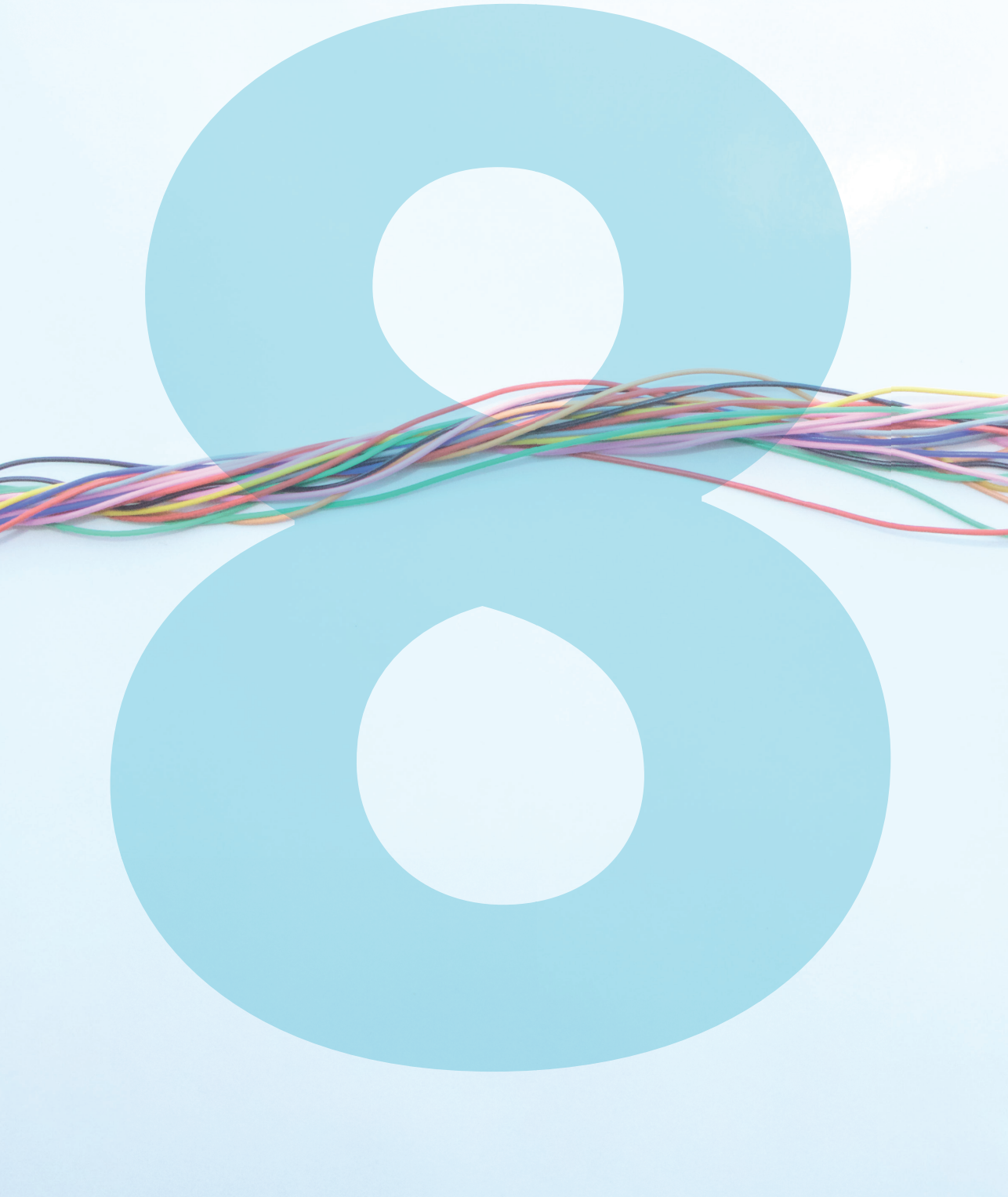
Peripheral nerve damage : diagnosis and prediction of recovery

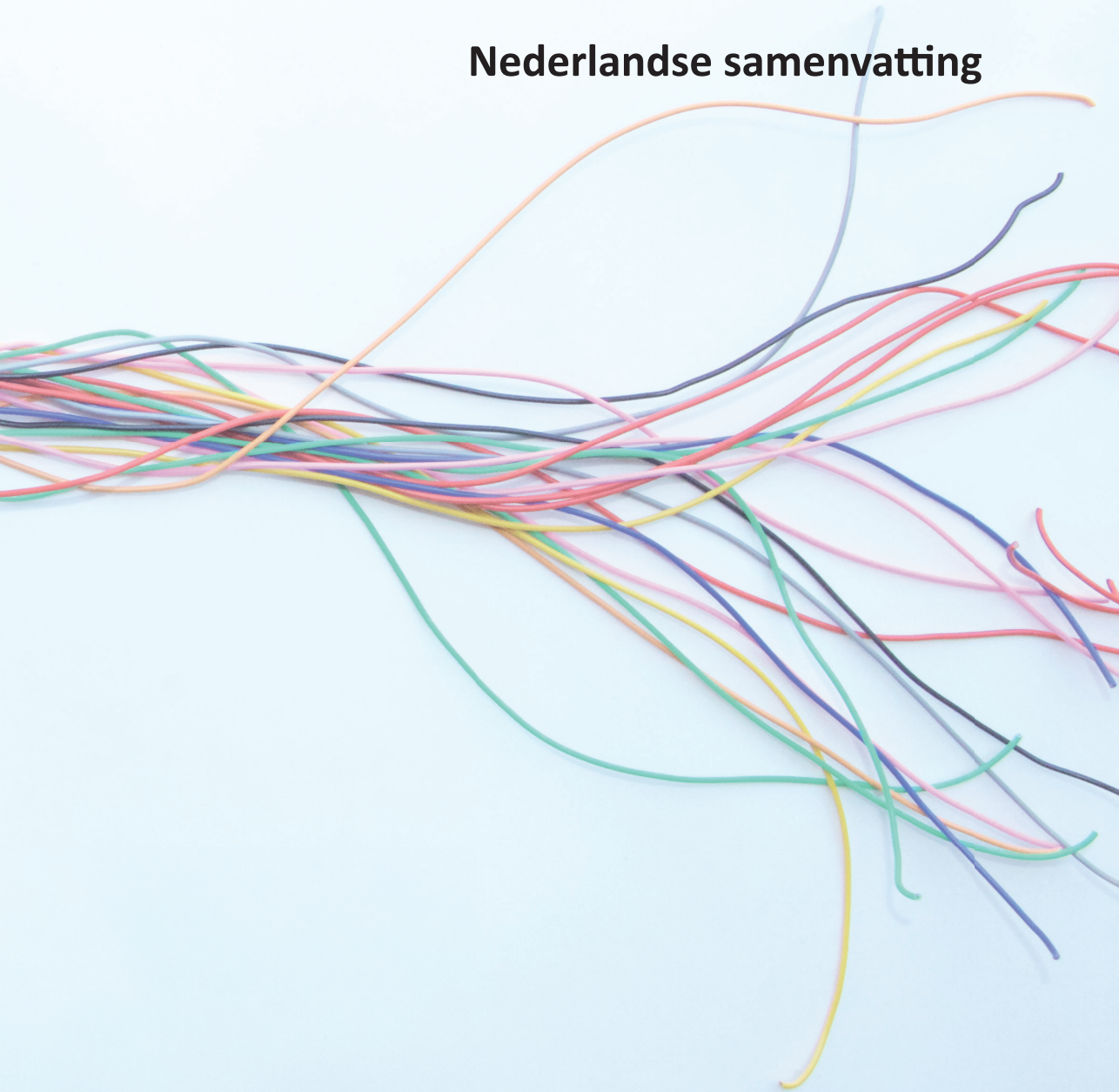
Datema, M.



Summary and discussion

& future perspectives

Nederlandse samenvatting



SUMMARY

This thesis contains studies concerning diagnostic aspects of peripheral nerve damage and the prediction of its recovery. We focussed on diffuse nerve pathology as in symmetrical, distal polyneuropathies and local nerve compression syndromes, and on possible combinations of both.

In **chapter 2** we studied the diagnostic value of Neuropads® and water immersion skin wrinkling (WISW) in 35 patients with small fibre neuropathy (SFN) and 61 age- and sex-matched healthy controls. We adopted a clinical definition of SFN as the gold standard for this study. The Neuropad® is an adhesive pad impregnated with a blue cobalt II chloride solution that changes color from blue to pink when in contact with water (sweat). This pad measures sudomotor function, one expression of autonomic control that is peripherally exerted through small nerve fibres around the sweat glands. The Neuropad was applied on both feet on the metatarsal head of the first toe of both feet and photographs of the pad were taken at 10 and 15 minutes after applying. The test was considered abnormal when the Neuropad remained blue in one or both feet. Sensitivity of the Neuropad after 10 minutes was 49% and specificity 77%. After 15 minutes sensitivity lowered to 29% with an increase of specificity to 93%.

Wrinkling after water immersion results from local vasoconstriction, influenced by vasomotor function via small, autonomic nerve fibres.[1] WISW was performed by placing the hands of the subjects in a bowl of warm water (starting with 40° Celsius) for 30 minutes. Photographs of the pulp of digit II-V were taken and scored. The images did not allow scoring in more than three categories as in previous studies when observed in real life.[1,2] In our study, the observers assigned a score of 0,5 (minimal wrinkling) as soon as any visible change had occurred in the pulp of one or more digits. In this study problems occurred in some aged patients, who already had wrinkled hands before water immersion, although only a few patients had considerable wrinkling of the pulpa. We tried to correct for this issue by instructing the observers to only assign a positive score for this subjects when the wrinkling had increased. We analyzed results of both hands: when one or both hands showed absence of wrinkling the test was considered abnormal. In this way, sensitivity of WISW was 66% and specificity 70%.

We also calculated the diagnostic yield of the combination of the Neuropad and WISW. When both tests had to be abnormal for the combination to be abnormal, the sensitivity of the combination was 23% and its specificity was 97%. Neuropad® has a high specificity when applied for 15 minutes and can thus be used in daily practice to confirm SFN. Water immersion skin wrinkling has a moderate sensitivity and specificity. Combining these two tests did not raise diagnostic accuracy much, but in case both tests are abnormal, the diagnosis SFN is quite certain. Clearly the Neuropad and WISW have favourable features: they are cheap, non-invasive, easy accessible, not time consuming and do not require a high degree of patient cooperation or specialized personnel.

Chapter 3 also describes the diagnostic value of a practical, cheap, and thus potentially attractive test for peripheral nerve damage. Tinel's sign generally refers to the phenomenon

that paraesthesiae can be provoked by percussion of the tip of regenerating axons in the course of a damaged nerve. The presence of Tinel's sign is considered mandatory before a new treatment for painful diabetic and idiopathic polyneuropathy is performed, namely decompressive nerve surgery at several sites in the legs. These sites are the common peroneal nerve at the fibular neck, the deep peroneal nerve over the dorsum of the ankle and the tibial nerve below the medial malleolus.[3] The underlying hypothesis is that patients with polyneuropathy are more vulnerable to nerve entrapment at sites of known anatomic narrowing.[4,5] The presence of Tinel's sign at these sites is used as a criterion for this 'triple decompression surgery'.[4,6-8] However, except for the study of Lee and Dellon there appear to be no other studies that systematically evaluated the diagnostic yield of the Tinel sign for compression neuropathies in the legs.[9]

We studied the diagnostic value of Tinel's sign in 91 patients who were referred for nerve conduction studies (NCS) because of suspicion of a peripheral nerve disorder in the legs. We assigned patients to one of three categories, based on the diagnoses reached by the neurologist treating the patient: subjects without nerve pathology, patients with distal symmetrical peripheral neuropathy (DSPN) and patients with other nerve pathology. The presence or absence of Tinel's sign was systematically assessed by a trained technician at the fibular neck, over the dorsum of the ankle and below the medial malleolus and at one additional site, i.e. below the lateral malleolus overlying the sural nerve. This nerve is not known to be involved in a specific compression neuropathy, but is involved in diabetic and other types of neuropathy. Tinel's sign below the lateral malleolus overlying the sural nerve was present 30/182 times (16.5%) and this prevalence was similar to that at the other three sites. Furthermore, Tinel's sign did not occur more often in patients with electrophysiologically shown nerve entrapment, than in subjects without nerve entrapment. Sensitivity of Tinel's sign was 30% and specificity was 86% for entrapment of the peroneal nerve at the fibular neck, and 44% and 75% respectively for the peroneal nerve at the dorsum of the ankle. Sensitivity was 17% and specificity was 81% for the tibial nerve at the medial malleolus. Sensitivity and specificity for Tinel's sign in diagnosing entrapment neuropathies in the subgroup of patients with DSPN was comparable to the values found in the total group of subjects. The receiver operating characteristics (ROC) analysis of the Tinel sum score showed that the sign was not able to discriminate patients without nerve pathology from patients with any nerve pathology, or from those with DSPN. Hence we concluded that Tinel's sign occurs commonly and did not indicate nerve entrapment in a heterogeneous group of patients nor in a subgroup of patients with DSPN. Tinel's sign did not signify the presence of any nerve pathology, nor the presence of DSPN.

We investigated leg nerves because Tinel's sign is currently used as a criterion for triple decompression surgery in the legs. In **chapter 4** we briefly reviewed the evidence for this practice, which mainly consists of large observational cohort studies.[9-15] The results of these cohort studies are consistent in that approximately 80% of patients report improvements in pain and sensation suggesting that triple decompression surgery could be of tremendous benefit to patients with diabetic peripheral neuropathy (DPN).[12,14,15] We found these results not convincingly enough for several reasons. Firstly, none of these observational studies included a randomized control group, so the magnitude of the placebo effect cannot be estimated. This is especially relevant given that many of outcome measures concerned

subjective sensory or pain-related domains. Furthermore, it is known that surgery in general can lead to a strong placebo effect.[16] Secondly, neuropathic pain caused by DPN tends to fluctuate even without treatment,[17] resulting in regression to the mean, as patients are most likely to undergo surgery when their symptoms are particularly severe. Thirdly, clinical improvements may have been caused at least partially by improved glycemic control, as participation in a trial may have also have resulted in changes in medical diabetes care.

The current treatment strategy used by proponents of decompressive surgery consists of a sequence of steps that includes examination for the presence of Tinel's sign as an indicator of nerve entrapment. To rigorously determine whether surgery is of benefit to patients with diabetic neuropathy, we believe that each of these steps merits a thorough analysis, followed by a randomised blinded study on long-term outcome. As we found in chapter 3 that Tinel's sign is not useful as a first step, i.e. the diagnosis of nerve entrapment, the question arises whether the evidence for subsequent steps, i.e. decompressive surgery, is at present strong enough to base treatment decisions on, or whether such decisions should be postponed until confirmatory studies are available. We prefer the latter choice. From 2008-2013, a controlled, randomized, double-blinded, prospective study on this surgery was performed at the University of Texas Southwestern Medical Center. [18] Publication of the results is, four years after completion of this study, still eagerly anticipated.

In **chapter 5** we critically reviewed the results of another surgical procedure for the treatment of nerve entrapment; revision surgery after failure of neurolysis for ulnar nerve entrapment. We retrospectively describe the outcome of 26 consecutive patients who all underwent anterior subcutaneous transposition after failed neurolysis. This procedure was performed by one experienced nerve surgeon using the same technique in every patient. Because of this homogeneity, it is unlikely that differences in outcome were the result of differences in treatment. Data were collected by systematic telephonic surveys. Pain and/or tingling improved in 35%, motor function in 23% and sensory disturbances in 19% of all patients. Improvement in at least one of the three clinical modalities was found in 58%. However, a deterioration in one of the three modalities was noted in 46% of patients. On the patient satisfaction scale, 62% reported good or excellent outcome. Patients with a good/excellent outcome were a median of 11 years younger than patients with a fair/poor outcome. Other factors that affect outcome may play a role, but they remain unidentified. Remarkably, among the satisfied patients were several whose initial symptoms only partly resolved or even deteriorated. A partial explanation for this contradiction might be the fact that cessation of progression of symptoms can be perceived as a desirable result. However, the modest results of secondary subcutaneous transposition for ulnar nerve entrapment should be mentioned when counselling patients with failed neurolysis to manage patients' expectations. Patients, especially those who are elderly, might even consider not undergoing a secondary procedure.

The last two chapters concerned decompression of the median nerve in carpal tunnel syndrome (CTS). From March 2012 until July 2014 we prospectively collected data on 227 adult patients undergoing primary decompression surgery for electrophysiologically proven CTS. NCS were performed preoperatively in all patients and comprised motor and sensory nerve conduction tests according to the CTS guidelines of the Dutch Society of

Neurology.[19] Patients filled out questionnaires with the aid of trained research nurses at three points in time: within two weeks prior to surgery, three months post-surgery and one year post-surgery. CTS symptoms were measured using the first part of the Boston Carpal Tunnel Questionnaire (BCTQ) which includes 11 questions concerning severity, frequency and duration of pain and tingling at night and daytime, numbness and loss of dexterity.[20] Depressive symptoms were quantified using the Center for Epidemiologic Studies Depression Scale (CES-D), a commonly used validated questionnaire based on the diagnostic and statistical manual of mental disorders, fifth edition (DSM-V).[21] The presence and severity of scar pain and proximal palm pain were measured using the Palmar Pain Scale, a scale developed and validated specifically for pain after CTR.[22] The first item of this scale concerns the severity of pain at the scar and/or the proximal palm and the second item concerns activity limitations because of this pain. We calculated the sum of these items resulting in a sum score ranged 0 to 9. Finally, to determine whether patients were satisfied with the results of surgery, we asked whether their symptoms had been relieved on a seven-point scale from: 1) completely resolved to 7) symptoms have become much worse. Open CTR was performed by one of three experienced neurosurgeons applying the same technique under local anaesthesia.[23] We used data of outcome after one year only because symptoms including palmar pain, continued to decrease from three to 12 months post surgery and we felt that the measurements at one year were therefore more likely to reflect an end stage than the measurements after three months.

In **chapter 6** we studied the relation between depression and outcome of carpal tunnel release (CTR). Twenty-three patients (11%) had a CES-D score of ≥16 indicating a clinically relevant depression.[24,25] Preoperatively, patients with depression had a higher, i.e. worse, BCTQ score than patients without depression: median 3.3 (interquartile range 2.6-3.5) vs 2.7 (2.3-3.1). After one year, depressed patients still had a higher BCTQ score: median 1.4 (1.2-2.1) vs 1.1 (1.0-1.6), had more palmar pain (73% palmar pain score >0 vs 42%) and were less satisfied (55% not completely resolved vs 33%). However, multivariable analysis showed that depression was not an independent predictor of residual CTS symptoms or satisfaction after one year. The small difference of 0.3 points in postoperative BCTQ score between depressed and non-depressed patients we found, has little or no clinical importance. Furthermore, it was not related to depression and was partially due to the somewhat higher BCTQ score at baseline. Interestingly, CES-D decreased from baseline to one year by a median of 2 points. This correlated with the decrease in BCTQ score (Pearson correlation 0.268). The causality of this relation is unknown. A possible explanation for this decrease could be a more postoperative well-being due to the relief of symptoms such as pain and tingling. Another reason might be the fact that the CES-D includes one question on sleep. Many patients with CTS wake up from their symptoms at night. As surgery relieves these nocturnal complaints in the majority of patients, the decrease in CES-D scores postoperatively is likely to be partially explained by a lower score assigned to this 'sleep question'.

In **chapter 7** we focused on differences in symptom profile between patients of 70 years and older (n = 75) and those younger than 70 years (n = 152), before and after CTR. The total preoperative BCTQ score did not differ between the two age groups and there were no significant differences on the scores on the 11 individual items of the BCTQ preoperatively either. Nevertheless, the absence of a measurable SNAP of the median nerve occurred

almost twice as often in the older than in the younger patients, indicating far more severe NCS abnormalities in the elderly. One year after CTR, the total BCTQ differed significantly between the age groups, but the difference of 0.2 points was small. More interestingly, the older group exhibited more residual numbness and paraesthesiae one year after CTR. The outcome of CTR in terms of the occurrence of palmar pain and the patient satisfaction did not differ significantly between the age groups. We discussed several possible explanations for these findings at the end of this chapter.

DISCUSSION AND FUTURE PERSPECTIVES

Diagnosis

Every study on diagnostic accuracy of a test needs a gold standard, used to establish the presence or absence of the target condition, which it should ideally do with 100% probability. Unfortunately, diagnostic tests with 100% sensitivity and 100% specificity are rare if they exist at all, and the reason to search for a new test is often because the tests that are in use have shortcomings. Using one of these suboptimal tests as the reference standard leads to incorrect labelling of some test results as either 'normal' or 'abnormal', which will probably lead to under- or overestimating the diagnostic yield of the new test. A pathological tissue diagnosis or post-mortem investigation is often considered the true gold standard. In the past decade, a large role has been assigned to measuring intra-epidermal nerve fibre density (IENFD) in skin biopsies in patients with SFN.[26-29] It is indeed attractive to adopt abnormal IENFD as the gold standard for SFN, as the technique directly assesses what is supposed to be the key mechanism in SFN: a decrease or abnormal morphology of the small nerve fibres in the skin. Therefore, critics might say that we should have used abnormal IENFD as the gold standard in chapter 2. However, apart from the practical issues that come along with pathological investigations, it is not always correct to accept the results of the pathologist as unequivocally true. A study in 67 SFN patients found a sensitivity of skin biopsy of 88%, which is high, but 12% of patients identified as having SFN by clinical examination and quantitative sensory testing (QST) had a normal IENFD.[30] A study on IENFD in patients with diabetes mellitus with normal NCS showed a decrease in IENFD in both patients wíth and wíthout neuropathic symptoms.[31] This raises questions about the correlation between neuropathic symptoms and IENFD, although this correlation was found to be good by others.[29,30] In other words, the density and morphology of intra-epidermal nerve fibres does not necessarily tell us something about the function of this fibres, while their function, or actually dysfunction, is what causes symptoms. An alternative gold standard could be a clinical definition of SFN, as we used in chapter 2. This seems justified since we are interested in tests that correctly identify the group of patients with typical SFN signs and symptoms. On the contrary; why should one look for a new test if the clinical diagnosis is considered the gold standard? We feel that , like in many matters, taking the best of both would be the answer here. The proposed definition of 'definite SFN' from the Diabetic Neuropathy Study Group of 2009[32] that combines clinical criteria and abnormal IENFD or QST might be the best candidate for the gold standard in future studies on diagnostic options for SFN.

When considering the diagnostic value of Tinel's sign in the legs in chapter 3, the choice of the gold standard was almost even harder. The only other study reporting sensitivity and

specificity for Tinel's sign used success of decompressive surgery, defined as improvement of pain and/or recovery of sensibility, as the gold standard.[9] Instead, our aim was to examine an assumption that is implicit in the rationale for decompressive surgery, being that Tinel's sign can accurately identify nerve entrapment. Therefore we chose another commonly used indicator of nerve entrapment; NCS. A drop in conduction velocity or amplitude across the fibular head is a widely accepted, reliable indicator for entrapment of the common peroneal nerve.[33] Nerve conduction criteria for tibial nerve entrapment and deep peroneal nerve entrapment at the dorsum of the ankle are less well defined. Most authors chose to classify these nerve compression syndromes, if at all, using clinical criteria.[34-36] However, it can be difficult to distinguish symptoms of nerve compression from those caused by DSPN, as both conditions can result in burning pain and paraesthesiae in the toes and the sole of the foot. We attempted to circumvent this problem by using published quantitative abnormality thresholds. Sensory NCS are considered to be more sensitive for medial tarsal tunnel syndrome by some,[36] but a prolonged tibial nerve DML was increased in 74% of patients with a clinical diagnosis of tarsal tunnel syndrome.[37] This is the parameter used in our study. Similarly, one study and several case reports described prolonged DML of the peroneal nerve in all patients with a compression of the deep peroneal nerve on the dorsum of the ankle ('anterior tarsal tunnel syndrome').[35,36,38,39] We therefore believe that the DML prolongation used here is a valid approach to establish nerve entrapment, perhaps not for individual diagnostic use, but certainly for a group-wise statistical approach.

It has been argued that Tinel's sign is particularly useful in patients with such severe diabetic neuropathy that there is no response on standard NCS.[4] Whether this is relevant is unclear as NCS was not used or mentioned as a criterion for surgery in published studies on decompressive surgery.[3,6-8] However, we acknowledge that the use of routine NCS for superimposed nerve entrapment; i.e. nerve entrapment in addition to a known polyneuropathy, is not ideal, especially not for entrapment of the tibial nerve in the tarsal tunnel. The use of additional sensory measurements of smaller nerve branches as the medial and lateral plantar nerves might have been a better gold standard here, although this comes along with some practical issues. Nevertheless, the frequent occurrence of Tinel's sign over the sural nerve is, on itself, convincing evidence that the sign is a common occurrence and should therefore not be interpreted as a proof of nerve entrapment. To settle the issue we suggest a randomized controlled, double-blinded trial on decompressive surgery for patients with painful DSPN. This trial should include patients with and without signs of nerve compression in the legs as measured with extensive NCS. The presence of Tinel's sign on the fibular head, dorsum of the foot and below the lateral malleolus may be assessed, but should not be an inclusion criterion. One leg should be treated with surgical decompression, the other leg with sham surgery, in such a way that patient, caretakers and observers of the outcome measures are blinded to treatment site. By this design, the patient serves as his/her own control. We calculated that a sample of 22 patients would suffice to resolve the issue (appendix chapter 4). Furthermore, in future studies, alternative diagnostic options to diagnose local nerve entrapment in the legs should be explored, such as the use of ultrasound or magnetic resonance neurography using diffuse tensor imaging (DTI) of nerves.[40]

Predicting recovery

One of the key issues in the work of a physician is choosing an appropriate therapy for each individual patient. Many factors contribute to the chance of success. Firstly, a correct diagnosis is an obvious prerequisite for successful treatment . This is not straightforward, as discussed above. Furthermore, the efficacy of a treatment is practically always based on the outcome of a group of patients with homogenous disease characteristics. Since every individual has its unique way of responding to an intervention, good results in a group are no guarantee for a good result in an individual. Therefore, predicting who will respond well to treatment and who will not, is often a challenge. Modern randomized controlled trials (RCTs) on new drugs often try to meet this shortcoming by performing analyses on subgroups of patients, based on age, gender or other patient characteristics. However, for most surgical interventions, no RCT's have been performed. The knowledge about its efficacy is based on many years of experience and on the data of observational studies.[41]

In our observational study on patients with failure of ulnar nerve decompression, we found a higher age in patients with a poor outcome after revision surgery, compared to patients with a good outcome (chapter 5). Unfortunately, no other factors contributing to outcome were identified in this study. A factor that may play an additional role in the results of secondary subcutaneous transposition, might be timing of surgical intervention. For patients with ulnar neuropathy at the elbow (UNE), usually three months of conservative treatment to wait for spontaneous recovery is advocated. It is not known what percentage of the patients who initially present with UNE will indeed recover after conservative treatment. For those who do not, earlier timing of surgery might have led to a better outcome of neurolysis, should earlier identification have been possible. The same reasoning holds for patients after primary neurolysis. It is not known how long a patient should wait after neurolysis for UNE to expect any recovery. It might be that if symptoms are not alleviated within weeks after neurolysis, a transposition should be performed at that time. At present, the interval between neurolysis and transposition is usually months to several years, during which the ulnar nerve might still be compressed. Naturally this ongoing compression is detrimental for the ulnar nerve and presumably effects outcome of transposition negatively. Although we did not find a significant difference in duration between the first procedure and secondary subcutaneous transposition, we still consider this to play a role. The interval between neurolysis and transposition in our patients ranged from 5-34 months. Following the hypothesis that intervention should be done within a short 'window of opportunity' i.e. weeks after failure of neurolysis, it is only logical that the results of secondary transposition after five months are no different from those after 34 months: the damage is already done. A future study on this subject should ideally be a randomized controlled trial with three treatment groups; 1) sham surgery; 2) subcutaneous transposition within 4 weeks of the first procedure and 3) subcutaneous transposition within 4-6 months after the first procedure. We feel that a sham procedure is justified here because the results of secondary transposition in the literature vary from moderate to good, and were only moderate in our homogeneous series of patients.

In our prospective study on 227 patients with CTS we concluded that there was no relation between depression and the results of CTR after one year. There is therefore no reason to be concerned about the success of CTR in depressed patients, or at least no less or more than in non-depressed patients. We added several other possible predictors of recovery after CTR in our multivariate analysis, in order to study their contribution to outcome after one year. We found only a small contribution of a higher preoperative symptom score and we were unfortunately not able to identify any other factors associated with outcome. The number of papers on this subject is large, but a review from 2010 emphasizes the fact that many of them have methodological flaws and that there is a need for well-designed prospective studies using agreed measures of outcome.[42] The authors were however certain that age, sex or weight of the patient were not related to outcome of CTR. We agree with the authors on these points and dare say that we conducted a prospective study with outcome measures that matter to patients, such as relief of symptoms and overall satisfaction, as they suggested.[42] Nevertheless, we did not find a major factor related to poor outcome of CTR either. We suggest that future studies should focus on new possible predictors, instead of the ones that already have been the subject of many studies. The diameter of the median nerve at the level of the carpal tunnel on ultrasound has been suggested as one such.[43] The radiological aspects of the nerve on DTI could provide more insight in the pathophysiology of CTS; i.e. more axonal damage versus more demyelination,[40] and could thereby possibly identify patients with a higher chance on success of CTR. Although it should be noted that this technique would be much too expensive to implement in daily care, at least in the near future. However, we propose the contrasting hypothesis that no single individual factor predicts the outcome of CTR reliable. If one existed, it would probably have been identified already, considering the high prevalence of CTS. An interplay of various intrinsic and extrinsic factors, that on their own do not determine the result of CTR, is more likely to influence CTR. Finally, innovations in the treatment of CTS should be further explored. A promising new technique is brief electrical stimulation of the median nerve directly after CTR which resulted in accelerated axonal regeneration in a small group of patients, compared to patients who only underwent CTR.[44,45] We look forward to hear the results of larger studies on the clinical effect of electrical stimulation in addition to CTR.

REFERENCES

1. Teoh HL, Chow A, Wilder-Smith EP. Skin wrinkling for diagnosing small fibre neuropathy: comparison with epidermal nerve density and sympathetic skin response. Journal of neurology, neurosurgery, and psychiatry 2008;79:835-7.

2. Wilder-Smith EP, Guo Y, Chow A. Stimulated skin wrinkling for predicting intraepidermal nerve fibre density. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2009;120:953-8.

3. Valdivia Valdivia JM, Weinand M, Maloney CT, Jr., Blount AL, Dellon AL. Surgical treatment of superimposed, lower extremity, peripheral nerve entrapments with diabetic and idiopathic neuropathy. Annals of plastic surgery 2013;70:675-9.

4. Dellon AL. Diabetic neuropathy: review of a surgical approach to restore sensation, relieve pain, and prevent ulceration and amputation. Foot & ankle international 2004;25:749-55.

5. Dellon AL, Mackinnon SE, Seiler WAt. Susceptibility of the diabetic nerve to chronic compression. Annals of plastic surgery 1988;20:117-9.

6. Aszmann OC, Kress KM, Dellon AL. Results of decompression of peripheral nerves in diabetics: a prospective, blinded study. Plastic and reconstructive surgery 2000;106:816-22.

7. Macare van Maurik JF, van Hal M, van Eijk RP, Kon M, Peters EJ. Value of surgical decompression of compressed nerves in the lower extremity in patients with painful diabetic neuropathy: a randomized controlled trial. Plastic and reconstructive surgery 2014;134:325-32.

8. Wood WA, Wood MA. Decompression of peripheral nerves for diabetic neuropathy in the lower extremity. The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons 2003;42:268-75.

9. Lee CH, Dellon AL. Prognostic ability of Tinel sign in determining outcome for decompression surgery in diabetic and nondiabetic neuropathy. Annals of plastic surgery 2004;53:523-7.

10. Dellon AL. Diabetic neuropathy: medical and surgical approaches. Clinics in podiatric medicine and surgery 2007;24:425-48, viii.

11. Dellon AL, Muse VL, Nickerson DS, et al. Prevention of ulceration, amputation, and reduction of hospitalization: outcomes of a prospective multicenter trial of tibial neurolysis in patients with diabetic neuropathy. Journal of reconstructive microsurgery 2012;28:241-6.

12. Dellon AL, Muse VL, Scott ND, et al. A positive Tinel sign as predictor of pain relief or sensory recovery after decompression of chronic tibial nerve compression in patients with diabetic neuropathy. Journal of reconstructive microsurgery 2012;28:235-40.

13. Liao C, Zhang W, Yang M, Ma Q, Li G, Zhong W. Surgical decompression of painful diabetic peripheral neuropathy: the role of pain distribution. PloS one 2014;9:e109827.

14. Valdivia JM, Dellon AL, Weinand ME, Maloney CT, Jr. Surgical treatment of peripheral neuropathy: outcomes from 100 consecutive decompressions. Journal of the American Podiatric Medical Association 2005;95:451-4.

15. Zhong W, Zhang W, Yang M, Li G, Ma Q, Yang X. Impact of diabetes mellitus duration on effect of lower extremity nerve decompression in 1,526 diabetic peripheral neuropathy patients. Acta neurochirurgica 2014;156:1329-33.

16. Dowrick AS, Bhandari M. Ethical issues in the design of randomized trials: to sham or not to sham. The Journal of bone and joint surgery American volume 2012;94 Suppl 1:7-10.

17. Young RJ, Ewing DJ, Clarke BF. Chronic and remitting painful diabetic polyneuropathy. Correlations with clinical features and subsequent changes in neurophysiology. Diabetes care 1988;11:34-40.

18. https://clinicaltrials.gov/ct2/show/study/NCT00703209)

19. Dutch Association of Neurology (Nederlandse Vereniging voor Neurologie N. Dutch Guideline - Diagnosis and treatment of carpal tunnel syndrome. 2005.

20. Levine DW, Simmons BP, Koris MJ, et al. A self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome. The Journal of bone and joint surgery American volume 1993;75:1585-92.

21. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Applied Psychological Measurement 1977;1:385-401.

22. Atroshi I, Lyren PE, Ornstein E, Gummesson C. The six-item CTS symptoms scale and palmar pain scale in carpal tunnel syndrome. The Journal of hand surgery 2011;36:788-94.

23. Bozentka DJ KB. Open Carpal Tunnel Release. Atlas of the Hand Clinics 2002;7:181-9.

24. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. Psychology and aging 1997;12:277-87.

25. Myers JK, Weissman MM. Use of a self-report symptom scale to detect depression in a community sample. The American journal of psychiatry 1980;137:1081-4.

26. Chan AC, Wilder-Smith EP. Small fiber neuropathy: Getting bigger! Muscle & nerve 2016;53:671-82.

27. Lauria G, Lombardi R. Small fiber neuropathy: is skin biopsy the holy grail? Current diabetes reports 2012;12:384-92.

28. Myers MI, Peltier AC. Uses of skin biopsy for sensory and autonomic nerve assessment. Current neurology and neuroscience reports 2013;13:323.

29. Sommer C, Lauria G. Skin biopsy in the management of peripheral neuropathy. The Lancet Neurology 2007;6:632-42.

30. Devigili G, Tugnoli V, Penza P, et al. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. Brain : a journal of neurology 2008;131:1912-25.

31. Loseth S, Stalberg E, Jorde R, Mellgren SI. Early diabetic neuropathy: thermal thresholds and intraepidermal nerve fibre density in patients with normal nerve conduction studies. Journal of neurology 2008;255:1197-202.

32. Tesfaye S, Boulton AJ, Dyck PJ, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes care 2010;33:2285-93.

33. van Dijk JG, Reenalda H, Bollen EL, den Heijer JC. Nerve conduction velocity to different muscles in peroneal pressure neuropathy. Electromyography and clinical neurophysiology 1991;31:145-50.

34. Ahmad M, Tsang K, Mackenney PJ, Adedapo AO. Tarsal tunnel syndrome: A literature review. Foot and ankle surgery : official journal of the European Society of Foot and Ankle Surgeons 2012;18:149-52.

35. Logullo F, Ganino C, Lupidi F, Perozzi C, Di Bella P, Provinciali L. Anterior tarsal tunnel syndrome: a misunderstood and a misleading entrapment neuropathy. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 2014;35:773-5.

36. Oh SJ. Neuropathies of the foot. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2007;118:954-80.

37. Mondelli M, Morana P, Padua L. An electrophysiological severity scale in tarsal tunnel syndrome. Acta neurologica Scandinavica 2004;109:284-9.

38. Andresen BL, Wertsch JJ, Stewart WA. Anterior tarsal tunnel syndrome. Archives of physical medicine and rehabilitation 1992;73:1112-7.

39. Borges LF, Hallett M, Selkoe DJ, Welch K. The anterior tarsal tunnel syndrome. Report of two cases. Journal of neurosurgery 1981;54:89-92.

40. Naraghi AM, Awdeh H, Wadhwa V, Andreisek G, Chhabra A. Diffusion tensor imaging of peripheral nerves. Seminars in musculoskeletal radiology 2015;19:191-200.

41. Reitsma AM, Moreno JD. Surgical research, an elusive entity. The American journal of bioethics : AJOB 2003;3:49-50.

42. Turner A, Kimble F, Gulyas K, Ball J. Can the outcome of open carpal tunnel release be predicted?: a review of the literature. ANZ journal of surgery 2010;80:50-4.

43. Marschall A, Ficjian A, Stradner MH, et al. The Value of Median Nerve Sonography as a Predictor for Short- and Long-Term Clinical Outcomes in Patients with Carpal Tunnel Syndrome: A Prospective Long-Term Follow-Up Study. PloS one 2016;11:e0162288.

44. Gordon T, Amirjani N, Edwards DC, Chan KM. Brief post-surgical electrical stimulation accelerates axon regeneration and muscle reinnervation without affecting the functional measures in carpal tunnel syndrome patients. Experimental neurology 2010;223:192-202.

45. Willand MP, Nguyen MA, Borschel GH, Gordon T. Electrical Stimulation to Promote Peripheral Nerve Regeneration. Neurorehabilitation and neural repair 2016;30:490-6.

LETSEL VAN PERIFERE ZENUWEN

DIAGNOSTIEK EN HET VOORSPELLEN VAN HERSTEL

Dit proefschrift rapporteert onderzoeken over het vaststellen van schade van perifere zenuwen en over het voorspellen van herstel daarvan. De onderzoeken waren gericht op diffuse zenuwschade in het kader van symmetrische distale polyneuropathieën, op lokale zenuwcompressiesyndromen en op mogelijke combinaties van beide.

In **hoofdstuk 2** onderzochten we de diagnostische waarde van Neuropads® en de huidrimpeltest bij 35 patiënten met een dunnevezelneuropathie (DVN) en 61 gezonde personen van overeenkomstige leeftijd en geslacht. We hanteerden een klinische definitie van DVN als een praktische goudstandaard. De Neuropad is in essentie een pleister, geïmpregneerd met een oplossing van kobaltblauwchloride, hetgeen van kleur van blauw naar roze verandert na contact met water, in dit geval zweet. De pleister meet hiermee de sudomotoriek, oftewel zweetfunctie, één van de functies van het autonome zenuwstelstel. Zweten wordt teweeggebracht door sympathische zenuwvezels die de zweetklieren innerveren. De Neuropad werd beiderzijds op de bal van de voet geplakt en na 10 en 15 minuten gefotografeerd. De test werd als afwijkend beschouwd indien de Neuropad niet verkleurde op één of beide voeten. Bij beoordeling na 10 minuten was de sensitiviteit 49% en de specificiteit 77%. Na 15 minuten nam de sensitiviteit af tot 29% maar steeg de specificiteit naar 93%.

Rimpeling van de huid na een onderdompeling in warm water ontstaat door lokale vasoconstrictie, beïnvloed door vasomotorische autonome zenuwvezels.[1] De huidrimpeltest werd uitgevoerd door de patiënten te vragen de handen gedurende 30 minuten in warm water te houden (watertemperatuur 40° Celsius bij aanvang). De mate van rimpeling van de vingertoppen van wijsvinger t/m pink werd beoordeeld op basis van foto's van de vingers. Op deze manier was een gradering in drie categorieën mogelijk, anders dan bij directe beoordeling.[1,2] Er ontstond een probleem bij de beoordeling van de vingers van sommige oudere patiënten, bij wie vóór de test ook al rimpels op de vingertoppen werden gezien. We hebben geprobeerd dit op te lossen door de beoordelaars te instrueren alleen een score toe te kennen als de rimpeling was toegenomen. We analyseerden de resultaten van beide handen: de test werd als afwijkend beschouwd wanneer één of beide handen geen rimpeling toonden. Dit leverde een sensitiviteit van de huidrimpeltest op van 66% en een specificiteit van 70%. We berekenden ook de diagnostische waarde van de combinatie van de Neuropad en de huidrimpeltest. Bij een afwijkende combinatie, in de zin dat beide testen afwijkend waren, was de sensitiviteit van de combinatie zoals verwacht lager dan de afzonderlijke testen, namelijk 23%, en steeg de specificiteit tot 97%.

De Neuropad heeft een hoge specificiteit bij beoordeling na 15 minuten en kan dus goed gebruikt worden om de diagnose DVN te bevestigen. De huidrimpeltest heeft een matige sensitiviteit en specificiteit. Het combineren van de testen resulteerde in slechts een geringe toename van de diagnostische precisie, maar als beide testen afwijkend zijn, is de diagnose DVN vrijwel zeker. In vergelijking met andere opties hebben de Neuropad en huidrimpeltest

de volgende voordelen: ze zijn goedkoop, niet-invasief, makkelijk toegankelijk, kosten weinig tijd, zijn makkelijk te beoordelen en berusten niet sterk op coöperatie van de patiënt.

Hoofdstuk 3 beschrijft eveneens de diagnostische waarde van een praktische, goedkope en daarmee aantrekkelijke test voor het vaststellen van perifere zenuwschade. Het teken van Tinel verwijst in het algemeen naar het fenomeen dat tikken of kloppen op het uiteinde van herstellende axonen in een beschadigde zenuw, tintelingen of een stroomgevoel kan opwekken. Het teken van Tinel heeft o.a. een plaats gekregen in het traject naar een nieuwe operatieve behandeling voor pijnlijke diabetische en idiopathische polyneuropathieën, die sinds het begin van deze eeuw toegepast wordt: decompressie van de zenuwen op verschillende plaatsen in de benen. Dit zijn de n. peroneus communis bij de hals van de fibula, de n. peroneus profundus op het proximale deel van de voetrug en de n. tibialis juist onder de mediale malleolus.[3] De onderliggende hypothese is dat de zenuwen van patiënten met polyneuropathie kwetsbaarder zijn voor beknelling op plekken die van nature anatomisch krap zijn.[4,5] De aanwezigheid van het teken van Tinel op deze plekken wordt gebruikt als criterium voor deze 'drievoudige decompressiechirurgie'.[4,6-8] Behoudens één onderzoek van Lee & Dellon, is ons geen onderzoek bekend waarin systematisch de diagnostische waarde van het teken van Tinel voor het bestaan van zenuwcompressie in de benen is onderzocht.[9]

Wij hebben dat verricht bij 91 patiënten, verwezen voor zenuwgeleidingsonderzoek wegens een mogelijke zenuwaandoening in de benen. Op basis van de uiteindelijke diagnose van de behandelend neuroloog, werden zij in drie categorieën verdeeld: personen zonder zenuwpathologie, patiënten met een distale symmetrische perifere neuropathie (DSPN) en patiënten met andere zenuwpathologie. Voor dit doel opgeleide laboranten beoordeelden systematisch de aan- of afwezigheid van het teken van Tinel op de genoemde drie plaatsen en op nog een vierde plek: juist onder de laterale malleolus, waar de n. suralis loopt. Deze zenuw is frequent aangedaan bij polyneuropathieën, maar er is geen zenuwcompressiesyndroom van de n. suralis bekend. Het teken van Tinel bleek 30 van de 182 keren aanwezig op deze plek, ongeveer even vaak als op de andere drie plekken. Verder was het teken van Tinel niet vaker aanwezig bij patiënten mét aangetoonde zenuwcompressie dan bij patiënten zónder zenuwcompressie. De sensitiviteit van het teken van Tinel voor compressie van de n. peroneus bij de fibulahals was 30% en de specificiteit 86%; voor de n. peroneus op de voetrug was dit 44% en 75% en voor de n. tibialis 17% en 81%. In de groep patiënten met DSPN waren deze waarden vergelijkbaar groot. De 'receiver operating characteristic'(ROC)-curve van de somscore van het teken van Tinel liet geen twijfel over: het teken is niet geschikt om patiënten zonder en met evidente zenuwpathologie van elkaar te onderscheiden. We concludeerden dan ook dat het teken van Tinel niet wijst op zenuwcompressie in een heterogene patiëntengroep, en evenmin in een subgroep van patiënten met DSPN. Het teken van Tinel was ook al niet gevoelig voor de aanwezigheid van andere vormen van zenuwschade of DSPN.

Zoals gezegd onderzochten we het teken van Tinel omdat dit gebruikt wordt als criterium voor decompressiechirurgie in de benen. In **hoofdstuk 4** gaven we een kort overzicht van de bewijskracht voor deze behandeling, welke voornamelijk bestaat uit grote, observationele cohort studies.[9-15] De resultaten van deze onderzoeken zijn consistent: ongeveer 80% van de patiënten rapporteert afname van pijn en verbetering van de sensibiliteit in de benen.

Dit suggereert dat deze drievoudige decompressiechirurgie een heel gunstig resultaat kan opleveren voor patiënten met pijnlijke DSPN.[12,14,15] We uitten een aantal kritiekpunten op deze onderzoeken. Ten eerste bevatte geen van deze onderzoeken een controlegroep, waardoor de omvang van het placebo-effect niet te beoordelen is. Dit is relevant omdat de meeste uitkomstmaten een beoordeling van pijn of sensibiliteit betroffen. Verder is het bekend dat chirurgische ingrepen over het algemeen een sterk placebo-effect hebben.[16] Ten tweede fluctueert de ernst van neuropathische pijn altijd in enige mate, ongeacht een eventuele behandeling,[17] hetgeen kan leiden tot het fenomeen regressie naar het gemiddelde, aangezien patiënten het meest geneigd zijn om zich te laten opereren als de klachten ernstig zijn. Ten derde zou een klinische verbetering deels het resultaat kunnen zijn van verbeterde glucosecontrole, daar deelname aan een klinisch onderzoek mogelijk ook leidde tot betere diabeteszorg.

Het huidige beleid zoals gevoerd door voorstanders van de drievoudige decompressiechirurgie bestaat uit een aantal stappen, waaronder beoordeling van aanwezigheid van het teken van Tinel als teken van zenuwbeknelling. Wij pleitten voor een grondige herbeschouwing van al deze stappen om te kunnen beoordelen of decompressiechirurgie daadwerkelijk waardevol is, liefst gevolgd door een gerandomiseerd onderzoek met geblindeerde beoordeling van de uitkomst op lange termijn. Aangezien wij in hoofdstuk 3 aantoonden dat het teken van Tinel niet duidt op zenuwcompressie en dus niet geschikt is om eer een beslissing ten aanzien van operatie op te baseren, rijst de vraag of de bewijskracht voor de daaropvolgende stappen, d.w.z. uiteindelijk decompressiechirurgie, voldoende sterk is om de keuze voor deze behandeling te rechtvaardigen, of dat dit soort beslissingen moet worden uitgesteld tot daar meer bewijs voor is. Wij hebben een voorkeur voor dat laatste. Van 2008-2013 is aan de Universiteit van Texas Southwestern Medical Center een dergelijk gerandomiseerd, 'dubbel-blind', prospectief onderzoek met een controlegroep uitgevoerd.[18] We wachten in spanning op de resultaten van dit onderzoek, die helaas nog niet gepubliceerd zijn.

In **hoofdstuk 5** keken we kritisch naar de resultaten van een andere chirurgische ingreep ter behandeling van zenuwcompressie: revisiechirurgie na het falen van neurolyse (ofwel decompressie) van een beklemming van de n. ulnaris ter hoogte van de elleboog. We beschreven het resultaat van 26 patiënten die bij de revisieprocedure werden behandeld met een anterieure subcutane transpositie. Ze werden allen geopereerd door dezelfde ervaren neurochirurg, die steeds dezelfde techniek toepaste. Hierdoor is het onwaarschijnlijk dat verschillen in uitkomst berustten op verschillen in de behandeling. De gegevens werden verzameld door middel van gestandaardiseerde telefonische vraaggesprekken. Pijn en/of tintelingen verbeterden bij 35%, de motoriek bij 23% en sensibele stoornissen bij 19% van de patiënten. Verbetering op minimaal één van deze domeinen werd gezien bij 58%, maar een achteruitgang op één van deze domeinen werd gezien bij 46% van de patiënten. Wanneer gevraagd werd naar tevredenheid, beoordeelde 62% van de patiënten het resultaat van hun revisieoperatie als goed of uitstekend. Deze patiënten waren 11 jaar jonger (mediaan) dan de patiënten die hun resultaat als matig/slecht beoordeelden. We vonden geen andere factoren die de uitkomst zouden kunnen beïnvloeden. Opvallend was dat een aantal patiënten die tevreden waren over het resultaat, slechts gedeeltelijke verbetering of zelfs achteruitgang van hun symptomen had gemeld. Een gedeeltelijke verklaring voor deze tegenstrijdige bevinding kan zijn, dat patiënten het tot een halt brengen van verdere achteruitgang van hun

klachten ook als gunstig resultaat kunnen ervaren. Deze matige resultaten van secundaire subcutane transpositie na een eerder gefaalde neurolyse van de n. ulnaris, moeten in de toekomst worden besproken met patiënten, om zo realistische verwachtingen te scheppen. Met name oudere patiënten zouden dan ook kunnen overwegen om af te zien van een revisieoperatie.

De laatste twee hoofdstukken betroffen decompressie van de n. medianus bij patiënten met een carpaletunnelsyndroom (CTS). Van maart 2012 tot juli 2014 verzamelden we prospectief gegevens van 227 volwassen patiënten die een primaire decompressie ondergingen i.v.m. een elektrofysiologisch bewezen CTS. Het zenuwgeleidingsonderzoek werd preoperatief bij alle patiënten verricht en omvatte motorisch en sensibel geleidingsonderzoek conform de CTS-richtlijn van de Nederlandse Vereniging voor Neurologie.[19] Met behulp van getrainde onderzoeksverpleegkundigen vulden de patiënten verschillende vragenlijsten in op drie momenten: binnen twee weken voorafgaand aan de operatie, drie maanden na de operatie en een jaar na de operatie. Klachten van het CTS werden gekwantificeerd met de 'Boston Carpal Tunnel Questionnaire' (BCTQ) die 11 vragen bevat aangaande ernst en duur van pijn en tintelingen (zowel 's nachts als overdag), verminderd gevoel van de hand en krachtsverlies/ verlies van handigheid. De 'Center for Epidemiologic Studies Depression Scale' (CES-D) werd gebruikt om depressieve symptomen vast te leggen. Dit is een veel gebruikte vragenlijst die gestoeld is op de vijfde editie van de 'Diagnostic and statistical manual of mental disorders' (DSM-V).[20] De aanwezigheid en ernst van littekenpijn en proximale pijn in de handpalm werd gemeten met de 'Palmar Pain Scale', een schaal die speciaal ontwikkeld is voor pijn na operatie van CTS, die een somscore van 0-9 punten oplevert.[21] Tot slot werd gevraagd naar tevredenheid van de patiënt door te vragen naar de mate waarin de symptomen waren veranderd, op een schaal van 1 (compleet hersteld) tot 7 (veel slechter geworden). Open decompressie van de n. medianus werd verricht onder lokale verdoving door één van de drie ervaren neurochirurgen die allen dezelfde techniek hanteerden.[22] We gebruikten de gegevens van de vragenlijsten één jaar na de operatie, omdat we zagen dat de symptomen en de pijn in de handpalm nog afnamen van drie maanden tot één jaar. We meenden dat de uitkomst na één jaar dus een betere weergave was van het eindresultaat.

In **hoofdstuk 6** onderzochten we de relatie tussen depressie en de uitkomst van carpale-tunnelchirurgie. Drieëntwintig patiënten (11%) hadden een depressiescore ≥16, hetgeen wijst op een klinisch relevante depressie. [23,24] Preoperatief hadden depressieve patiënten een hogere, d.w.z. slechtere, BCTQ score dan patiënten zonder depressie: mediaan 3.3 punten (interkwartielafstand 2.6-3.5) vs. 2.7 (2.3-3.1). Een jaar na de operatie hadden depressieve patiënten nog steeds een hogere BCTQ score: mediaan 1.4 (1.2-2.1) vs 1.1 (1.0-1.6). Ze hadden tevens meer pijn in de handpalm (73% palmar pain score >0 vs. 42%) en waren minder tevreden (55% niet volledig hersteld vs. 33%). De multivariabele analyse toonde echter aan dat depressie geen onafhankelijke voorspeller was van resterende klachten van CTS of tevredenheid van de patiënt na één jaar. Het verschil in postoperatieve BCTQ score tussen depressieve en niet-depressieve patiënten was dusdanig klein (0.3 punt) dat het klinisch niet of nauwelijks van belang is. Bovendien was dit verschil niet gerelateerd aan depressie en werd het gedeeltelijk verklaard doordat depressieve patiënten preoperatief ook een iets hogere BCTQ-score hadden. Een interessante bevinding was dat de CES-D score een jaar na de operatie was afgenomen t.o.v. vóór de operatie, met een mediaan van 2

punten. Deze afname correleerde met de afname van de BCTQ-score (Pearson correlatie coëfficiënt 0.27). De oorzaak van deze relatie is onbekend. Een mogelijke verklaring voor deze afname in depressiescore is dat patiënten zich algeheel prettiger voelen na operatie van hun CTS doordat symptomen als pijn en tintelingen zijn weggenomen. Een andere reden kan zijn dat de CES-D een vraag over slapen bevat, terwijl veel patiënten met CTS klagen over nachtelijk ontwaken door hun klachten. Aangezien deze nachtelijke klachten bij de meerderheid van de patiënten wordt weggenomen door de operatie, is de afname van de CES-D score mogelijk ten dele verklaard door een afname van de score op de 'slaapvraag' hierin.

In **hoofdstuk 7** hebben we ons gericht op verschillen in symptomatologie tussen patiënten met CTS van 70 jaar en ouder (n = 75) en patiënten jonger dan 70 jaar (n = 152), vóór en na carpaletunnelchirurgie. De totale preoperatieve BCTQ score verschilde niet significant tussen de leeftijdsgroepen en er waren preoperatief eveneens geen significante verschillen in de 11 individuele vragen van de BCTQ tussen deze twee leeftijdsgroepen. Desondanks werden ernstige afwijkingen van het zenuwgeleidingsonderzoek veel vaker gezien bij de oudere patiënten dan bij de jongere patiënten; we vonden bij ouderen bijna twee maal zo vaak afwezigheid van een meetbare SNAP van de n. medianus. Eén jaar na de operatie had de oudere groep een significant hogere totale BCTQ-score, maar dit verschil was met 0.2 punten erg klein. Interessanter was dat oudere patiënten postoperatief meer resterende doofheid van de hand en tintelingen in de hand rapporteerden dan de patiënten jonger dan 70 jaar. Het resultaat van de operatie wat betreft handpalmpijn en tevredenheid verschilde niet significant tussen de groepen. We bespraken enkele mogelijke verklaringen voor deze bevindingen.

REFERENTIES

1. Teoh HL, Chow A, Wilder-Smith EP. Skin wrinkling for diagnosing small fibre neuropathy: comparison with epidermal nerve density and sympathetic skin response. Journal of neurology, neurosurgery, and psychiatry 2008;79:835-7.

2. Wilder-Smith EP, Guo Y, Chow A. Stimulated skin wrinkling for predicting intraepidermal nerve fibre density. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2009;120:953-8.

3. Valdivia Valdivia JM, Weinand M, Maloney CT, Jr., Blount AL, Dellon AL. Surgical treatment of superimposed, lower extremity, peripheral nerve entrapments with diabetic and idiopathic neuropathy. Annals of plastic surgery 2013;70:675-9.

4. Dellon AL. Diabetic neuropathy: review of a surgical approach to restore sensation, relieve pain, and prevent ulceration and amputation. Foot & ankle international 2004;25:749-55.

5. Dellon AL, Mackinnon SE, Seiler WAt. Susceptibility of the diabetic nerve to chronic compression. Annals of plastic surgery 1988;20:117-9.

6. Aszmann OC, Kress KM, Dellon AL. Results of decompression of peripheral nerves in diabetics: a prospective, blinded study. Plastic and reconstructive surgery 2000;106:816-22.

7. Macare van Maurik JF, van Hal M, van Eijk RP, Kon M, Peters EJ. Value of surgical decompression of compressed nerves in the lower extremity in patients with painful diabetic neuropathy: a randomized controlled trial. Plastic and reconstructive surgery 2014;134:325-32.

8. Wood WA, Wood MA. Decompression of peripheral nerves for diabetic neuropathy in the lower extremity. The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons 2003;42:268-75.

9. Lee CH, Dellon AL. Prognostic ability of Tinel sign in determining outcome for decompression surgery in diabetic and nondiabetic neuropathy. Annals of plastic surgery 2004;53:523-7.

10. Dellon AL. Diabetic neuropathy: medical and surgical approaches. Clinics in podiatric medicine and surgery 2007;24:425-48, viii.

11. Dellon AL, Muse VL, Nickerson DS, et al. Prevention of ulceration, amputation, and reduction of hospitalization: outcomes of a prospective multicenter trial of tibial neurolysis in patients with diabetic neuropathy. Journal of reconstructive microsurgery 2012;28:241-6.

12. Dellon AL, Muse VL, Scott ND, et al. A positive Tinel sign as predictor of pain relief or sensory recovery after decompression of chronic tibial nerve compression in patients with diabetic neuropathy. Journal of reconstructive microsurgery 2012;28:235-40.

13. Liao C, Zhang W, Yang M, Ma Q, Li G, Zhong W. Surgical decompression of painful diabetic peripheral neuropathy: the role of pain distribution. PloS one 2014;9:e109827.

14. Valdivia JM, Dellon AL, Weinand ME, Maloney CT, Jr. Surgical treatment of peripheral neuropathy: outcomes from 100 consecutive decompressions. Journal of the American Podiatric Medical Association 2005;95:451-4.

15. Zhong W, Zhang W, Yang M, Li G, Ma Q, Yang X. Impact of diabetes mellitus duration on effect of lower extremity nerve decompression in 1,526 diabetic peripheral neuropathy patients. Acta neurochirurgica 2014;156:1329-33.

16. Dowrick AS, Bhandari M. Ethical issues in the design of randomized trials: to sham or not to sham. The Journal of bone and joint surgery American volume 2012;94 Suppl 1:7-10.

17. Young RJ, Ewing DJ, Clarke BF. Chronic and remitting painful diabetic polyneuropathy. Correlations with clinical features and subsequent changes in neurophysiology. Diabetes care 1988;11:34-40.

18. (https://clinicaltrials.gov/ct2/show/study/NCT00703209)

19. Dutch Association of Neurology (Nederlandse Vereniging voor Neurologie N. Dutch Guideline - Diagnosis and treatment of carpal tunnel syndrome. 2005.

20. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Applied Psychological Measurement 1977;1:385-401.

21. Atroshi I, Lyren PE, Ornstein E, Gummesson C. The six-item CTS symptoms scale and palmar pain scale in carpal tunnel syndrome. The Journal of hand surgery 2011;36:788-94.

22. Bozentka DJ KB. Open Carpal Tunnel Release. Atlas of the Hand Clinics 2002;7:181-9.

23. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. Psychology and aging 1997;12:277-87.

24. Myers JK, Weissman MM. Use of a self-report symptom scale to detect depression in a community sample. The American journal of psychiatry 1980;137:1081-4.