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Prevalence of post-traumatic neuropathic pain after digital nerve repair and finger amputation

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KEYWORDS

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Summary *Introduction:* Post-traumatic neuropathic pain is a major factor affecting the quality of life after finger trauma and is reported with considerable variance in the literature. This can partially be attributed to the different methods of determining neuropathic pain. The Douleur Neuropathique 4 (DN4) has been validated to be a reliable and non-invasive tool to assess the presence of neuropathic pain. This study investigated the prevalence of neuropathic pain after finger amputation or digital nerve repair using the DN4 questionnaire.

Methods: Patients with finger amputation or digital nerve repair were identified between 2011 and 2018 at our institution. After a minimal follow-up of 12 months, the short form DN4 (S-DN4) was used to assess neuropathic pain.

Results: A total of 120 patients were included: 50 patients with 91 digital amputations and 70 patients with 87 fingers with digital nerve repair. In the amputation group, 32% of the patients had pain, and 18% had neuropathic pain. In the digital nerve repair group, 38% of the patients had pain, and 14% had neuropathic pain.

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Secondly, of patient-, trauma-, and treatment-specific factors, only the time between trauma and surgery had a significant negative influence on the prevalence of neuropathic pain in patients with digital nerve repair.

Conclusion: This study shows that persistent pain and neuropathic pain are common after finger trauma with nerve damage. One of the significant prognostic factors in developing neuropathic pain is treatment delay between trauma and time of digital nerve repair, which is of major clinical relevance for surgical planning of these injuries.

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Introduction

Chronic pain is a major health problem, and one of the most important chronic pain syndromes is post-traumatic neuropathic pain.¹ Post-traumatic neuropathic pain patients suffer from spontaneous pain in the absence of noxious stimuli. Besides the pain, the sensory disturbances are typical for neuropathic pain. These can vary between loss or gain or even combinations. Allodynia (the experience of pain evoked by normally non-painful mechanical and/or thermal stimuli) and/or hyperalgesia (exaggerated pain experience induced by noxious stimuli) are expressions of pain. Cold intolerance and thermal allodynia or hyperalgesia are commonly reported following after nerve trauma.²⁻⁴ These debilitating neuropathic pain symptoms usually have profound negative effects on the quality of life, complicate rehabilitation, and preclude return to work, with no predictable curative therapies at hand.^{1,5}

The overall prevalence of neuropathic pain in the general population is 7% to 10%.^{6,7} However, after hand trauma, it is not completely clear. There are huge variations in the reports on the prevalence of different common injuries of the hand, such as digital nerve injury and finger amputation. After nerve repair, an incidence of 4.6% of post-traumatic neuropathic pain is described with a range of 0% to 20%,⁸ and for finger amputations, an incidence of 3% to 30% has been reported. Cold intolerance has a range of 2% to 53% after nerve repair and 4 to 8% for finger amputations.⁹⁻¹¹ Additionally, the dogma that digital nerves should be repaired to prevent post-traumatic neuropathic pain has been questioned lately, because lack of evidence and substantial differences in results.^{8,12} One of the reasons for this large difference may be the variety of methods that are used to determine neuropathic pain. Objective and subjective measures are combined or interchanged.⁸ In some reports, reoperation rates are used as a threshold to estimate the prevalence of neuropathic pain after hand trauma.⁹ As a result, the true prevalence of post-traumatic neuropathic pain remains unclear.

Several tools have been developed to quantify neuropathic pain, both subjectively and objectively.¹³ However, the pain remains a subjective symptom, and a simple questionnaire with high accuracy to determine neuropathic pain would be of considerable value in clinical practice. The Douleur Neuropathique 4 questionnaire (DN4) was developed by the French Neuropathic Pain Group in 2005 and is capable of determining the presence of neuropathic pain with high sensitivity and specificity.¹⁴ The DN4 has been

translated and validated in more than 15 languages and has been used as a reliable tool to diagnose neuropathic pain.¹⁵

The aim of the current study is to investigate the prevalence of post-traumatic neuropathic pain following digital nerve repair and finger amputation using the DN4 and examine which factors are associated with more neuropathic pain on the DN4.

Methods

Study design

This study has a cross-sectional design following the STROBE statement.¹⁶ All patients consented to the use of their data in this study. The medical ethics review board approved the study protocol (MEC-2019-0834).

Patients

Patients treated with digital nerve repair or finger amputation in the department of plastic and hand surgery of our institution between 2011 and 2018 were invited to participate in this study.

The medical records of patients with digital nerve trauma and digital amputation were screened for eligibility. The possibly eligible patients were identified with their electronically stored diagnosis treatment codes; furthermore, a selection on digital nerve repair or finger amputation was performed. Data were collected between March and June 2020. In this period, patients were asked to participate via mail, e-mail, or telephone.

Patients with amputations at DIP, PIP, or MCP levels were included. Patients were excluded if the amputation was more distal than the distal interphalangeal joint or more proximal than the metacarpal phalangeal joint. Other exclusion criteria were as follows: younger than 18 years, non-traumatic amputation, such as amputation for the treatment of malignancy, vascular disease or diabetic neuropathy, use of grafts during the repair, and a follow-up of less than one year.

Additional data that were collected consisted of age, BMI, diabetes, tobacco dependence, treatment side, hand dominance and type of trauma; sharp or crush, time between trauma and treatment, and additional pain treatment during follow-up, such as a visit to a pain physician or further operation.

Table 1 Questions of the Douleur Neuropathique 4 short form. Every question answered with yes yields one score point.

DOES THE PAIN HAS ONE OR MORE OF THE FOLLOWING CHARACTERISTICS?	Yes/No
Burning PAINFUL COLD ELECTRIC SHOCKS	
Is the pain associated with one or more of the following symptoms in the same area?	
TINGLING PINS AND NEEDLES NUMBNESS ITCHING	Yes/No

Neuropathic pain questionnaire

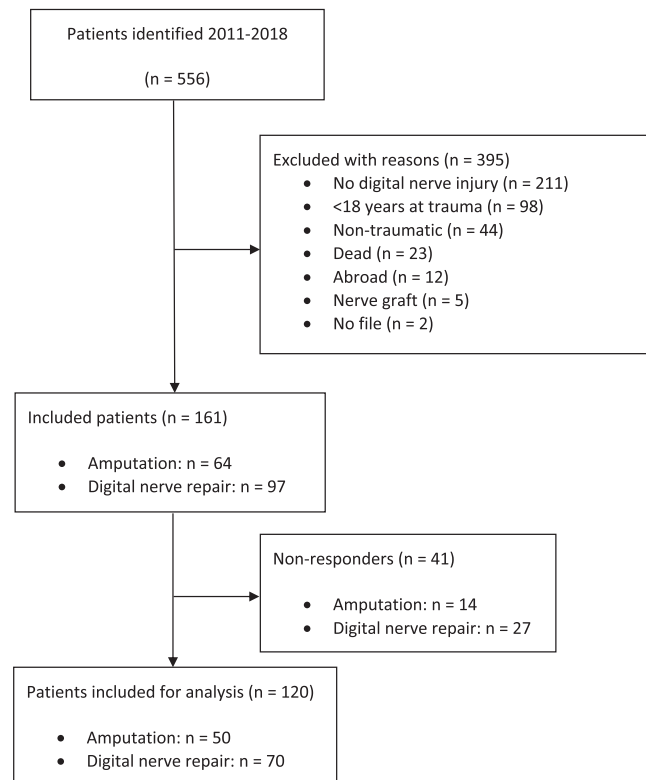
The prevalence of neuropathic pain was determined using the short form DN4 (S-DN4). Patients were requested to complete the S-DN4 questionnaire for every injured finger. This questionnaire focuses on neuropathic pain with seven questions, see [Table 1](#). In comparison to the complete DN4, the S-DN4 has the advantage of only asking questions that can be answered remotely. The full DN4 also contains tests for which the patient must be present at the examination. Each question that is answered with yes counts as one point. The total score is 7, with 0 meaning no pain. Following a validation by Van Seventer et al., a score of 4 or more is considered positive.¹⁷ When patients scored less than 4 points on the DN4, we scored them to be “non-neuropathic pain” patients. Any score of 4 or more points was classified as “neuropathic pain.”

Statistics

Since S-DN4 scores did not differ between fingers within one single patient, we analyzed on a patient level. A multivariate regression analysis was used to assess the association between different variables on the continuous outcome of the S-DN4-score, separately for each group. Because of sample size restrictions, we were unable to use the same number of variables for each group. The amputation group variables were trauma mechanism (sharp or blunt), time between trauma and surgery, hand dominance, gender, and age. In the nerve repair group, the variables were trauma mechanism (sharp or blunt), time between trauma and surgery, hand dominance, gender, age, smoking, and diabetes. A linear regression analysis was performed to assess the association of time between trauma and surgery on the S-DN4 score in the nerve repair group. Analysis was performed using R statistical computing. A p-value of smaller than 0.05 was considered statistically significant.

Results

The search on diagnosis-treatment codes resulted in 556 patients treated between 2011 and 2018 at our institution. Of this group, 161 patients were treated with digital nerve repair or finger amputation and eligible for the study. A

**Figure 1** Flowchart of eligible patients.

detailed flowchart is depicted in [Figure 1](#). Forty-one patients (25%) could not be reached or failed to respond. A total of 120 patients were included in the analysis. Fifty patients with 91 digital amputations and 70 patients with 87 fingers with a digital nerve repair completed the questionnaire. The mean follow-up period was 44 months (range 22-97) in the amputation group and 55 months (range 18-109) in the digital nerve repair group. Patient characteristics of the two groups are shown in [Table 2](#).

In the amputation group, 32% of patients reported pain on the S-DN4. The prevalence of neuropathic pain (score > 4) was 18%, see [Figure 2](#). In the digital nerve group, 38% of patients reported pain; however, the prevalence of neuropathic pain was 14%, see [Figure 3](#).

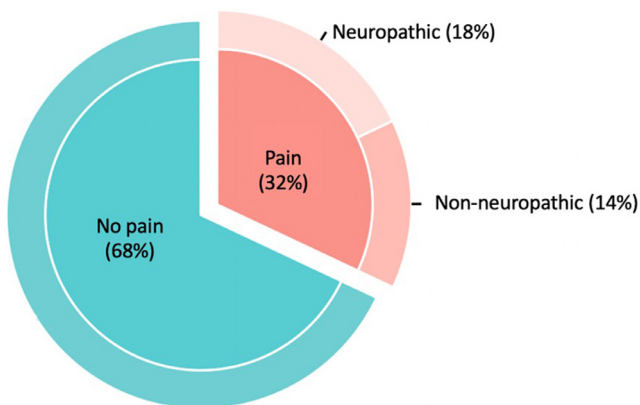
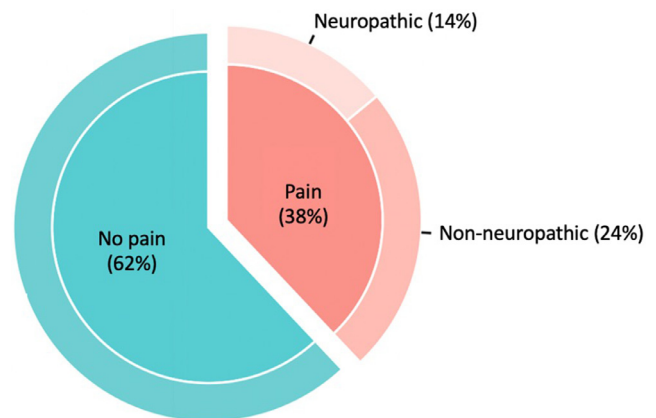
The regression analysis showed that in the amputation group, none of the tested variables was associated with

Table 2 Characteristics of patients with digital amputation and digital nerve repair.

	AMPUTATION	DIGITAL NERVE REPAIR
N	50	70
AGE AT SURGERY, MEAN (SD)	48 (17)	40 (16)
BMI, MEAN (SD)	26 (4)	25 (5)
SEX, MALE%	98	67
DOMINANT SIDE TREATED, YES%	58	46
SMOKING, YES%	36	36
DIABETES, YES%	10	24
AFFECTED FINGERS, MEDIAN [INTERQUARTILE RANGE]	1 [1-2]	1 [1-1]
DAYS TO SURGERY, MEDIAN [INTERQUARTILE RANGE]	0 [0-0]	4 [2-6]
MEAN FOLLOW-UP, MONTHS (RANGE)	44 (25-97)	55 (18-109)
TRAUMA, SHARP%	54	91
DN4 SCORE, MEDIAN [INTERQUARTILE RANGE]	0 [0-2]	0 [0-2.75]
DN4 SCORE \geq 4, YES%	18	14

Table 3 Amputation group: the results of multivariate regression of factors possibly affecting the S-DN4 score .

VARIABLE	BETA COEFFICIENT	P-VALUE	95%CI
Sharp trauma	-0,84	0,19	[-2.1 - 0.4]
Time to surgery	-0,00	0,88	[-0.1 - 0]
Dominant side affected	0,48	0,45	[-0.8 - 1.7]
Male gender	0,59	0,79	[-3.8 - 4.9]
age	0,00	0,70	[0 - 0]

**Figure 2** The prevalence of pain in the amputation group. The total group consisted out of 50 patients. Patients with pain that scored 4 or more points on the S-DN4 are further classified to have neuropathic pain.**Figure 3** The prevalence of pain in the digital nerve repair group. The total group consisted out of 70 patients. Patients with pain that scored 4 or more points on the S-DN4 are further classified to have neuropathic pain.

the outcome on the S-DN4 (see Table 3). The same analysis in the digital nerve repair group showed that the time from trauma and treatment had a statistically significant relation (see Table 4). In Figure 4, the prediction of S-DN4 scores based on the time to treatment is shown. The majority of patients with a nerve repair are treated within the first week after the trauma. Patients operated with a delay of more than three weeks after trauma have significantly higher DN4 scores.

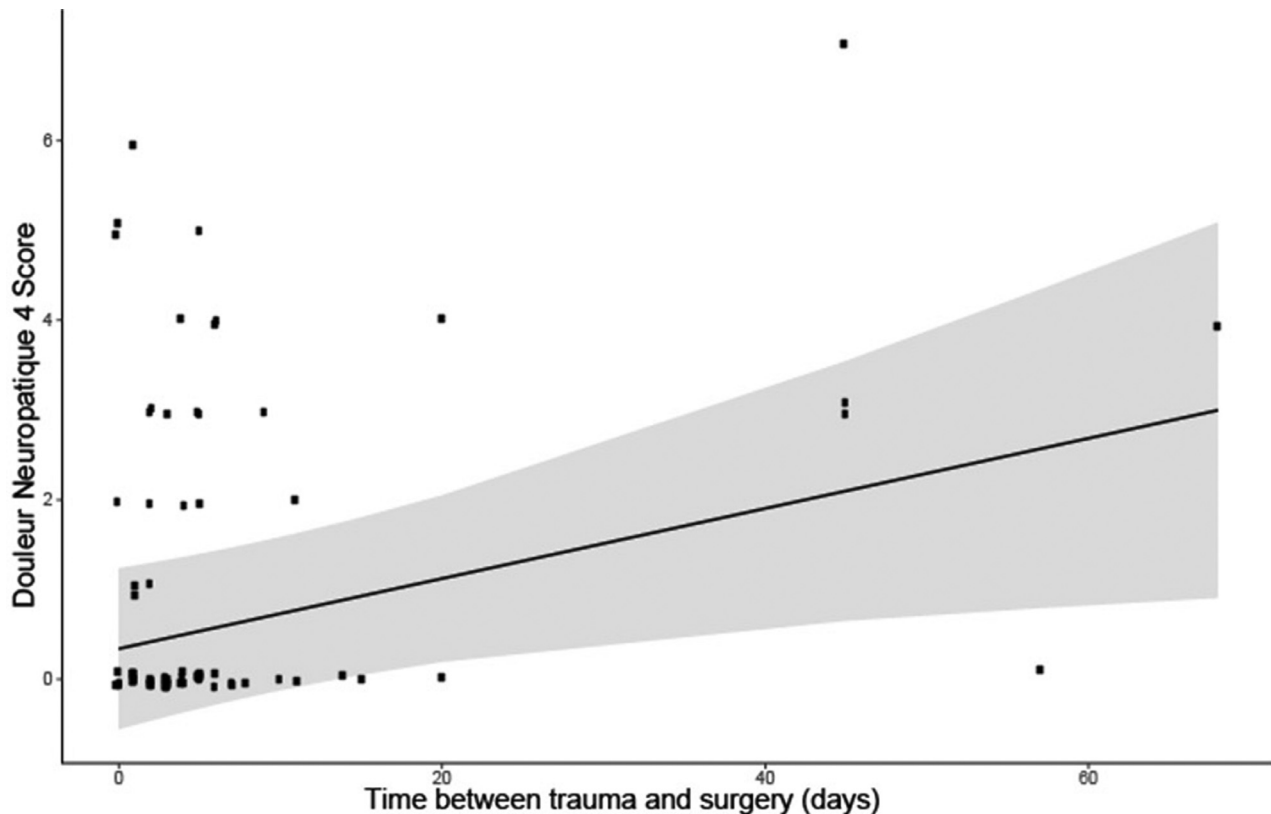
In the amputation group, 25% ($n = 4$) of patients that stated to have pain during this study, previously visited the outpatient clinic with pain complaints and got referred to a pain physician. One patient with pain had a re-operation.

The indication was the removal of a nail remnant. Of the patients that now stated not to have pain, 17% ($n = 6$) had previously been referred to the pain managing specialist and 12% ($n = 4$) had a re-operation. The indications were removing nail remnant (50%), osteosynthesis material (25%), and a bone spur (25%).

In the digital nerve repair group, 11% ($n = 3$) of patients that stated to have pain during this study previously visited the outpatient clinic with pain complaints and got referred to a pain managing specialist. Seven percent ($n = 2$) of the patients with pain had a re-operation. The indications for the operation were the removal of osteosynthesis material

Table 4 Digital nerve repair group: the results of multivariate regression of factors possibly affecting the S-DN4 score .

VARIABLE	BETA COEFFICIENT	P-VALUE	95%CI
Sharp trauma	-0,26	0,76	[-1.9 - 1.4]
Time to surgery	0,04	0,02	[0 - 0.1]
Dominant side affected	0,80	0,08	[-0.1 - 1.7]
Male gender	0,38	0,43	[-0.6 - 1.3]
Age	-0,00	0,58	[0 - 0]
Smoking	-0,80	0,23	[-2.1 - 0.5]
Diabetes	0,88	0,23	[-0.5 - 2.3]

**Figure 4** Association of time between trauma and surgery and the S-DN4 score in the digital nerve repair group. Linear regression, beta coefficient: 0.04 $p = 0.02$ 95% CI [0-0.1].

(50%) and the removal of a bone spur (50%). Of the patients in this group that now stated not to have pain, no one had previously been referred to the pain managing specialist. Five percent ($n = 2$) of these patients had a re-operation. The indications were the removal of the osteosynthesis material.

Discussion

The current study investigated the prevalence of post-traumatic neuropathic pain after digital nerve repair and finger amputation using the S-DN4. In the amputation group, 32% had complaints of pain, and 18% fulfilled the criteria of neuropathic pain as scored with the S-DN4. Additionally, the digital nerve repair group depicted 38% with any type of pain and 14% with neuropathic pain. In the amputation group, 25% with pain symptoms were referred to the pain

physician, and from the digital nerve group, 11% got a referral. Lastly, the digital nerve repair group showed that the time from trauma to treatment had a statistically significant relation in the respect that patient treated with a delay of more than 3 weeks showed a significant higher score on the S-DN4.

In this study, the observed prevalence of neuropathic pain after finger amputation is 18% and 14% in the digital nerve repair group. This prevalence is higher in comparison with most other studies.^{9,10} An explanation for this difference could be the method of determining the presence of neuropathic pain. These studies reported neuropathic pain based on patients symptoms,¹⁰ or whether the patient had received either medical treatment or surgery for neuropathic pain.⁹ In the present study, all patients with digital nerve repair or traumatic amputation were included. Although they qualified as having neuropathic pain based on the S-DN4, many have not found it debilitating enough to

seek further treatment for their pain. When patients were asked whether they still had pain in the amputation stump or repaired finger, 32% and 38% answered yes, respectively. In the majority of patients, this did not qualify as neuropathic pain. This pain could be classified as chronic pain as it persisted longer than 3 months.¹⁸

Van der Avoort et al. found a post-traumatic neuropathic pain incidence of 7.8% in the finger amputation group as compared to 1% in the digital nerve repair group.⁹ However, a major limitation of the study design is the categorization of neuropathic pain based solely on operative findings of a neuroma. The current study has shown that a majority of the patients had non-surgical management of the pain by a multi-disciplinary pain team, which was almost 25% in the amputation group and 11% in the digital nerve repair group. Other studies show a vast discrepancy in neuropathic pain after finger amputations ranging from 3% to 30%, in digital nerve repair group 0% to 30%, and for cold intolerance even ranging from 2% to 53%.⁸ The possible reason for these findings is the lack of uniformity in definition and classification of neuropathic pain making any comparison invalid due to the heterogeneity of the definition.

The International Association for the Study of Pain (IASP) defines neuropathic pain as abnormal pain arising as a direct consequence of a lesion or disease affecting the somatosensory system and is also a different kind of entity that requires other treatment regimens as compared to chronic pain.¹⁹ Additionally, neuropathic pain is a complex diagnosis that may contain components of mechanical or thermal allodynia and hyperalgesia. Cold intolerance is one of the most known symptoms after nerve injury, which is a thermal hyperalgesia and/or allodynia.²⁻⁴ However, in most studies, only a binary outcome (yes or no) is used to assess for cold intolerance, which can mean unpleasant feeling in the cold. The failure to utilize validated instruments measuring different grades of cold intolerance like the Cold Intolerance Symptom Severity (CISS) questionnaire has been a limiting factor for evidence synthesis in neuropathic pain.^{20,21} Another factor has been the failure to use standardized methods for quantifying neuropathic pain in hand surgery studies. The Quantitative Sensory Testing (QST) is a validated quantitative instrument that uses different components to determine the grade of mechanical and thermal types of neuropathic pain with high accuracy.²² However, its limitation is low usability with time-consuming execution in the field. The S-DN4 has been shown to be a quick and easy method to determine neuropathic pain and has been validated in more than 15 languages and is now one of the gold standards in diagnosing neuropathic pain among the pain management community.¹⁵

The etiology of chronic pain is complex, probably multifactorial, with a number of uncertainties.²³ According to Zhou et al., demonstrated factors such as diabetes, smoking, and alcohol consumptions were associated with neuropathic pain after peripheral nerve injury.²⁴ Vlot et al. showed that age, mechanism of injury, and multiple digit involvement were associated with neuropathic pain development after digital amputation.¹⁰ Surgeon's experience level has also been shown to be a prognostic factor.²⁵ In the amputations group of the current study, the mechanism of injury (sharp or blunt), time between trauma and surgery, hand dominance, gender, or age were not significant factors

to impact the neuropathic pain outcome. Vlot et al. had a larger sample of 1083 patients, possibly enabling smaller differences to be measured.¹⁰

In this study, the repair of digital nerves cohort showed that only time between trauma and surgery showed a significant impact on neuropathic pain. In other studies, age has been shown to interfere with nerve regeneration and developing neuropathic pain after nerve injury,²⁶⁻²⁸ though not consistently.²⁵ Although widely reported that age has a significant impact on the outcome after nerve injury,^{29,30} our study did not demonstrate a measurable impact in terms of neuropathic pain development. An explanation could be that our population mainly consists of men with a limited age distribution. Gender has not been found to influence nerve neuropathic pain.³¹ This study excluded patients where grafts were used during the repair of the digital nerve. These patients were excluded because the use of auto or allografts could interfere with the outcome.³²

Besides the peripheral element of the etiology of nerve repair after nerve injury, there is a central component. Minutes after the transection of a peripheral nerve, cortical remapping occurs.^{33,34} In this process, the loss of afferent input leads to a takeover by adjacent cortical areas. Studies show that this cortical remapping should be considered during rehabilitation to improve functional outcomes.³⁵

Recent reviews have shown that the level of evidence to support the repair of the digital nerve is weak.^{8,12} Dunlop et al. showed that there was an inconsistency in the reported post-traumatic neuropathic pain, which ranged from 0% to 53 cold intolerance was included as a form of neuropathic pain.⁸ Only 8 of 30 papers included in their systematic review reported neuroma complication rates after nerve repair. In addition, no reported prognostic factors to influence the presence of neuropathic pain were demonstrated. However, in the current study, the only prognostic factor for influencing neuropathic pain is the time between the trauma and digital nerve repair. To our knowledge, this is the first study that has investigated time to treatment as a prognostic factor using a validated neuropathic pain questionnaire. A systematic review and meta-analyses on prognostic factors for sensory recovery after digital nerve repair showed that performing repair or reconstruction within 15 days of injury correlated with improved sensory recovery.³⁶ Another meta-analysis has also shown that delay of nerve injury treatment significantly influences prognosis.³¹ A possible explanation may be that after nerve injury, there is fibrosis and scarring of the nerve endings and that delayed treatment hampers uncomplicated tensionless coaptation of nerve endings.

The concept of repairing a nerve to reconnect it with their end organs allowing for an active physiological regeneration to reduce neuropathic pain is also a paradigm shift in the current existing symptomatic neuroma treatments.³⁷ An example of that is targeted muscle reinnervation (TMR) which actively directs regenerating axons into a distal adjacent motor branch. Dumanian et al. showed in a randomized controlled trial that patients during an amputation treated with TMR had a significant lower incidence of neuropathic pain as compared to standard care.³⁸ The results of the NEON study - a randomized controlled trial to investigate the efficacy of digital nerve repair - are expected to provide level 2 evidence for digital nerve repair.³⁹ In this study,

the data were analyzed as per patient and not anatomy as it has shown patients with multiple affected fingers reported the same outcomes per finger. Chronic pain and specifically neuropathic pain have a high impact on the quality of life,^{1,5} independent of the number of affected fingers. The fact that patients with multiple finger injuries, either have neuropathic pain in all fingers or in no fingers, supports the possibility of a genetic predisposition.⁴⁰

Limitations and strengths

The design of this study has limitations. Although this study reported the prevalence of neuropathic pain after finger trauma, it did not explore in detail the impact of the pain on the activities in daily life. Further prospective studies should incorporate the use of DN4 and measure the impact with validated patient-centered quality of life instruments, such as the EQ-5D and the Michigan Hand Questionnaire.^{41,42} There is added value of combining the objectively measured neuropathic pain and patient-reported outcomes. For this study, we used the S-DN4. The study of Van Seventer et al. validated this questionnaire for the Dutch language.¹⁷ They found that the sensitivity of the original DN4 was 75%, and the specificity was 79%. For the S-DN4, they found the sensitivity was 74%, and the specificity was 79% when a cut-off value of 4 points was used. The difference between the short form and the S-DN4 is a set of 3 questions a physician has to answer based on physical examination. The three examinations are hypoesthesia to touch, secondly to pinprick, and lastly if brushing was painful. End neuromas formed from transection or amputation have other symptomatic characteristics as opposed to neuroma-in-continuity as a result of primary nerve repair and in light of these perspectives is the S-DN4 useful in highlighting possible causation or just in determining a subgroup that would benefit from further clinical screening.⁴³

In this study, the inclusion criteria were inclusive to ensure adequate numbers for recruitment. In this context, we estimated recalling patients for physical examination would outweigh the gain in sensitivity and specificity. Therefore, no physically measured outcomes are reported in this study. However, this study had a high response rate in our population. In spite of historical evidence, the hand injury population has poor compliance for follow-up. Also, the use of a reliable and well-utilized instrument to assess the prevalence of neuropathic pain in this study added to its strength.

Conclusion

This is the first report of the use of a validated neuropathic questionnaire (S-DN4) to screen for the prevalence of neuropathic pain after finger amputation and digital nerve repair. Post-traumatic pain and chronic pain occur frequently after finger amputations and digital nerve repair, which may have a substantial impact on quality of life. Treatment delay of longer than three weeks has a significant higher chance in developing neuropathic pain, which may modify current clinical practice; however, a prospective randomized trial should be conducted to verify this conclusion.

Ethical approval

Ethical approval was obtained. The medical ethics review board approved the study protocol (MEC-2019-0834).

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

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