 patients (56%) were unemployed, including two patients who were retired, and after follow up 6 of these unemployed patients had returned to work.

Patients that were employed during surgery demonstrated a greater decrease in VAS score than patients that were unemployed (p<0.05). 18 patients (53%) received workers compensation before surgery, this decreased to 10 (29%) after surgical treatment. A total of 13 patients (38%) were involved in litigation. Workers compensation and litigation were not predictive of the outcome.

Patients who smoked at the time of surgery had a significantly worse outcome than patients who did not smoke (mean post-operative VAS score 3.5 vs. 6.8, p=0.001). The RR of smoking on insufficient pain relief was 2.06 (95% CI: 1.24 - 3.42) This RR was evaluated for confounding by duration of pain, employment status and age.

Table 4. Pain modalities

Pain modality	Severe		Moderate		Mild		None		p-value
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	
Spontaneous pain	15	10	10	13	4	4	4	7	0.14
Pain at pressure	25	15	5	11	1	4	2	4	0.009
Pain with movement	19	11	9	11	1	9	4	3	0.03
Hypersensitivity	22	13	5	11	1	5	5	5	0.03

Pre- and post-operative grading of different pain modalities by patients.; p-value: obtained with Wilcoxon signed rank test

Table 5. Pain medication usage in satisfied and unsatisfied patients

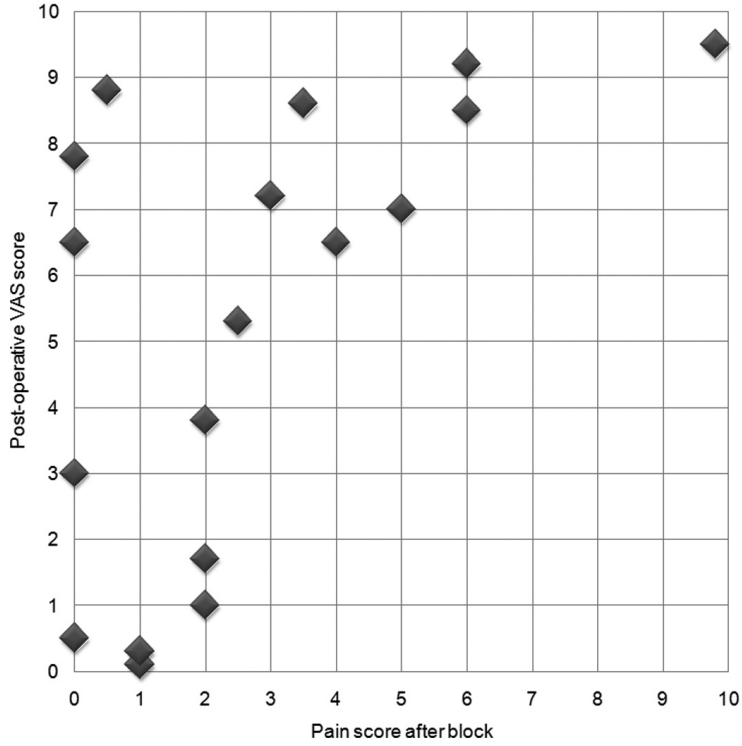
Pain medication	Number of unsatisfied patients (n=15)		Number of satisfied patients (n=19)	
	Pre-operative	*Follow-up*	*Pre-operative*	*Follow-up*
Paracetamol	1	4	3	2
NSAID	5	3	5	4
Weak opiate	0	2	0	0
Strong opiate	1	1	0	0
Adjuvant	3	4	3	2
Other	0	4	0	0

Table 6. Frequency of pain medication usage in satisfied and unsatisfied patients

Frequency	Number of unsatisfied patients (n=15)		Number of satisfied patients (n=19)	
	Pre-operative	*Follow-up*	*Pre-operative*	*Follow-up*
≥3 times a day	3	5	3	0
1-2 times a day	3	4	2	0
> Once a week	0	0	3	3
Once a week	0	1	0	2
Less often or never	9	5	11	14

Wilcoxon signed-rank test for difference in usage between pre-operative and follow-up periods: unsatisfied patients: p=0.08 (increased usage); satisfied patients: p= 0.055 (decreased usage)

Figure 1. Graph: pain after diagnostic nerve block vs. post-operative pain



Spearman's rank correlation coefficient: 0.538, p<0.05

Table 7. Patient satisfaction following different surgical procedures

Procedure	N	Satisfied (%)[a]
Neuroma treatment	42	18 (43%)
Digital nerve	18	9 (50%)
SBRN	18	6 (33%)
LABCN	4	3
Dorsal ulnar nerve	1	1
PBMN	1	0
Relocation into muscle	10	4 (40%)
Relocation into bone	9	3 (33%)
Nerve repair (incl. neurotube, autograft)	6	3 (50%)
Relocation elsewhere (incl. loop, nerve sheath)	17	8 (47%)
Neurectomy adjacent nerves (secondary procedure)	10	4 (40%)

[a] *Satisfaction percentages calculated for N>5; SBRN: superficial branch of the radial nerve; LABCN: lateral antebrachial cutaneous nerve; PBMN: palmar branch of the median nerve*

The pooled RR estimates ranged between 2.08 and 2.29, indicating no confounding of these factors, and there was no clear effect modification present. Smoking was significantly related to a lower BMI (23.7 vs. 27.9, $p<0.05$) and there was some effect modification present (table 9). Patients with a normal BMI did not show the same deteriorating effect from smoking, compared to patients with a BMI above 25 (RR 1.2 vs. 3.7). The same was found for sex: males had a lower RR for smoking on outcome than females (RR 1.7 vs. 3.0). Past smoking was not related to a worse outcome and even showed better pain relief than never smokers, with a mean post-operative VAS score of 2.6. Outcome was not related to the number of pack years smoked or the duration of smoking cessation prior to surgery.

Table 8. Prognostic factors

Variable	N	Follow-up VAS score	Satisfied (%)	Insufficient pain relief	RR
Duration of pain					
<48 months	24	4.1	16	12	
≥48 months	10	6.1	3	8	2.50 (0.68-9.20)
Diagnostic nerve block					
VAS score <3.5	12	3.8	8	6	
VAS score ≥3.5	6	8.2**	1	6	2.00 (1.14-3.52)
Smokes					
yes	12	6.8	4	11	2.06 (1.24-3.42)
no	22	3.5**	15	9**	
Employed					
yes	15	3.2	11	6	
no	19	5.9*	8	14*	1.84 (0.94-3.62)

*RR: relative risk for insufficient pain relief, defined as at less than 3 points decrease on the VAS, or a final score higher of 2 or higher; *p<0.05; ** p<0.01*

Table 9. Stratification of smoking on BMI and sex

Stratified by		RR
BMI	<25	1.23 (0.72-2.10)
	≥25	3.75 (1.62-8.68)*
Sex	male	1.73 (0.83-3.61)
	female	3.00 (1.19-7.56)*

*RR: relative risk ratio of smoking for insufficient pain relief; *p<0.05*

Discussion

Painful neuromas are often therapy resistant. When referred to pain management teams, neuroma patients are often regarded as having no chance of improvement of their symptoms. It is relatively unknown that in some patients, peripheral nerve surgery can provide a permanent effect on pain relief, as opposed to the life-long use of analgesic medication or medical devices (e.g. nerve stimulators).

This prospective follow up study was performed to evaluate the result of treatment on multiple outcome domains and to establish prognostic factors for insufficient pain relief following surgical treatment. Furthermore, we looked at the predictive value of commonly used diagnostic nerve blocks. We found that 56% of patients were satisfied with treatment results. There was a significant decrease in pain and disability and little or no improvement in cold intolerance, quality of life, or symptoms of psychopathology. Evaluating patient and surgery specific determinants, we found several prognostic factors predictive of insufficient pain relief including unemployment, nicotine use and poor pain relief following diagnostic nerve block.

To accurately study the effect of treatment for neuropathic pain, the use of appropriate outcome measures is essential.[23] Most studies performed in the area of neuroma pain focus on only one aspect of treatment outcome,[24-29] The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommended 6 core outcome domains that should be considered in chronic pain research: pain; physical functioning; emotional functioning; improvement and satisfaction with treatment; other symptoms and adverse events during treatment; and patients' disposition and characteristics.[17] We assessed all of these areas using previously validated, reliable measures.

Reliable pain measurement is difficult, since pain is a highly subjective symptom. Other studies often use ill defined or non validated outcome measures for pain.[28,30-34] We applied the VAS to assess pain pre- and post-operatively and used cut-off scores for a reliable and clinically useful decrease in pain on the VAS.[14]

Remaining or recurrent pain after surgical neuroma treatment can be explained by secondary displacement of the translocated neuroma, failure to identify the presence of more than one neuroma in the same patient,[33] or injury of neighboring nerve branches. Following complete neurectomy of the injured nerve, adjacent nerves may start to transmit sensory signals from the denervated skin area.[35] This process is desirable for normal sensory recovery, but can lead to recurrent or sustained pain in surgically treated neuroma pain patients. There is increasing evidence that hyperalgesia is independent of input from injured afferents, suggesting that ectopic activity originating from a neuroma is not necessary for development of hyperalgesia.[36-38] As previously described by Stokvis et al.[2], patients surgically treated for a painful neuroma in

the upper extremity showed a significant decrease in spontaneous pain after follow up. However, the intense symptoms of cold intolerance, also called thermal hyperalgesia, remained unchanged. In our study, symptoms of hypersensitivity improved to some extent. However, the number of patients without any hypersensitivity did not decrease following surgical treatment.

Careful patient selection for surgical treatment is critical for a successful outcome of neuroma pain treatment.[9] In the diagnostic workup of neuroma pain patients, a diagnostic nerve block with 1% lidocaine is often performed.[13] It is proposed that insufficient pain relief following a diagnostic block is a contraindication to surgery.[33] Unfortunately, more has been written on the description of techniques of various nerve blocks than on evaluating the benefits to the patient,[39] and statistically significant evidence for the diagnostic or prognostic value of peripheral nerve blocks for neuroma pain diagnosis has, to our knowledge, not been described in literature before. We found the effect of a diagnostic peripheral nerve block to be significantly predictive of the amount of pain following surgery for painful neuromas. For patients with a good response to the block, success chances were significantly higher. We should take into account the fact that the majority of patients with an unsuccessful nerve block were not surgically treated and were not included in our study. This may bias the predictive value of an unsuccessful diagnostic nerve block, since the patients that were operated despite the poor block result, may represent a different patient group than patients that were not operated. It emphasizes the need for placebo controlled studies in determining the true predictive value of this often used diagnostic tool.

Longer duration of pain was significantly correlated to a higher post-operative VAS score for pain. This is common finding in literature, and may be explained by changes in pain processing in the central nervous system (CNS) that can occur during the chronic phase of neuropathic pain and sustain patients' pain.[7] However, patients with a highly therapy resistant pain problem will subsequently have a longer duration of pain and more surgical procedures, regardless of the cause.

Employment status was related to a better outcome, and the literature on neuroma pain outcome supports this result.[7]. The finding by Suter[40] that employed patients had less severe symptoms prior to treatment was also present in our patient population; however, we also found a significantly greater improvement in pain score for employed patients. Furthermore, Suter stated that employed patients experience a feeling of satisfaction that alleviates the perception of pain and disability and that working facilitates recovery from injury. Therefore, it would be valuable to focus on activity and employment in the treatment and rehabilitation of chronic pain patients.[4]

Nicotine is known to have central analgesic properties in humans, but paradoxically, also has peripheral nociceptive effects. Chronic nicotine use produces a stable, long-lasting, mechanical hypersensitivity that exacerbates mechanical sensitivity

resulting from peripheral nerve injury.[41] The effect of nicotine on neuropathic pain has become increasingly known in basic research. However, clinical research is to our knowledge restricted to a single case series with two patients. In this study by Richards et al [42], patients experienced a marked reduction in neuropathic pain following smoking cessation, and their pain returned once they resumed smoking. In our study, smokers had a significantly worse outcome, with less reduction in pain and a lower satisfaction compared to non smokers. We found a RR of smoking on insufficient pain relief of 2.1 (1.2 - 3.4).

In males and patients with a low BMI, the deteriorating effect of smoking was less obvious. This might be explained by the absence of a central analgesic effect of nicotine on pain in women. In a study by Jamner et al.[43], the transdermal administration of nicotine led to decreased sensitivity to pain in men but not in women, suggesting a difference in the central effect of nicotine on pain regulatory mechanisms between men and women.

Although the exact mechanism of nicotine on neuropathic pain, influenced by BMI and gender, needs to be elucidated, smoking cessation in patients sustaining plastic surgery should be encouraged.[44,45] Chronic exposure to cigarette smoke produces profound changes in physiology that may contribute to peri-operative morbidity.[44] It is known to impair digital blood flow and wound healing in the hand[46,47] and increases the risk of postoperative wound-related complications, such as dehiscence and wound infection.[44,48]

There are some limitations to this study that should be discussed. Our study population existed of patients referred to a tertiary referral center for expertise in the field of neuropathic pain treatment, sometimes following multiple ineffective treatments. This is likely reflected in the severe and therapy resistant nature of our patients' complaints and therefore negatively influences outcome compared to other medical centers and neuropathic pain disorders.

We included neuropathic pain patients with neuromas of any of the peripheral sensory nerve branches in the upper extremity. This has provided a somewhat heterogeneous patient group, with some subgroups of more rarely affected sensory nerve branches, but increased the overall applicability of our outcomes.

Given the reasonably low incidence of painful neuromas, our study was based on a relatively large number of patients. Most studies that have been performed evaluating painful neuroma treatments comprised case series with small patient numbers,[12,24,29,49-54] or had a retrospective design.[34,55,56]

Our study was conducted as a prognostic follow up study. This type of study is readily used to accurately study prognostic factors for treatment outcome. Since data collection was prospective, information bias was largely avoided and response rates were high. We were able to compare pre-and post-operative findings for all included

patients, with complete follow up for 34 out of 35 patients returning the primary questionnaire.

Neuroma pain following upper extremity nerve injury remains a difficult problem; patients experience high disability and low quality of life. Surgical treatment can effectively decrease pain, disability and workers compensation rates. Unfortunately, insufficient pain relief following surgical neuroma treatment is a common finding. Our results could lead to improved patient selection and treatment strategies. If a diagnostic nerve block is ineffective in relieving pain, patients will most likely not benefit from surgical treatment. Patients should be encouraged to focus on activity and employment instead of their symptoms. Smoking should be strongly discouraged in all patients who will undergo surgical neuroma treatment.

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Chapter 8:

General Discussion

The purpose of this thesis was to explore why a large number of patients with neuroma pain still have insufficient pain relief following surgical neuroma treatment, and to explore the optimal strategies for surgical treatment and chronic pain prevention of individual patients. In the previous chapters we have presented our results. The outcome of our studies will subsequently be used to answer the research questions posed in the introduction.

Patient selection

Which are important prognostic factors for insuff icient pain relief?

After reviewing the literature (chapter 2) and performing a prognostic follow-up study (chapter 7) we found the following prognostic factors for a worse outcome following surgical neuroma treatment:

- Neuromas of the superficial branch of the radial nerve[1,2]
- Neuromas of digital nerves[2,3]
- No 'discrete nerve syndrome'[4]
- Receiving workers' compensation[2,3,5,6]
- Unemployment[4,6]
- Litigation involvement[4,7]
- Increasing number of previous operations[2,6]
- Longer duration of pain[6]
- Smoking[8]

The superficial branch of the radial nerve (SBRN) is vulnerable to the formation of painful neuromas that are difficult to treat, due to its anatomical location and overlapping sensory pattern with neighboring nerves.[6]

Incorrect relocation, into a small muscle with significant excursions (i.e. intrinsic or thenar musculature), can cause insufficient pain relief. In chapter 5 we observed that approximately 89% of patients with SBRN relocation into small muscles or bone were unsatisfied following surgical treatment. Patients with neuromas of the digital nerves face the same problems in achieving satisfactory outcome.

Discrete nerve syndrome is a collective term for a condition in which a single nerve can account for both the neurological findings and the distribution of neuropathic pain.[4] Patients with poorly localized, ill-defined signs and symptoms will likely have an increased chance of being incorrectly diagnosed and receiving inappropriate treatment.

In chapter 2, we learned that patients seem to benefit less from treatment when continued disability is important for their pending litigation. In this context, patients

involved in workers' compensation can have an interest in reporting poor outcome. Litigation and workers' compensation were not predictive of a worse (reported) outcome in our prospective follow-up study (chapter 7). This seeming contradiction could well be explained by differences between the litigious climates of the countries were these studies were performed.

Being employed increases the chance of a satisfactory outcome following surgical neuroma treatment (chapters 2 and 7). Although in chapter 7 employed patients had less severe symptoms prior to treatment, we also found a greater decrease in pain score for employed patients. In chronic pain patients, employment can lead to lower physical and emotional distress.[9]

Patients with a longer duration of pain have an increased chance of insufficient pain relief following surgical neuroma treatment; this relation was observed in chapters 2, 5 and 7, and may be explained by changes in pain processing in the central nervous system (CNS) that can occur during the chronic phase of neuropathic pain and sustain patients' pain.[10-12] Furthermore, patients with a highly therapy resistant pain problem regardless of its cause, will subsequently have a longer duration of pain and are more likely to undergo multiple surgical procedures.

A prognostic factor found in chapter 7 that has not been reported in neuroma pain literature before, is smoking. Smokers have a significantly worse outcome following surgical neuroma treatment, with less reduction in pain and a lower satisfaction rate compared to non smokers. The relative risk (RR) of smoking on insufficient pain relief is 2.1. With a prevalence of smoking of 35% our patient population, a great benefit may be achieved by stimulating smoking cessation.[8,13,14]

Diagnosis

Can we use ultrasonography for diagnosis and localization of neuromas in the upper extremity?

Ultrasonography (US) equipment used in clinical settings has reached frequencies up to 20MHz at present and frequency and resolution are steadily increasing. Known advantages of US are its noninvasiveness, safety, portability and low costs. High-resolution US was able to depict the small cutaneous nerve branches in the hand and wrist that are often involved in neuroma formation. In chapter 3, the sensory branch of the radial nerve, the palmar branch of the median nerve, the dorsal branch of the ulnar nerve and the palmar digital nerves were visualized in great detail using the Vevo 770 US system with 15-82.5 MHz real-time micro visualization scan heads.

Using this technique, it will be possible to assess individual nerve fascicles in a damaged peripheral nerve and determine the degree of injury in neuroma in continuity lesions. When the exact location of an upper extremity neuroma is unclear, US may help in surgical planning and reduce the size of surgical incisions and wound beds.[15,16] Furthermore, high resolution US can serve to locate the cause of remaining or recurrent pain following surgical neuroma treatment, i.e. the unintentional dislocation of a relocated nerve end.

Is the diagnostic nerve block a predictive diagnostic tool?

Misdiagnosis and failure to identify the presence of distal reinnervation or central sensitization may be avoided by the use of a local diagnostic nerve block, which can identify the sensory nerves involved in the neuropathic pain symptoms.[6,17] In chapter 7, we found the effect of a diagnostic peripheral nerve block to positively predict the effect of surgical neuroma treatment.

Unfortunately, false positive results were common. This could be explained by the placebo effect of the block, which is common in chronic pain patients.[18-20] There was no data from patients that received a diagnostic nerve block, but did not undergo surgery. Therefore, this test's sensitivity or specificity could not be calculated.

In chapters 5 and 7, all patients who underwent surgery following an ineffective diagnostic nerve block experienced insufficient pain relief at follow-up. This indicates that these patients should not sustain surgery and be referred to a pain specialist for alternative options to reduce pain.

Determinants of outcome

Which are the most important outcome measures for peripheral neuropathic pain research?

In chapter 6 we studied possible outcome measures on their importance for patient satisfaction following surgical neuroma treatment. Pain, measured with a visual analogue scale (VAS), the evaluative dimension of pain according to the McGill Pain Questionnaire (MPQ_PRI-e) and disability, measured with the DASH and SF-36 physical component, are the most important outcome domains. Other symptoms that are important for patient outcome are cold intolerance (CISS) and activity avoidance due to fear of re-injury (TSK-AA). Which outcome measure should be chosen in clinical practice depends on the amount of time available and the specific questions that need to be answered. The use of time consuming instruments, i.e. the MPQ, gives a more specific evaluation of the patient's problem, while short measures, such as the

VAS, have a higher response rate.

A presumed disadvantage of the VAS has been that patients may adjust their criteria for success over time by becoming less stringent.[21] The results from chapter 6 provide a different conclusion: the amount of pain on a VAS indicated as tolerable by neuroma pain patients does not change following surgical treatment. The VAS has a good test-retest reliability (r=0.80[22]), is easy-to-use in clinical practice and readily interpretable by the clinician. A decrease of at least 30 mm or a score below 20 mm on the VAS represents a relevant change in pain. These cut-off points were used to evaluate patients' outcome in chapter 7.

Treating hyperalgesia

Can hyperalgesia be sustained by pain conduction via adjacent nerves; and how can we treat this hyperalgesia?

As described in chapter 4, cold intolerance, or thermal hyperalgesia, has a prevalence of 91% in patients surgically treated for neuroma pain. Although surgery significantly decreases spontaneous neuroma pain, it does not improve symptoms of cold intolerance. In chapter 7 we found similar results: symptoms of hypersensitivity are improved to some extent following surgical treatment, but the proportion of patients with symptoms of hypersensitivity does not decrease.

These findings can be explained by the observations made in small animal research, that ectopic activity originating from a neuroma is not necessary for the development of hyperalgesia.[23-25] The recruitment of axons from adjacent nerves will continue the input of pain signals to the CNS. This process is desirable for normal sensory recovery, but can lead to recurrent or sustained pain in surgically treated neuroma pain patients. Furthermore, injury to a cutaneous branch of a peripheral nerve can result in central sensitization that spans multiple spinal segments and can, therefore, cause pain to be perceived in neighboring nerve distributions.[26]

In chapter 5, the problems in achieving satisfactory pain relief for a population of patients with neuropathic pain of the SBRN was studied. It seems that the recruitment of adjacent nerves may be a significant cause for insufficient relief from pain and hyperalgesia. In accordance with this theory, neurectomies of neighboring nerves such as the LABCN and PIN have relatively good satisfaction rates (approximately 50%) for this hard-to-treat patient population.

Clinical implications

What is the most effective treatment strategy for neuroma pain patients?

Neuroma pain patients experience very high disability and low quality of life compared to a normal population. Many treatment methods have been proposed, such as, injections of the nerve stump with various chemical agents, transcutaneous electrical nerve stimulation (TENS), topical lidocaine, repeated nerve blocks, desensitization techniques and adjuvant pain medication like antidepressants and anticonvulsants.[27] Although pain specialists are not always aware of this option, peripheral nerve surgery can provide a permanent effect on pain relief, as opposed to the life-long use of analgesic medication or medical devices. Currently used treatment strategies focus primarily on surgical repair or denervation of the injured nerve. As we observed in chapter 7, surgical neuroma treatment effectively decreased pain and upper extremity disability in approximately 50% of patients. Unfortunately, the other 50% experienced insufficient pain relief.

In chapter 5 we compared treatment methods for SBRN neuralgia, known for its unfavorable outcome. Nerve repair often fails to provide a satisfactory outcome. Preferably, denervation with relocation of the nerve end into the brachioradial muscle should be performed without undue delay. Relocation of the nerve end elsewhere (i.e. small muscles of the hand and lower arm, the distal radius, end-to-side anastomosis) has only an 11% chance of achieving patient satisfaction.

From the results found in chapters 2, 4, 5 and 7 we can propose a general treatment strategy for painful neuromas in the upper extremity:

Patients presenting to any clinician with complaints suspect of neuroma pain not responding to desensitization or adjuvant pain control should be referred to a Plastic/Hand Surgeon without delay, to assess the possibilities for surgical treatment. The diagnosis of neuroma pain can be made with a thorough medical history and physical examination. If the diagnosis remains unclear, a high resolution US examination of the suspected nerve(s) should be performed.

To assess central centralization processes, damage to multiple nerves and the role of neighboring nerves in transmitting pain signals, a diagnostic block of the most likely involved nerves should be performed. Patients with no or little pain reduction following this diagnostic block should not undergo surgical neuroma treatment.

Patients should be properly informed about the expected effects of surgical treatment. They should be encouraged to focus on activity and employment instead of focusing on their symptoms. Smoking should be strongly discouraged.

When a patient is found eligible for surgical neuroma treatment, effort should be made to perform the procedure without delay. During surgery, the neuroma is excised

and the nerve end placed preferably into a sufficiently large, well vascularized muscle bed without large excursions. In case of an overlapping sensory pattern of adjacent nerves, these are neurectomized to decrease post-operative hyperalgesia. It is unlikely that symptoms of cold intolerance are improved by denervation of the injured nerve.

Case – continued

What happened to Mr. Dolor?

In August 2009, Mr. Dolor sustained an US examination of the operated area. It seemed that the SBRN had been pulled out of the thenar musculature and had formed a new neuroma located superficially beneath the skin. Diagnostic nerve blocks of the SBRN and PIN performed at the outpatient clinic significantly decreased symptoms of pain and hyperalgesia. After being explained the potential benefits to his recovery and outcome, Mr. Dolor started working therapeutic hours and entered a smoking cessation program.

In November 2009, the SBRN was surgically relocated into the brachioradial muscle and after that a PIN neurectomy was performed. Following his recovery, Mr. Dolor's pain and hyperalgesia improved to a tolerable level. He returned to his previous job as a plastic processer and was again able to perform his tasks as a father of two young children.

Recommendations for future research

Today, there are still patients who do not benefit from surgical neuroma treatment and some interesting topics for future research remain.

Research comparing epidemiological, patho-histological and molecular biological characteristics of nerve injury patients with and without chronic neuropathic pain could provide new insights in its etiology and pathogenesis of painful neuromas. Novel peripheral nerve imaging techniques like high resolution ultrasound[16] and diffusion-tensor imaging[28] are rapidly improving and will be able to aid the diagnostic and follow-up processes of patients undergoing surgical treatment.

The accuracy of diagnostic nerve blocks, in selecting patients eligible for surgical neuroma treatment, should be further determined. A randomized controlled trial using placebo controlled nerve blocks and subsequent surgical treatment would provide accurate estimates of this test's sensitivity and specificity.[18] However, since the diagnostic nerve block is already considered the gold standard to assess surgical eligibility, this type of research might raise important ethical issues.

A well-designed randomized trial would also be appropriate to compare seemingly effective surgical treatment strategies. To date, only one RCT has been performed in the field of neuroma pain treatment,[29] and its patient numbers were relatively small; the study compared two surgical treatment methods in 20 lower extremity neuroma patients. To increase the power of statistical analyses, large patient numbers are desirable. However, given the fact that neuroma pain is (fortunately) uncommon, large study populations are hard to obtain. Multicenter studies could provide sufficiently large patient numbers needed for high quality research.

New insights in human neurobiology will provide possibilities for the development of new types of drugs for neuropathic pain treatment. Several key molecules associated with nociception have been suggested as potential targets. One example is glial cell line-derived neurotrophic factor (GDNF), which has shown to exert a potent analgesic effect on hyperalgesia as well as a protective effects against the development of neuropathic pain in rats.[30,31]

A completely new therapeutic strategy, gene therapy, could be used to treat and even prevent painful neuromas in the future. It has already been used to express neural growth factors guiding peripheral nerve regeneration[32] and may also be used to inhibit the expression of local proteins essential for neuroma formation.[33]

To ensure best medical practice, clinicians should continue to familiarize themselves with the rapidly progressing field of neuropathic pain treatment. They should stay aware of the available options for treating, and ultimately preventing painful neuromas.

Final considerations

As we are nearing the end of the Decade of Pain Control and Research, it is important to reflect on what has been accomplished in the management of chronic neuropathic pain, as well as the challenges that lie ahead.

There has been an enormous increase in knowledge of the nature and mechanisms of pain. Great effort has been made to objectively measure symptoms of pain. The next ten year period has been appointed the 'Decade of the Mind', and will undoubtedly lead to even greater insights in the origin and treatment of chronic neuropathic pain. It is important to remember however that pain is a subjective experience by definition, and relieving patients' suffering must be the ultimate goal of any treatment.

New techniques to (surgically) treat pain have to make the leap from bench to bed in order to be effective. The clinician then has to decide whether what is possible is also desirable in the context of Hippocrates' "do no harm". All of these considerations have to be made against rapidly changing legal, economic and social backgrounds.[34]

It is important to acknowledge that neuropathic pain management requires a personalized approach, taking into account the broad scale of physical, emotional, and social problems that affect the daily life of chronic neuropathic pain patients.

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Summary

Chapter 1: Introduction

The major impact of chronic pain on public health is reflected by the declaration of the present decade as the "Decade of Pain Control and Research", mandated by the USA Congress. Neuropathic pain is thought to be a particularly distressing chronic pain condition that is often under-diagnosed and under-treated. Approximately 3-5% of all patients involved in peripheral nerve injury develop a symptomatic neuroma. Symptomatic neuromas cause intense spontaneous burning, shooting or electric pain, lowered thresholds for pain (hyperalgesia) and pain at touch (allodynia). Patients with a painful neuroma usually experience great disability, leading to high costs for society.

A neuroma is formed by the combination of regeneration of neural fibers and excessive fibrous tissue proliferation, which results in contraction of nerve fibers within the scar tissue. Its diagnosis is usually based on patients' history and clinical examination, including a Tinel's test and a diagnostic nerve block. Although many treatment methods have been proposed, none has shown to be entirely effective in achieving sufficient pain relief.

Objective and research questions

The purpose of this thesis was to explore why a large number of patients with neuroma pain still have insufficient pain relief following surgical neuroma treatment, and to explore the optimal strategies for surgical treatment and chronic pain prevention of individual patients. The following research questions were discussed in this thesis:

- Which are important prognostic factors for insufficient pain relief?
- Can we use ultrasonography for diagnosis and localization of neuromas in the upper extremity?
- Is the diagnostic nerve block a predictive diagnostic tool?
- Can hyperalgesia be sustained by pain conduction via adjacent nerves; and how can we treat this hyperalgesia?
- Which are the most important outcome measures for peripheral neuropathic pain research?
- What is the most effective treatment strategy for neuroma pain patients?

Chapter 2: Insufficient pain relief after surgical neuroma treatment

Patient-specific prognostic factors, predicting insufficient pain relief after surgical neuroma treatment, can help clinicians in the process of patient selection, treatment and care. We performed a review of the literature to evaluate these prognostic factors.

A computerized bibliographical database (PubMed Medline) was searched for relevant studies, and all reference lists were checked. We found 14 cohort studies that indicate possible prognostic factors. The factors that seem to predict the amount of postoperative pain are neuromas of the radial sensory branch (RSB) and digital nerves, discrete nerve syndrome, workers' compensation, employment status, litigation involvement, duration of pain and the number of previous operations. In chronic neuropathic pain patients, changes in the central nervous system at the level of spinal cord and in the somatosensory cortex may play a role in sustaining pain.

Chapter 3: Diagnostic ultrasonography of cutaneous nerve branches

Ultrasonography (US) can be used to identify peripheral nerves. It is a non-invasive, cost-effective and easy-to-use technique. However, the resolution of the current US equipment, with frequencies of 5–20 MHz, does not allow accurate and detailed visualization of the superficial cutaneous branches of the median, ulnar and radial nerves in the hand and wrist and digital nerves, which are often involved in upper extremity neuroma formation. Recent advances in US imaging techniques have permitted frequencies over 80 MHz, with a spatial resolution down to 30 microns. In this study, we compared peripheral nerve imaging with the VisualSonics Vevo 770 system equipped with 15-82.5 MHz transducers to a commonly used 5-12 MHz US system, in two cadaver arms and two healthy test subjects. The Vevo 770 system was able to accurately identify the small cutaneous nerves in the hand and wrist. It could also depict the median nerve and its fascicles in greater detail compared to the 5-12 MHz US system. High resolution US could be used for clinical diagnosis, localization and follow-up of neuropathies and nerve injuries.

Chapter 4: Cold intolerance in surgically treated neuroma patients

Cold intolerance, or thermal hyperalgesia, is a common long-term consequence of upper-extremity nerve injury. It is defined as abnormal pain of the hand and fingers after exposure to mild or moderate cold, with or without discoloration, numbness, weakness, or stiffness. Cold intolerance can seriously affects patients' lifestyle, work, and leisure activities. This study aimed to investigate the prevalence and severity of cold intolerance in patients with injury related neuromas of the upper extremity and improvement of symptoms after surgical neuroma treatment. The cold intolerance symptom severity (CISS), visual analogue scale (VAS) and disabilities of the arm, shoulder and hand (DASH) questionnaires were filled out by 33 patients surgically treated for upper extremity neuroma pain. The follow-up questionnaire was filled by

30 of these patients after a mean follow-up time of 24 months. We found a prevalence of cold intolerance of 91% before surgery, with a mean CISS score above the cutoff point for abnormal cold intolerance. The VAS score for pain decreased significantly following surgical treatment ($p<0.01$), and disability was also reduced. However, the overall severity of cold intolerance did not decrease at all. Furthermore, we found that duration of pain and follow-up period were unrelated to the CISS score. From our results, it seems unlikely that cold intolerance will fade with time or surgical treatment.

Chapter 5: The 'unforgiving' superficial branch of the radial nerve

The sensitivity of the superficial branch of the radial nerve (SBRN) for the development of neuropathic pain is well documented, and achieving satisfactory pain relief remains extremely difficult. This study evaluated different surgical treatment strategies for neuropathic pain caused by lesions or adhesions of the SBRN. Surgical records were searched for patients with SBRN neuralgia. Data were collected from medical files. The effect of a pre-operative diagnostic nerve block was determined. Study outcomes were patient satisfaction and post-operative pain scored with the numerical rating scale (NRS). Forty-nine patients underwent 34 neurolyses and 49 denervations of the SBRN. Multiple nerves innervating the dorsoradial wrist area were involved; including the posterior interosseous nerve (PIN) and lateral antebrachial cutaneous nerve (LABCN). 29 patients achieved satisfactory results (59%). The median NRS pain score decreased from 7.5 to 2.5 ($p<0.001$). Operations relocating the SBRN into the brachioradial muscle achieved significantly higher patient satisfaction rates than relocation of the nerve end elsewhere ($p=0.04$). PIN and LABCN neurectomies also provided satisfactory pain relief. Higher post-operative pain scores and lower success rates were found in patients with an unsuccessful diagnostic nerve block.

Chapter 6: Determinants of patient satisfaction

To accurately study treatment methods for neuropathic pain, the use of appropriate outcome measures is essential. There is a growing demand to investigate the relationship between patient satisfaction and relevant clinical outcomes. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommended 6 core outcome domains that should be considered in chronic pain research. These 6 core outcome domains are (I) pain; (II) physical functioning; (III) emotional functioning; (IV) participant ratings of improvement and satisfaction with treatment; (V) other symptoms and adverse events during treatment; and (VI)

patients disposition and characteristics data. The purpose of this study was to find the outcome domains most important for patient satisfaction after surgical treatment for neuropathic pain, caused by peripheral nerve injury. Thirty-four patients surgically treated for upper extremity neuroma pain were followed prospectively. They returned validated questionnaires on the core outcome domains of chronic pain pre- and post-operatively, including the VAS, McGill Pain Questionnaire (MPQ), DASH, Short Form-36 (SF-36), Symptom CheckList-90 (SCL-90), Tampa Scale of Kinesiophobia (TSK) and the CISS. Cut-off values for meaningful change were calculated using the reliable change index (RCI) and the clinical significant change (CSC) cut-off value. We compared satisfied and unsatisfied patient groups for all outcome domains. The most important outcome domains were found to be 'pain', 'physical functioning' and 'other symptoms'; 'Emotional functioning' was not related to satisfactory outcome. The VAS for pain was most important for patient satisfaction, and a decrease of at least 30 mm or a score below 20 mm on the VAS were found to represent relevant changes in pain. The amount of pain indicated as bearable by patients, did not change after treatment.

Chapter 7: Surgical treatment of neuroma pain

We performed a prospective follow-up study to study the success of surgical neuroma treatment and evaluate prognostic factors. Primary outcomes were patient satisfaction and pain scored pre- and post-operatively on a VAS. Secondary outcomes included upper extremity function, quality of life and symptoms of psychopathology. VAS scores after diagnostic nerve blocks were documented at the outpatient clinic before surgery. Surgical treatment consisted of neuroma resection and nerve repair or proximal transposition of the involved sensory nerve into muscle or bone. Thirty-four patients were included, with an average follow up time of 25 months. The mean VAS score decreased from 6.8 to 4.9 after surgery ($p<0.01$), fifty percent of patients were satisfied with surgical results. Upper extremity function improved significantly ($p=0.001$). Neuroma patients had a significantly lower quality of life compared to a normal population. Patients that were employed during surgery demonstrated a greater decrease in VAS score than patients that were unemployed ($p<0.05$). The VAS scores after diagnostic nerve block were predictive of post-operative VAS scores ($p=0.05$). Furthermore, smoking was significantly related to worse outcome (RR 2.06, $p<0.05$). The results could lead to improved patient selection and treatment strategies.

Chapter 8: General Discussion

In the discussion, results from previous chapters were used to answer the research questions posed in the introduction. Using these answers, we propose a general treatment strategy for painful neuromas in the upper extremity:

Patients presenting to any clinician with complaints suspect of neuroma pain not responding to desensitization or adjuvant pain control should be referred to a Plastic/Hand Surgeon without delay, to assess the possibilities for surgical treatment. The diagnosis of neuroma pain can be made with a thorough medical history and physical examination. If the diagnosis remains unclear, a high resolution US examination of the suspected nerve(s) should be performed. To assess central centralization processes, damage to multiple nerves and the role of neighboring nerves in transmitting pain signals, a diagnostic block of the nerve(s) possibly involved should be performed. Patients with no or little pain reduction following this diagnostic block should not undergo surgical neuroma treatment. Patients should be properly informed about the expected effects of surgical treatment. They should be encouraged to focus on activity and employment instead of their symptoms. Smoking should be strongly discouraged. It seems unlikely that symptoms of cold intolerance are improved by denervation of the injured nerve. When a patient is found eligible for surgical neuroma treatment, effort should be made to perform the procedure without great delay. During surgery, the neuroma is excised and the nerve end placed preferably into a sufficiently large, well vascularized muscle without large excursions. In case of an overlapping sensory pattern of adjacent nerves, these are neurectomized to decrease post-operative hyperalgesia. Furthermore, it is important to acknowledge that neuropathic pain management requires a personalized approach, for individual patients.

During the Decade of Pain Control and Research there has been an enormous increase in knowledge concerning chronic neuropathic pain and its treatment options. To ensure best medical practice, clinicians should continue to familiarize themselves with this rapidly progressing field of research.

Samenvatting (Summary in Dutch)

Hoofdstuk 1: Inleiding

De grote invloed van chronische pijn op de volksgezondheid wordt weerspiegeld door de verklaring van het huidige decennium (2001 - 2011) als het "Decennium van pijnbestrijding en het pijnonderzoek", door het Congres van de Verenigde Staten. Neuropathische pijn wordt beschouwd als een zeer hardnekkige chronische pijn, welke vaak ondergediagnosticeerd en onderbehandeld wordt. Ongeveer 3-5% van alle patiënten met perifere zenuwschade ontwikkelen een symptomatisch neuroom. Symptomatische neuromen veroorzaken intense spontane pijn met een brandend, schietend of elektrisch karakter, verlaagde pijndrempels (hyperalgesie) en pijn bij lichte aanraking (allodynie). Patiënten met een pijnlijk neuroom raken hierdoor vaak ernstig geïnvalideerd.

Een neuroom wordt gevormd door de combinatie van regeneratie van zenuwvezels en overmatige verbindweefseling, resulterend in een kluwen zenuwvezels verstrikt in littekenweefsel. De diagnose wordt meestal gesteld op basis van de anamnese en het lichamelijk onderzoek, inclusief de test van Tinel en een diagnostische zenuwblokkade. Patiënten met een pijnlijk neuroom vormen een groep die moeilijk te behandelen is. Er zijn veel verschillende behandelmethoden voorgesteld, maar geen van deze is volledig effectief gebleken in het verschaffen van complete pijnverlichting.

Doelstelling en onderzoeksvragen

Het doel van dit proefschrift was om te onderzoeken waarom veel patiënten met een pijnlijk neuroom onvoldoende pijnverlichting ervaren na chirurgische neuroombehandeling, en om de optimale strategie voor de chirurgische behandeling en preventie van chronische pijn in neuroompatiënten te onderzoeken. In dit proefschrift werden de volgende onderzoeksvragen gesteld:

- Wat zijn belangrijke prognostische factoren voor onvoldoende pijnverlichting?
- Kunnen we echografie gebruiken voor de diagnose en lokalisatie van neuromen in de bovenste extremiteit?
- Wat is de diagnostische waarde van de tijdelijke perifere zenuwblokkade?
- Kan hyperalgesie in stand worden gehouden door de geleiding van pijn via aangrenzende zenuwen en hoe kunnen we deze hyperalgesie behandelen?
- Welke zijn de belangrijkste uitkomstmaten in het onderzoek naar perifere neuropathische pijn?
- Wat is de meest effectieve strategie voor de behandeling van pijn in neuroompatiënten?

Hoofdstuk 2: Onvoldoende pijnverlichting na chirurgische neuroombehandeling

Patiënt-specifieke prognostische factoren die onvoldoende pijnverlichting na chirurgische neuroombehandeling voorspellen, kunnen van belang zijn om verschillende patiënten een gepaste behandeling aan te bieden. We hebben een literatuurstudie uitgevoerd om deze prognostische factoren te evalueren. Via een geautomatiseerde bibliografische database (PubMed Medline) werden 14 cohort studies geïdentificeerd die mogelijke prognostische factoren onderzochten. De factoren die de mate van postoperatieve pijn lijken te voorspellen zijn: neuromen van de sensibele tak van de nervus radialis en digitale zenuwen, het 'discrete zenuw-syndroom', een arbeidsongeschiktheidsuitkering, aan het werk zijn, een lopende juridische beroepszaak, de duur van de pijn en het aantal eerder doorgemaakte operaties.

In patiënten met chronische neuropathische pijn vinden veranderingen in het centrale zenuwstelsel plaats, onder andere in het ruggenmerg en de somatosensorische cortex. Deze veranderingen kunnen ook een rol spelen bij het instandhouden van neuroompijn.

Hoofdstuk 3: Diagnostische echografie van cutane zenuwtakken

Echografie is een niet-invasieve, kosteneffectieve en eenvoudig te gebruiken techniek welke kan worden gebruikt om perifere zenuwen te identificeren. Echter, met de huidige resolutie van echo-apparatuur, met frequenties van 5-20 MHz, is het niet mogelijk om de kleine cutane takken van de nervus medianus, ulnaris, radialis en digitale zenuwen nauwkeurig en gedetailleerd af te beelden. En juist deze zenuwen zijn vaak betrokken bij neuroomvorming in de bovenste extremiteit. Recente ontwikkelingen hebben het mogelijk gemaakt om ultrageluidsfrequenties van meer dan 80 MHz te bereiken. Dit gaat gepaard met een zeer hoge resolutie. In onze studie vergeleken we het VisualSonics Vevo 770-systeem, uitgerust met 15-82.5 MHz transducers, met een klinisch veelgebruikt 5-12 MHz echosysteem, op de beeldvorming van perifere zenuwen in twee kadaverarmen en twee gezonde proefpersonen. Met het Vevo 770-systeem was het mogelijk de individuele fascikels van de n. medianus weer te geven. Het systeem was bovendien in staat om de kleine cutane zenuwen in de hand en pols nauwkeurig te identificeren. Hoge resolutie echografie zou in de toekomst kunnen worden gebruikt voor de diagnose, lokalisatie en de follow-up van neuropathieën en zenuwletsels.

Hoofdstuk 4: Koude intolerantie in chirurgisch behandelde neuroompatiënten

Koude intolerantie, of thermale hyperalgesie, is een veelvoorkomend lange termijn gevolg van zenuwletsel in de bovenste extremiteit. Koude intolerantie wordt gedefinieerd als abnormale pijn van de hand en vingers na blootstelling aan lichte of matige koude, met of zonder verkleuring, gevoelloosheid, zwakte of stijfheid. Koude-intolerantie kan patiënten ernstig aantasten in hun werk en vrijetijdsbesteding. Het onderzoek had als doel om de prevalentie en ernst van koude intolerantie bij patiënten met een neuroom in de bovenste extremiteit te onderzoeken, evenals de verbetering van symptomen na chirurgische neuroombehandeling. De 'cold intolerance symptom severity' (CISS), de 'visual analogue scale' (VAS) en de 'disabilities of the arm, shoulder and hand' (DASH) vragenlijsten werden ingevuld door 33 patiënten, allen operatief behandeld voor neuroompijn in de bovenste extremiteit. De follow-up vragenlijsten werden ingevuld door 30 van deze patiënten, na een gemiddelde follow-up tijd van 24 maanden. We vonden een prevalentie van koude intolerantie van 91% vóór operatie. Na operatie nam de ernst van koude intolerantie niet af. Dit terwijl de hoeveelheid spontane pijn na operatie wel significant was gedaald. Verder vonden we dat de CISS score onafhankelijk was van de duur van de pijn en de follow-up periode.

Hoofdstuk 5: 'De genadeloze' sensibele tak van de nervus radialis

De gevoeligheid van sensibele tak van de nervus radialis ('sensory branch of the radial nerve' of SBRN) voor het ontwikkelen van neuropathische pijn na trauma is welbekend. Het bereiken van voldoende pijnverlichting blijft uiterst moeilijk voor deze zenuw. Deze studie evalueerde verschillende chirurgische behandelstrategieën voor neuropathische pijn veroorzaakt door beschadigingen of adhesies van de SBRN. Operatielijsten werden doorzocht naar patiënten met SBRN neuralgie. Patiëntfactoren werden verzameld uit medische dossiers. Ook het effect van de pre-operatieve diagnostische zenuwblokkade werd bepaald. De uitkomsten waren patiënttevredenheid en afname in pijn zoals gescoord met de 'numerical rating scale' (NRS). Negenenveertig patiënten ondergingen 34 neurolyses en 49 denervaties van de SBRN. Meerdere zenuwen die de dorsoradiale pols innerveren werden behandeld, inbegrepen de n. interosseus posterior (PIN) en de laterale antebrachiale cutane zenuw (LABCN). Negenentwintig patiënten waren tevreden met het resultaat van de behandeling (59%). De mediane NRS pijnscore daalde spectaculair van 7,5 naar 2,5 ($p<0,001$). Denervaties van de SBRN met het begraven van het zenuwuiteinde in de m. brachioradialis waren significant vaker succesvol in het behalen van een goede

patiënttevredenheid ten opzichte van het begraven van de zenuw elders (p=0,04). PIN en LABCN neurectomieën gaven ook voldoende pijnverlichting. Een kleinere afname in pijnscore en lagere slagingspercentages werden gevonden in patiënten geopereerd na een weinig effectieve diagnostische zenuwblokkade.

Hoofdstuk 6: Determinanten van patiënttevredenheid

Er is een toenemende vraag naar onderzoek over relatie tussen patiënttevredenheid en relevante klinische uitkomstmaten. Het 'Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials' (IMMPACT) heeft 6 belangrijke uitkomsten aanbevolen bij onderzoek naar chronische pijn. Deze 6 uitkomsten zijn (I) pijn; (II) lichamelijk functioneren; (III) emotioneel functioneren; (IV) verbetering en tevredenheid met de behandeling; (V) andere symptomen en bijwerkingen tijdens de behandeling, en (VI) patiëntfactoren. Het doel van deze studie was het vinden van de optimale set uitkomstmaten voor de patiënttevredenheid na chirurgische behandeling van neuropathische pijn veroorzaakt door perifere zenuwschade. Vierendertig patiënten, chirurgisch behandeld voor de neuroompijn in de bovenste extremiteit, werden prospectief gevolgd. Gevalideerde vragenlijsten over de belangrijkste uitkomstmaten van chronische pijn werden pre-en postoperatief ingevuld, waaronder de VAS, McGill Pain Questionnaire (MPQ), DASH, Short Form-36 (SF-36), Symptom Checklist-90 (SCL-90), Tampa Schaal van Kinesiofobie (TSK) en de CISS. Drempelwaarden waarden voor klinisch en statistisch betekeningsvolle verandering werden berekend met behulp van de 'reliable change index' (RCI) en de 'clinical significant change' (CSC) waardes. Uitkomsten werden vergeleken tussen de tevreden en ontevreden patiëntengroepen. De belangrijkste uitkomstmaten bleken te zijn: (I) pijn, (II) lichamelijk functioneren en (V) andere symptomen. Er was geen relatie tussen (III) emotioneel functioneren en patiënttevredenheid. De VAS voor pijn was de belangrijkste uitkomst voor patiënttevredenheid, en een daling van ten minste 3 punten of een score lager dan 2 punten op de VAS bleek een relevante verandering in pijn weer te geven. De mate van de pijn die door neuroompatiënten als draaglijk werd beschouwd, veranderde niet na de behandeling.

Hoofdstuk 7: Chirurgische behandeling van neuroompijn

We hebben een prospectieve follow-up studie uitgevoerd, om het succes van de chirurgische behandeling van neuroompijn te evalueren en prognostische factoren te bestuderen. De primaire uitkomstmaten waren patiënttevredenheid en pijn(afname) gescoord met de VAS. Secundaire uitkomstmaten waren handfunctie, kwaliteit van

het leven en symptomen van psychopathologie. VAS scores na de diagnostische zenuwblokkade werden voor de ingreep gedocumenteerd op de polikliniek. Chirurgische behandeling bestond uit resectie van het neuroom en zo mogelijk zenuwreconstructie of het proximaal begraven van de betrokken sensibele zenuw in spier of bot. Vierendertig patiënten werden geïncludeerd, met een gemiddelde follow-up tijd van 25 maanden. De gemiddelde VAS score daalde van 6,8 naar 4,9 na operatie ($p<0,01$), 50% van de patiënten was tevreden met de chirurgische resultaten. De handfunctie verbeterde aanzienlijk ($p=0,001$). Wel hadden neuroompatiënten een significant lagere kwaliteit van leven in vergelijking met een normale populatie. Patiënten die nog werkten toonden een grotere afname in de VAS-score dan patiënten die werkeloos waren ($p<0,05$). VAS scores na diagnostische zenuwblokkade waren voorspellend voor de postoperatieve VAS scores ($p=0,05$). Verder was roken significant gerelateerd aan een slechtere uitkomst (Relatief Risico van 2,06; $p<0,05$). De resultaten van dit onderzoek kunnen leiden tot een betere selectie van patiënten en therapeutische strategieën.

Hoofdstuk 8: Algemene Discussie

In de discussie worden de in de inleiding gestelde onderzoeksvragen beantwoord en wordt een algemene strategie voor de behandeling van pijnlijke neuromen in de bovenste extremiteit voorgesteld:

Een patiënt die zich presenteert met klachten welke duiden op neuroompijn en niet reageert op desensibilisatie of adjuvante pijnbestrijding moet worden doorverwezen naar een Plastisch (Hand) Chirurg om de mogelijkheden voor chirurgische behandeling te beoordelen. De diagnose neuroompijn kan worden gemaakt op basis van de anamnese en het lichamelijk onderzoek. Als de diagnose onduidelijk blijft, kan een echo-onderzoek uitkomst bieden. Om te beoordelen of er sprake is van centrale sensitisatie processen, schade aan meerdere zenuwen, of naburige zenuwen die de pijnsignalen doorgeven, moet een diagnostische blokkade van mogelijk betrokken zenuw(en) worden uitgevoerd. Alleen patiënten met een aanzienlijke pijnvermindering na deze diagnostische blok zijn geïndiceerd voor een chirurgische neuroombehandeling. Tevens dienen deze patiënten goed te worden geïnformeerd over de verwachte effecten van de chirurgische behandeling. Zij moeten worden aangemoedigd om zich te concentreren op (werk)activiteiten in plaats van hun symptomen en beperkingen. Roken moet sterk worden ontmoedigd. Wanneer een patiënt in aanmerking komt voor chirurgische neuroombehandeling, moet ernaar worden gestreefd binnen een jaar na het ontstaan van de klachten te opereren. Tijdens de operatie wordt het neuroom geëxcideerd en het zenuwuiteinde bij voorkeur begraven in een voldoende grote, goed doorbloede spier, zonder grote bewegingsexcursies. In het geval van een overlappend

sensibel patroon met aangrenzende zenuwen, kunnen deze worden doorgnomen om de kans op post-operatieve hyperalgesie te verkleinen. Verder is het belangrijk te erkennen dat bij de behandeling van neuropathische pijn een persoonsgerichte aanpak nodig is, gericht op individuele patiënten.

Gedurende het decennium van de pijnbestrijding en het pijnonderzoek is er een enorme toename geweest in kennis over chronische neuropathische pijn en haar behandelopties. Om een goede kwaliteit van zorg te behouden, moeten artsen zich vertrouwd blijven maken met dit snel vorderende onderzoek.

Appendices

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Curriculum Vitae

Annemieke Stokvis was born in Delft, the Netherlands, on November 6th, 1983. After secondary school at the Grotius College Delft, she started Medical School at the Rotterdam Erasmus University in 2002. During her medical training, she worked as a student-assistant at the Emergency Room and the SkillsLab of the Erasmus Medical Center. She was also an active member of the Medical Faculty Student Association (MFVR). In 2004 she was asked to participate in the Master of Science in Clinical Epidemiology program, provided by the Netherlands Institute for Health Sciences (Nihes). She assisted in a study performed by Prof.dr. Ewout Steyerberg, for the departments of Public Health and Gastroenterology of the Erasmus MC. After this, she moved to the Department of Plastic and Reconstructive Surgery. In 2005, she started up a new research project on the surgical management of painful neuromas, under supervision of Dr. Henk Coert and Dr. Han van Neck. She participated in the 2006 Harvard School of Public Health Summer Session, in Boston, USA. That year she also represented the Erasmus University as a team member in the Dutch University Quiz (VARA), broadcasted on national television. In July 2007 she graduated as a M.Sc. in Clinical Epidemiology and received the Nihes Award for Best Research Paper. During her senior internship, her affinity for General Practice became decisively clear. She graduated Medical School in April 2009, Cum Laude. After that, she continued her research project at the Department of Plastic and Reconstructive Surgery as a Ph.D. student, with Prof.Dr. S.E.R. Hovius as her promotor. She presented her research at multiple national and international conferences. September 1st, 2010 she started her General Practice training at the Erasmus MC.

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PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD student: Drs. A. Stokvis	PhD period: 2005-2010
Erasmus MC Department:	Promotor: Prof.dr. S.E.R. Hovius
Plastic & Reconstructive Surgery	Supervisors: Dr. J.H. Coert, Dr. J.W.
Research School: Nihes	van Neck

1. PhD training

	Year	Workload
Research skills		
- Statistics courses *(M.Sc.)*	2004-2006	13 ECTS
- Methodology courses *(M.Sc.)*	2004-2006	18 ECTS
- Analysis of Repeated Measurements *(Ph.D.)*	2010	1.9 ECTS
In-depth courses		
- Society & Health *(M.Sc.)*	2006	2 ECTS
Presentations		
- NVvH spring conference, Zwolle	2009	4 hours
- NVvH fall conference, Amsterdam	2009	4 hours
- ECSAPS, Rotterdam	2009	5 hours
- ESPRAS, Rhodes, Greece *(1 oral and 1 poster)*	2009	8 hours
- Research Lecture, Dept. of Neurology	2010	3 hours
- ASPN, Boca Raton, Florida, USA *(2 oral)*	2010	10 hours
- AAHS, Boca Raton, Florida, USA *(2 posters)*	2010	6 hours
International conferences		
- ESPRAS, Rhodes, Greece	2009	1 ECTS
- AAHS, Boca Raton, Florida, USA	2010	1 ECTS
- ASPN, Boca Raton, Florida, USA	2010	1 ECTS
Seminars and workshops		
- Nihes Seminars *(M.Sc.)*	2006	6 hours
- ESSER Course, Rotterdam	2009	½ ECTS
- Epidemiology Symposium, Erasmus MC	2009	8 hours
- CPO Autumn Symposium, Erasmus MC	2009	8 hours

2. Teaching activities

	Year	Workload
Lecturing 3rd year Medical Students		
- Nerve and tendon injury	2010	4 hours
- Anatomy of the upper extremity	2010	9 hours
Supervising Master's theses		
- Methodological and statistical support	2009-2010	12 hours