OUTCOME FOLLOWING PERIPHERAL NERVE INJURY OF THE FOREARM

Jetske Ultee

Outcome following peripheral nerve injury of the forearm
Jetske Ultee - Proefschrift Erasmus Universiteit Rotterdam

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OUTCOME FOLLOWING PERIPHERAL
NERVE INJURY OF THE FOREARM

Functioneel herstel na perifeer zenuwletsel van de onderarm

Proefschrift

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Voor Frits, Noa, India, Senna and Bo

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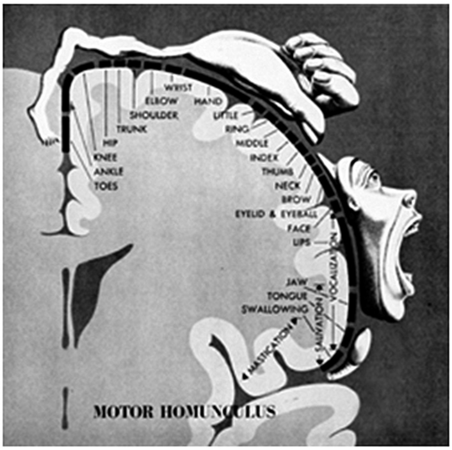
CHAPTER 1

INTRODUCTION

J. Ultee

INTRODUCTION

Loss of hand function can be a frightening experience, the hand is an integral part of what makes us human. Nowhere else in the body is there such an amazing and complex functioning of bones, joints, muscles, tendons, nerves, blood vessels and skin as in the hand. The proper function and balance of all these elements is required for the hand to function to its full potential. The hands are the primary tool for interacting with our environment and, through touch, are also crucial for receiving information about our surroundings.[1] About a quarter of the motor cortex in the human brain (the part of the brain which controls all movement in the body) is devoted to the muscles of the hands. This is usually illustrated with a drawing of a human figure draped over the side of the brain, body parts sized proportional to the amount of brain devoted to their movement, referred to as a *homunculus* - as illustrated in this drawing from Dr. Wilder Penfield's monograph "The Cerebral Cortex of Man".[2]



Until illness or injury forces people to focus on the importance of their hands, few people ever consider the consequences of being unable to use them. Any loss of hand function can have serious economic and psychological consequences. In fact, losing the use of your hand often means losing your job. Our hands are also part of our identity. Patients with severe upper extremity injuries can suffer psychologically from post-traumatic stress disorder.[4,5,6,7,8] Unfortunately, we often fail to appreciate the function of the upper limb until it is injured, and that happens quite often.

- *One third of all injuries seen in emergency rooms involves the upper extremity.*[9]
- *Two thirds of upper extremity injuries occur to individuals in their working years. The most common disabling work injuries in the United States involve the upper extremities, accounting for over one fourth of all disabling work injuries.* [10,11]
- *Children under the age of six are at greatest risk for crushing injuries of the hand.*[12]

Surprisingly considering incidence and consequences of trauma of the hand, hand surgery only emerged in a few countries as its own specialty.

During World War II with an unmatched number of survivors with hand injuries, there was a growing need for advancement in the care of acute injuries that predictably lead to impairment in hand function. In the early days of the war, patients were randomly assigned to plastic, orthopaedic, neurosurgical or general surgical units. Over time, however, it became increasingly evident that a multidisciplinary approach was necessary in the care of the injured hand. As a result, substantial advances have been made in recent decades in treating patients with hand injuries, degenerative disorders, and birth defects of the hand. Maybe the most impressive example of this is total transplantation of the hand, first performed in 1998. As opposed to the latest advances in hand surgery, the outcome of reconstruction of nerve injuries has made relatively little improvement.[13] How is it possible that despite considerable advances in understanding nerve regeneration and techniques, complete functional recovery after peripheral nerve injury rarely can be achieved?

Reports about peripheral nerve injuries and repair can be traced hundreds of years ago. Gabriele Ferrara (1543-1627) was the first surgeon to describe the technique of suturing the stumps of a transected nerve. His technique included precise identification of the nerve stumps; gentle traction; applying alcohol to disinfect the suture needle and suture thread using a mixture of red wine, rosemary, and roses; and gently sewing the retracted stumps together without damaging them. Oils were then applied, and the patient was confined to bed with the limb immobilized to prevent damaging the suture. This procedure, consisting of disinfection, appropriate identification of nerve stumps, correct suturing technique, and limb immobilization, closely resembles the surgical protocol of 21st century.[14] During the latter half of the 19th century, laboratory investigators made considerable progress understanding and influencing nerve trauma and repair. In World War II, the relative high occurrence of peripheral nerve injuries influenced experimental studies to further investigate the anatomy of the peripheral nerve. Poor outcome of peripheral nerve damage repair was recognized to be the result of failed axonal regeneration at the site of the repair. Combination of the introduction of microsurgical techniques and better understanding of nerve regeneration in the late 1950's have led to improved results in repair of acute nerve injuries and have extended the types of nerve repair that can be accomplished. Innovative techniques using microsurgical dissection, such as nerve transfers and end-to-side repairs are direct consequences of these advances. However, as emphasized before, in recent years, reconstruction of nerve injuries has made little improvement in functional outcome after repair of peripheral nerves. [15,16,46]

For this thesis two main traumatic mechanisms of peripheral nerve injury were evaluated, i.e. following ischemic compartment syndrome and following penetrating trauma. The following two case reports illustrate these mechanisms.

Case report 1 peripheral nerve injury by compression trauma

A 6 year old right handed girl sustained an uncomplicated supracondylar humeral fracture of her right arm after she fell of a trampoline. At the same day of injury the fracture was treated with closed reduction and application of a cast. After reduction she increasingly suffered from pain and swelling of her injured arm. Although her parents did mention this extreme discomfort several times to the medical staff the cast was only partly opened at the thumb; however pain and swelling did not decrease. When x-ray imaging revealed a good position of the fractured humerus the child was sent home. However in the following days parents and child frequently visited the hospital with complaints about severe pain, swelling and discolouring of the skin of the hand. Although the parents insisted on removal of the cast, their request was only followed *through two weeks after injury. After removal of the cast the superficial skin demonstrated several necrotic areas and the interphalangeal joints of the fingers were flexed with extended metacarpal joints (claw hand). The girl was unable to move her fingers and sensation of both hand and fingers was completely absent. Surgery to restore hand function was performed in two stages; the first stage consisted of excision, tenolysis, and neurolysis (six months after injury) and half a year later a vascularised innervated gracilis muscle transplantation for flexor repair and nerve grafts for the median and ulnar nerve were performed. Although there was a considerable improvement of function, wrist mobility (range of motion of -20/35 degrees), grip strength (20%) and sensation (protective) remained impaired. Fortunately after operation range of motion of the fingers turned out to be reasonable; although intrinsic function was impaired fingers could be maximally flexed and extended.*

Example of a child with an established Volkmann's Ischemic Contracture

This is a tragic example of a peripheral nerve compression injury with serious consequences. In humans, compression injuries can be induced by compartment syndrome. Direct muscle trauma, bleeding and localized pressure by casts or by circular dressings are all causes of compartment syndrome. Compartment syndrome injuries cause high pressure in surrounding tissue. Pressure compresses arterial blood supply of the nerve, predisposing the nerve and muscle to ischemic cell damage and cell death. Although the peripheral nervous system is relatively resistant to ischemia, long periods of stretch and compressive force can cause vascular compromise and neuronal ischemia. Delays in assessment and treatment of compartment syndrome can lead to nerve injury in the forearm and finally to the development of Volkmann's ischemic contracture.

When early diagnosed and properly treated the development of Volkmann's ischemic contracture can be prevented. The treatment of an established contracture is complicated and depends strongly on the severity of the infarction and the affected muscle and nerve tissue. Numerous articles have been written about this subject; however a comparison of the long-term results regarding the different techniques doesn't exist.[18-24]

Case report 2 peripheral nerve injury by penetrating trauma

A 20 year old male was presented at the first aid department after he had suffered a small laceration to the volar surface of his right wrist after falling on a broken bottle.
He reported a pulsatile bleeding and some numbness and weakness. The patient also reported he had seen "white cords" in his wrist. During examination, there was a 4cm transverse laceration 3cm proximal to the proximal wrist crease. There was absent sensation in the median nerve distribution and an absent radial pulse, with an abnormal Allen's test. On testing the Flexor digitorum superficialis of the index, long, and ring fingers did not function and furthermore the Flexor digitorum profundus to the index was weak. The ulnar nerve and the remaining tendons were thought to be intact. Following repair of flexor tendons, radial artery and median nerve hand therapy was initiated in the next day and a dynamic splint was applied. Based on retrospective study results his surgeon told him he would probably end up having a good functional outcome with little decrease in power, range of motion, or sensation because of his young age and location of injury. Unfortunately after 12 months he still experienced pain during exposure to cold and both grip and sensation were severely impaired. He decided to quit his study as professional gardener as he presumed he wouldn't be able to perform this job in the future due to his impairment.

The second case report is another tragic example of a peripheral nerve injury with severe consequences. Penetrating trauma, - another major traumatic mechanism of peripheral nerve injury of the forearm- is mostly caused by domestic or industrial accidents and has an estimated incidence of 1/1000 cases in the population per year.[44] The total incidence of nerve injuries after upper- or lower-limb trauma is 1.64%.[45] However, limited reported data are available to determine the incidence of peripheral nerve injuries. The mechanism of injury in penetrating peripheral nerve injuries is a cut by glass in more than 50%, followed by sharp metal objects and machinery.[31,32] Even after microsurgical nerve repair of the median or ulnar nerve, sensory recovery and strength cannot be expected to fully recover and most patients experience considerable loss of muscle function, impaired sensation and/or painful neuropathies or neuroma's.[46] As peripheral nerve repair techniques cannot easily be further refined, there is a need for understanding the mechanism behind impaired restoration of function.

Both case reports are illustrative of the severe consequences of peripheral nerve injury. These cases emphasize the need for further improvement of functional outcome after peripheral nerve injury. With better understanding of outcome we are able to evaluate and optimize our methods of treatment and at least adequately inform our patients. For that purpose the following questions have to be answered:

1. *What makes the outcome of peripheral nerve injuries so unpredictable i.e. why does the outcome and prognosis of acute nerve injury vary widely?*
2. *Can we identify prognostic factors for functional recovery after peripheral nerve injury?*
3. *How can we improve functional outcome after peripheral nerve injury?*

In the subsequent chapters of this thesis the aforementioned questions will be addressed.

In chapter 2 and 3 long term functional outcome of patients with peripheral nerve injury as a consequence of compartment syndrome was retrospectively evaluated. Although both mechanisms (compression injury and penetrating trauma) cause severe peripheral nerve injury of the forearm study characteristics for both groups are considerably different. In the compression group there had been an extensive diversity of location, severity of injury and timing of surgery. Different treatment modalities were performed, which made a thorough evaluation of results of treatment techniques possible.

In chapter 4, 5 and 7 outcome of patients with penetrating trauma of the peripheral nerve of the forearm was prospectively evaluated. Although method of treatment is pretty standard in this type of lesion, the final outcome is unpredictable (even considering severity and location of injury). Several factors like age, type of injury, level of injury and delay have been described to influence outcome results of peripheral nerve injury, but most of these studies are retrospective.[33-42] Although retrospective databases continue to be an important data source for outcome research, they also present several methodological challenges. Results of retrospective database studies can be very sensitive to influential cases. For example, an individual who is depressed and has a poor functional outcome can feel depressed as a consequence of his outcome or his depression could have led to poor outcome. If plausible alternative explanations to the findings when examining relationships between two variables are not considered, it could (especially in small sample size studies) dramatically change conclusions. Although a variety of tests for measuring sensitivity of findings to influential cases exists, retrospective databases often lack information on some of the variables that would be expected to influence the outcome measure of interest.
Our aim was, to identify prospectively predictors for functional recovery of penetrating

peripheral nerve injury of the forearm and to analyze their independent contribution in the outcome in the first year after repair.

Even in a prospective study design the specific function and complexity of peripheral nerve injury makes it difficult to reach an accurate view of the results of nerve repair in terms of restoration of function or to isolate the effect of the variables that may influence the outcome. Literature suggests combined assessments, scoring systems and questionnaires but there is still today only limited clinical documentation concerning applicability in the clinical trial setting. The general notion seems to be that a battery of methods encompassing all the above domains, including the estimation of pain/ discomfort, should be used.[42,43]

However, the choice of evaluating methods to minimise biases is not obvious and the definition of efficacy, or good outcome, is not always evident. Some of the problems can be mitigated by a using a strict research protocol, the use of a homogeneous study population and standardised treatment and assessment tools. Even if above mentioned conditions are met it can be difficult to reach an accurate view of the results of nerve repair in terms of restoration of function or to isolate the effect of the variables that may influence outcome. Standard evaluation protocols/ questionnaires for hand injury patients can have limited value for specific study purpose of peripheral nerve injury patients.

We have experienced the afore mentioned problems in the evaluation of cold intolerance, a common problem in peripheral nerve injury patients. Existing questionnaires were not precise enough for thorough analysis of different aspects of cold intolerance of peripheral nerve patients. Because for thorough analysis of all aspects of cold intolerance a reliable and validated questionnaire is needed, a renewed questionnaire for the evaluation of cold intolerance was introduced in chapter 6.

Finally, even with a strict prospective trial setting, a homogeneous study population and a standardised and reliable test battery (good) study results are not guaranteed. A reliable and successful prospective outcome study is largely dependent on high numbers of recruited patients, minimal loss of follow up, and maximum response rate to (postal) questionnaires. In chapter 8 different strategies were proposed to increase the aforementioned items.

Treatment of patients with injured peripheral nerves is challenging. The primary aim of this thesis is to analyze and discuss functional outcome after peripheral nerve injuries of the forearm. Retrospective evaluation of long term outcome of different treatment modalities of compression injuries of the forearm (compartment syndrome) resulting in Volkmann's ischemic contracture), prospective identification of prognostic factors for functional outcome in penetrating median or ulnar nerve injury and a proposition of a strategy for future prospective (multicentre) studies in this scientific area will contribute to better understanding of outcome after peripheral nerve injury. With the help of this information we are able to inform our peripheral nerve injury patients about their presumed course of rehabilitation and to optimize functional outcome by means of individual assigned treatment programs based on relevant prognostic factors.

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CHAPTER 2

VOLKMANN'S ISCHEMIC CONTRACTURE; PREVENTION AND TREATMENT

S E.R. Hovius, J. Ultee

INTRODUCTION

Volkmann's ischemic contracture, described in 1881 by Richard van Volkmann, is a condition of muscle ischemia, necrosis, and subsequent contracture of the lower arm.[29] Although the exact pathophysiology remained uncertain for a long time, understanding of the causes of this condition has evolved gradually. The compartment syndrome that is the basis for Volkmann's ischemic contracture can develop from a multitude of different insults, provided that the insults cause swelling of the soft tissues that are contained in an unyielding compartment.[30] As a result of this swelling, intramuscular pressure is elevated at a magnitude sufficient to reduce capillary perfusion. The deep flexor compartment of the forearm is the most likely to sustain ischemic injury because of its position next to the bone and its tight surrounding fascia.[11] The infarction, however, can extend to the superficial volar muscles, the extensor muscles, and the intrinsic hand musculature. The degree of damage is usually greatest at the center of the infarction; peripherally, it may be less pronounced because of the collateral circulation.[21] Volkmann's ischemic contracture is the end result of an unrecognized or inadequately treated compartment syndrome (Fig.1).

The uncertainty of the exact pathophysiology of this condition has impaired optimal treatment in the past. Better understanding of the causes in recent years provides insight in recognition and treatment of compartment syndrome. In spite of this, Volkmann's ischemic contracture still occurs, indicating the underestimation of the devastating effects of ischemia.[10,15] The treatment of an established contracture is complicated and depends strongly on the severity of the infarction and the affected muscle and nerve tissue. Several methods of treatment have been reported, but long-term results are unknown.[16,27,28,31] In this article emphasis is placed on preventive and diagnostic measurements of a compartment syndrome, as well as the management of an established Volkmann's contracture, in relation to long-term results with different methods of treatment.

COMPARTMENT SYNDROME AND PREVENTION

There are many causes for the development of an acute compartment syndrome but, in most cases, it is produced by skeletal trauma.[30] In this respect, the supracondylar fracture of the humerus in children is the most well-known injury associated with Volkmann's ischemic contracture (Fig.2). Mubarak[15] described, in 1979, 22 children with an ischemic contracture of the forearm. In his review, skeletal trauma preceded the compartment syndrome in 19 patients; nine patients developed their contracture after a supracondylar

fracture of the humerus, one after a shaft fracture of the humerus, and nine after a fracture of the forearm. In the authors' series between 1969 and 1996, 23 patients with Volkmann's ischemic contracture were treated. Nineteen developed the contracture after skeletal trauma; 14 after a supracondylar fracture of the humerus, and five after a fracture of the forearm. In three patients, there had been a crush injury and in one a rotation trauma. Comparable figures are also given by other authors.[6]
High-risk injuries such as a supracondylar fracture of the humerus therefore should be monitored carefully to facilitate early diagnosis of vascular injury or a compartment syndrome.

Figure 1. *A severe Volkmann's ischemic contracture.*

Copley reported 128 children with displaced supracondylar humeral fractures treated at his institution, of which there were 77 with absent or diminished pulses[5]. In five of them, the circulatory status remained disturbed. All five needed immediate vascular repair. In these cases, arteriography identified the occlusion. In one patient, vascular repair had been delayed 48 hours, resulting in Volkmann's ischemic contracture. Pirone[17] reported the relationship between the method of treatment of fractures of the supracondylar humerus and the number of complications, including Volkmann's contracture. In patients with a fracture of the supracondylar humerus, the complication rate was higher when treated with closed reduction and application of a cast compared with patients whose fractures were repaired operatively by Kirschner-wire fixation, skeletal traction, or open reduction with internal fixation. The examination of patients with a supracondylar fracture of the humerus is critical in determining the presence of early ischemia. An impending compartment syndrome is usually characterized by pain; sensory deficit; a swollen, tense, tender compartment; and reduction of active movement. Extreme, poorly localized pain, particularly with passive stretch of the muscle by manipulation of the digits and wrist, occurring a few hours after injury, is often the earliest and most obvious sign of a compartment syndrome. Color, capillary refill, and temperature may appear normal because of preservation of the major arterial flow to the limb. [19] Pain and loss of sensibility are not universal

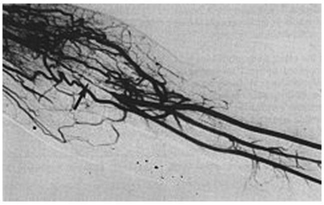


Figure 2. *Occlusion of brachial artery (arrow) following a supracondylar fracture of the humerus.*

findings, but in the authors' series, only one patient was asymptomatic; in all other patients, symptoms were present.[6]

Presence of impaired circulation requires aggressive management. In cases of a supracondylar fracture of the humerus this includes immediate opening of the cast or fracture reduction and pinning. This should be followed by careful re-evaluation of the circulatory state. If symptoms are still present for more than 30 minutes (to rule out transient spasm), immediate exploration is indicated.[5] Angiography may help diagnose or locate stenosis or vascular injury of the brachial artery. In the authors' series, in 9 of 23 patients, an angiograph was made. Seven-times, an impaired blood flow was seen; three times, there was total occlusion of the brachial artery. If signs of a compartment syndrome are present, decompression should be undertaken immediately to restore the microcirculation of the forearm.[8] In cases of a suspected vascular injury, decompression has to be combined with vascular exploration. Although compartment syndrome is a clinical diagnosis, it can be confirmed by preferably continuous measurements of intracompartmental tissue fluid pressure. The possibility of false positives or negatives must be emphasized, however.[9] If the ischemia occurring during a compartment syndrome is not corrected or is corrected too late by decompression and vascular repair, the muscles become necrotic and are eventually replaced by fibrous tissue, leading to contracture. The nerve damage caused by the initial ischemia can be aggravated by the subsequent muscle fibrosis. The most opportune timing for decompression is during the acute phase of the compartment syndrome-as soon as possible-but probably within 24 hours. Sheridan and Matsen[23] found that the frequency and severity of complications of the decompression were directly related to the promptness with which it was performed. In the authors' patient group, decompression was undertaken in three patients, but the interval between occurrence of symptoms and decompression in all these cases was more than 48 hours, which is presumably much too late.[5]

EVALUATION OF THE DAMAGE OF VOLKMANN'S ISCHEMIC CONTRACTURE

Treatment of an established Volkmann's contracture begins with assessment of the patient. Following a detailed history, a functional evaluation of the extremity is carried out. The active and passive range of motion of all joints of the upper extremity must be measured. Electromyography can produce information concerning nerve function and nerve regeneration and angiography is required for information regarding the vascular status. A relatively new tool in the determination of the severity and the extent of muscle damage in Volkmann's ischemic contracture is the use of CT scan or MR imaging, although the usefulness of these investigations has still to be evaluated.[13,28] In the authors' experience, MR imaging demonstrates fibrosis and the extent of loss of muscular tissue, but the operative technique, as yet, has not been altered by this information.

THE ESTABLISHED CONTRACTURE

Classification

A number of classifications are reported for different kinds of ischemic contractures.[1,21,27,28,31]. The most renowned classification is the one introduced by Seddon in 1964 and modified by Tsuge in 1975.[21,27,28] Tsuge divided patients with Volkmann's ischemic contractures in three types-mild, moderate, and severe. In the mild or localized type, the deep flexor muscles are partly degenerated. The fingers involved are most often the ring and the long fingers. When the degree of muscle degeneration is more extensive, the little and index fingers may also be affected. Sometimes there is a contracture of the thumb. There is usually no sensory disturbance but, if present, it is slight. A tenodesis effect can be demonstrated. In the moderate or classic type, the degeneration involves nearly all of the deep flexor muscles to the fingers and the pollicis longus, with partial involvement of the superficial muscles such as the flexor digitorum superficialis and wrist flexors leading to contracture. Neurologic signs are invariably present. The severe type results in degeneration of all flexor muscles and partial involvement of the extensor muscles. The neurologic signs are severe. Zancolli, in 1975, classified patients with Volkmann's ischemic contracture using four types-normal intrinsic muscle type (type I), paralytic intrinsic muscle type (type II), retracted intrinsic muscle type (type III), and combined type (type IV).[31] When using these classification systems, the authors found that a high percentage of the patients in their study were classified in the same group but, clinically, there was a great variety in the manifestation of the contracture. This and the fact that the aforementioned classifications are difficult to use in comparing pre- and postoperative hand function, urged the authors to develop their own evaluation system. The evaluation is based on Buck-Gramcko's classification designed for assessment of hands following tendon surgery, which is purely to determine motor function.[3] In addition to impaired motor function, however, Volkmann's ischemic contracture has mostly also a sensory deficit. To categorize the sensory impairment, the Semmes Weinstein test was used.[22] In children, sensory loss is difficult to test, but impairment can mostly be detected (Table 1). This evaluation can be used to determine which kind of treatment can

Table 1 *Hand function; Total active range of motion*

	Wrist	***Fingers***	***Thumb***
Good	> 90°	>160°	> 40°
Reasonable	> 70°	> 140°	> 30°
Unsatisfactory	> 25°	> 120°	> 20°
Poor	< 25°	< 120°	< 20°

be performed and to assess progress of hand function. Furthermore, CT scan or MR imaging can provide information on the extent of muscle damage, making a more precise evaluation possible, which can be better related to functional outcome (Fig. 3).

Timing of Intervention

In addition to the type of surgical procedure, the exact moment of intervention is a subject of discussion. Seddon[21,27,28] advocated a delay of at least 3 months after injury; Tsuge advised waiting for at least 6 months. With this delay, muscle tissue might spontaneously recover and intervention could possibly inflict more muscle damage. With delay, however nerves become thinned as a result of fibrotic compression and further joint stiffness can develop.[4] Especially in the more severe cases of Volkmann's contracture, early intervention is advised. In an early stage, severe muscle necrosis is easily differentiated from viable muscle tissue and can be removed. Chuang[4] compared patients who sustained late (more than 1.5 months) exploration with patients with an early exploration (within 3 weeks) followed by free muscle transplantation several months later. The results of the early exploration group were markedly better than those of the late exploration group. Zuker et al also achieved good results in patients in whom exploration and functioning free muscle transplantation took place in less than 1.4 years. In the authors' institution the same relationship could be noticed. We therefore do not advocate delay in the patients with insufficient or poor hand function (see Table 1).

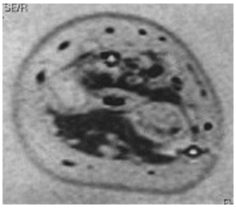


Figure 3. *An MR image of the forearm in a patient with Volkmann's ischemic contracture. Note the fibrosis that has replaced the normal muscle volume at the volar side.*

Another group of patients in which the authors have found early operation to be necessary are patients with severe neuralgia ("prolonged pain syndrome"). In the past 2 years, a severe neuralgia was encountered in three young patients with Volkmann's ischemic contracture, leading to very serious drug regimens to stop the pain. Prompt neurolysis and excision of fibrotic tissue immediately resolved the pain. In cases of Volkmann's ischemic contracture with reasonable to good hand function (see Table 1), however, it could be wise to wait for recovery before contemplating surgery. Independent of the timing of surgical intervention, to prevent joint stiffness, conservative therapy consisting of a combination of exercises and splinting should take place immediately when Volkmann's ischemic contracture is diagnosed.

Methods of Treatment

Treatment of Volkmann's ischemic contracture can vary, ranging from conservative through excision of fibrous tissue; neurolysis; tenolysis; proximal "muscle slide"; tendon lengthening; tendon transfers and nerve grafting; to free, vascularized, innervated musculocutaneous flaps. The treatment of an established contracture is complicated and depends strongly on the severity of the infarction and the affected muscle and nerve tissue. Although several methods of treatment are reported, long-term results for different treatment regimens are unknown.[16,27,28,31] In the authors' opinion, for contractures with ischemia of only a part of the deep forearm muscles and reasonable to good hand function (see Table 1), conservative management can be initiated, with physical therapy and splinting.[18] If this treatment is not sufficient or if the contracture is more severe, surgery should be performed.
Because most of the authors' cases are referred longer than 3 months following the ischemic event, with varying degrees of contractures, nerve damage, and stiffness of joints, the authors' treatment regimen consists of a two-stage approach. In the first stage, an inventory is made of the damage, fibrous and necrotic tissue is excised, and

neurolysis and tenolysis are performed. Following intensive therapy to mobilize stiff joints and after evaluation of nerve function 6 months later, definitive treatment can be mostly performed with nerve grafting, tendon transpositions, and innervated free vascularized muscle transfers, when necessary.

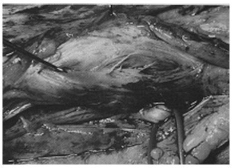


Figure 4. *Fatty degeneration in the infarcted area of the flexor muscles.*

Excision, Neurolysis, Tenolysis, and Capsulotomy

In an established contracture, the damaged tissue (i.e., fibrosis and fatty degeneration, either localized or severe) is excised through a volar, curved incision of the complete Forearm (Fig. 4). Care must be taken to identify the median and ulnar nerves with, respectively, the radial and ulnar artery starting proximally and distally of the scarred area to facilitate dissection. The median nerve is often the one the mid-forearm area. In patients with insufficient to poor hand function (see table 1), an hour class deformity of the nerve can be encountered (Fig 5).
In 1994, Ercetin et al[7] reported a classification of nerve lesions in three grades in ischemic contracture of Volkmann, ranging from a pearly white nerve without vasa vasorum (grade 1), followed by a constricted nerve section (hour-glass deformity), to eventually only fibrosis, where continuation of the nerve is not detectable.
If the nerve is in continuity, without deformity, following neurolysis, quite often a substantial recovery of sensation will occur. If the nerve is deformed-mainly when a substantial amount of forearm flexor muscles are fibrotic-a nerve graft is planned in the second stage, combined with a free muscle transfer. In these cases, the anterior interosseous nerve is identified and dissected out of the median nerve until healthy nerve fascicles are encountered. Following identification and dissection, the nerve is marked with an nonresorbable stitch. In all cases in which a second stage is planned, the dissected nerve is surrounded by a thin silastic sheet to prevent new adhesions (Fig.6). This technique greatly facilitates secondary intervention. Tenolysis is only useful if the muscle proximal to the tendon is still sufficient. In the authors' cases, tenotomy most often was performed in the distal forearm and involved the deep and superficial flexors of the fingers, the flexor pollicis longus, and the pronator teres. Sometimes the tendon could be lengthened. The muscle of the flexor

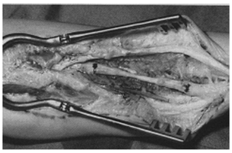


Figure 5. *An hourglass deformity of the median nerve in Volkmann's Ischemic contracture.*

Figure 6. *The silastic sheet around the median nerve facilitates dissection in the secondary stage.*

carpi radialis was more often damaged than the flexor carpi ulnaris. In the more severe, longstanding cases, persisting wrist flexion contracture is a problem (see Fig. 1). In these cases, therefore, the wrist flexion contracture should be released in the first stage. A wrist arthrodesis can be beneficial if the wrist contracture recurs after initial release. Sundararay et al[20] reported wrist arthrodesis in 11% of his series of 102 cases. The pronator contracture can be released by division of the interosseous membrane and the pronator quadratus, as described by Ercetin et al,[7] although the authors have not performed this release in their series. If a free muscle transfer is planned in the second stage, the proximal ends of the flexor tendons in the distal forearm are marked and surrounded by a thin silastic sheet for easier identification at the second stage (see Fig. 6). Regarding the hand, a claw deformity of the fingers, a contracted first web, and an extension contracture at the metacarpophalangeal joint of the thumb with a flexion contracture at the interphalangeal joint have been recorded by others.[26,31] In the authors' series, this was only demonstrated in longstanding cases. In most cases, flexion contractures at the proximal interphalangeal and interphalangeal joints were established, with slight to no movement in the fingers with the wrist in moderate flexion contracture (20°- 40°).

Following excision of the infarction with complete release, the fingers and thumb can mostly be stretched or nearly stretched. If not, capsulotomies of the metacarpophalangeal and proximal interphalangeal joints can be performed. Capsulotomies were only necessary in the authors' series in some of the very longstanding, untreated cases (i.e., several years following the ischemic event).

Muscle Slide Operation

Although Tsuge, Scaglietti, and others [20,26,27,28], advocate the 'muscle slide' operation in mild and moderate cases, the authors agree with Smith[24] that the contracture is caused by fibrotic, degenerated tissue. A 'slide' therefore does not release functional muscles as, for instance, in cerebral palsy. Instead, it releases noncontractile, fibrous and fatty tissue. In moderate cases, a full release requires an extensive dissection from the proximal humerus to the pronator quadrates and from the ulna posteriorly to the radius anteriorly. Furthermore, this operation does not create the possibility to selectively release one muscle more than another; the release is performed as a whole. It is also difficult to judge the remaining strength of the fingers following a slide operation. The authors therefore do not prefer this operation.

Tendon Lengthening

Tendon lengthening has been advocated in the past as a method of treatment to release the contracture, with or without excision of the infracted area.[21,28] The aim of the effective lengthening is not tot obtain full passive extension of the fingers and thumb, but just to create a more neutral position of the fingers. The tendons of the fingers and thumb are lengthened in a Z-fashion over a relatively long distance. If lengthening of the digital tendons does not correct the wrist contracture, the wrist flexor tendons also have to be lengthened. A major disadvantage of this technique is the additional weakening produced in already impaired muscle. One of the authors' hospital's former hand surgeons used to treat contractures with tendon lengthening only. In the-authors' survey, the recurrence rate of the contractures in these cases was extremely high. This procedure therefore is only sometimes used in combination with other procedures, such as tendon transfers or free muscle transplantation.

Tendon Transposition

In cases with sufficient remaining muscle tissue, apart from excision, neurolysis, and tenolysis, the authors recommend performing a tendon transposition or a free muscle flap. Tendon transfers can best take place when decompressed nerves have recovered maximally and contractures have been corrected with mobilization, splinting, and excision of fibrosis. The tendon transfers most often used, if the muscles function, are the brachioradialis to the flexor pollicis longus and the extensor carpi radialis longus to the deep flexor tendons of all four fingers. Persistent clawing of the fingers can be treated with an intrinsic transfer of the extensor digiti quinti and extensor indicis proprius or extensor carpi ulnaris.[24] In the authors' series, tendon transpositions improved wrist and hand function one to two categories when classified according to Table 1. Tendon transfers of the dorsal forearm obviously cannot be used if the extensors are weak.

Free Vascularized, Innervated Muscle Transfer

Manktelowra[14] described the guidelines for patient and muscle selection. It is clear that acceptor vessels and nerve have to be adequate, with the application of the best possible donor muscle. Regarding the donor muscle, Krimmer[12] compiled characteristics of donor muscles from the work of Brand and Strasser.[2,25] The gracilis muscle, for example, has a functional cross-sectional area of 3.7 cm^2; the lattisimus dorsi muscle, 8 cm^2; and the rectus femoris, 26 cm^2. The mean resting fiber length is 26 cm, 23 to 28 cm, and 8 cm, respectively. On the other hand, the deep flexor muscles of the fingers have a cross-sectional area of 10.8 cm^2 and a mean resting fiber length of 6.6 cm. The gracilis muscle can provide only 17% of the original contracting force of the flexor muscles to the fingers, but adds superficial and deep flexor contracting force. The rectus femoris muscle therefore seems more adequate than the gracilis muscle as far as cross-sectional area is concerned. The donor site morbidity of the gracilis muscle, however, is far less, and it offers the reliability of the major neurovascular pedicle, which makes this muscle the first choice. The lattisimus dorsi, being the second choice, has 33% of the total contracting force of the flexor muscles. At operation the free muscle is connected proximally to the medial epicondyle with several separate stitches and distally, under the same tension as in the donor area, to the deep flexor tendons. When using it for flexor reconstruction, the distal connection is performed in a Pulvertaft manner.

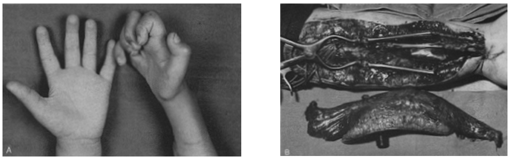
The metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints are placed in flexion with the wrist in a neutral position. Angiography is always performed in patients prior to muscle transplantation because they often have altered brachial artery flow or occlusion. Depending on the flow of the recipient artery, the anastomosis can be made in the forearm. If this is not sufficient, the brachial artery should be used as recipient artery with an interpositional vessel graft. The arthors lost one gracilis muscle in a patient with an occlusion of the distal brachial artery and, in retrospect, an insufficient spurt of blood out of the cut radial artery. Ercetin[7] advises the lattisimus dorsi in those cases because of its longer vascular pedicle. The venous anastomosis has always been to a comitant vein in the authors' series.

The nerve connection of the flap could always be made to the anterior interosseous nerve when using the volar side of the forearm, although dissection often had to take place more proximally, in the trunk of the median nerve, to encounter healthy fascicles. This dissection was always performed in the first stage, after which the nerve was marked and covered in a silastic sheet. The nerve suture to innervate the flap should be placed as distal as possible.

Concerning the flap, the skin island on the gracilis muscle is not reliable in the distal third, although skin is often needed in the distal forearm following free muscle transfer. A split skin graft was nearly always added. The skin flap most often was trimmed or excised after 1 to 1.5 years, providing the opportunity to perform adhesiolysis, if necessary (in two cases in the authors' series). In most free muscle transfer cases in the authors' series, sural cable grafts were necessary, specifically to reconstruct the median nerve, most often over a length of 5 to 8 cm. All children in the series who received a free muscle transfer increased dramatically in sensory recovery. Muscle strength was 60% of the healthy hand in the best case, with an average of 35%. It must be taken into account, however, that all patients had hardly any mobility or sensation (tested by Semmes Weinstein, if possible) before surgery (figs. 7A-7D).

Postoperative Management

Following surgery, in collaboration with the hand therapist, patients have to be encouraged to perform muscle strengthening exercises as soon as the first sign of innervation is detectable. Increasing muscle power can be expected for up to 2 years postoperatively. The final outcome of hand function after operation depends strongly on severity of the contracture preoperatively, the interval between development of the contracture and operation, the method of treatment and prompt participation in a hand rehabilitation program. Although sporadically mentioned, an additional problem in Volkmann's ischemic contracture is the development of a difference in forearm length.[33] In the authors' survey, this phenomenon was seen in all children except one. The only patient who did not demonstrate arm length-difference had surgery 2 month after injury. Furthermore, the interval between operation and evaluation in this patient was only 2 years. A number of patients experienced this length difference as even more disturbing than the impaired hand function. The length difference might be a result of impaired oxygenation of growth plates, remaining muscle, and nerve tissue. In this respect, early intervention may influence the final outcome of arm length. More research with respect to this subject should be performed. Children with Volkmann's ischemic contractures or their parents should be informed about the possibility of developing a length difference of the forearm (Fig. 8).



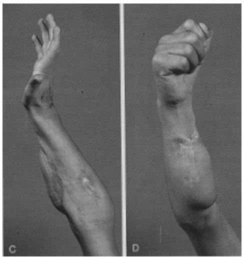


Figure 7. *A. Preoperative Volkmann's ischemic contracture. B. Intraoperative musculocutaneus gracilisflap to volar forearm. Postoperative extensive (C) and flexion (D) of fingers following free flap.*

SUMMARY

It may be concluded that treatment of patients with Volkmann's ischemic contracture is complicated and depends on a number of different variables.

Figure 8. *Long-term follow-up of Volkmann's ischemic contracture in the left forearm. Note the difference in forearm length.*

Optimal treatment of an established contracture requires a thorough examination of the extent of damage of the ischemia, followed by conservative therapy or operation. The most important measures concerning Volkmann's ischemic contracture, however, involve measures to prevent the contracture. It is poignant that very simple measures, such as monitoring high-risk injuries and immediate vascular repair or decompression if symptoms of a compartment syndrome are present, can prevent this disabling condition. The following summaries hopefully provide guidelines for prevention and treatment of Volkmann's ischemic contracture.

Prevention of Volkmann's Ischemic Contracture

1. High-risk injuries such as a supracondylar fracture of the humerus and a fracture of the forearm should, especially in children, be monitored carefully to detect early signs of ischemia. Patients have to be checked routinely, mainly for symptoms of pain, loss of sensibility and movement of fingers, but also for altered skin color and diminished capillary refill, pulse, and temperature of the hand. Compartment syndrome can still develop in spite of "normal" color, capillary refill, and temperature, however, because of preservation of the major critical flow to the limb.
2. Compartment syndrome is a clinical diagnosis and can be confirmed by preferably continuous measurements of intracompartmental tissue fluid pressure. The possibility of false positives or negatives must be emphasised, however.
3. Symptoms of ischemia in cases of fractures demand immediate opening of the cast or fracture reduction and pinning followed by careful re-examination of the vascular status. If symptoms are present for more than 30 minutes, immediate intervention should take place. If signs of high pressure are established, vascular exploration should be combined with the decompression. Angiography may be a helpful tool in determining the presence and location of stenosis and restoration of circulation after intervention.
4. In the treatment of a compartment syndrome, conservative measures such as opening the cast and administering vasoactive drugs are not sufficient.

Treatment of Volkmann's Contracture

1. Conservative therapy consisting of a combination of exercises and ortheses for wrist, hand, and fingers should start immediately when Volkmann's ischemic contracture is diagnosed. Stiffness of joints should at all times be prevented.
2. The extent of the infarction can be diagnosed by measurements of the active and passive range of motion, grip strength, and sensibility. CT scan and MR imaging are optional diagnostic procedures. Angiography is necessary, especially if free muscle transfer is considered.
3. Treatment can be conservative in patients with good to reasonable hand function (see Table 1). If, after 3 months, reasonable hand function deteriorates or does not improve, an operation can be considered.
4. Severe neuralgia in a patient who is suspected to have or has evident ischemic contracture should undergo surgery on a short-term basis.

5. In patients with poor hand function (see Table 1) and an extensive volar infarction, the authors advise a two-staged procedure, with early excision followed by a free vascularised muscle transplantation a few months later, with or without tendon transfers. If, in the first stage, the nerve is in continuity, without deformity, following neurolysis, quite often a substantial recovery of sensation will occur. If the nerve is deformed-mainly when a substantial amount of forearm flexor muscles are fibrotic- a nerve graft is planned in the second stage, combined with the free muscle transfer. In more severe, longstanding cases, with a flexion contracture of the wrist, wrist arthrodesis can be beneficial.
6. In all other patients diagnosed with insufficient hand function (see Table 1) and infarction of a considerable part of the deep and superficial flexors and neurologic signs, the authors advise excision of fibrotic muscle tissue, neurolysis, and tenolysis. Tenolysis is only useful if the muscle proximally of the tendon is still sufficient. Good results can be obtained if excision and neurolysis are combined with tendon transposition, specifically in the early cases.

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CHAPTER 3

FUNCTIONAL RESULTS AFTER TREATMENT OF VOLKMANN'S ISCHEMIC CONTRACTURE: A LONG-TERM FOLLOW-UP STUDY

J. Ultee, S.E.R. Hovius

ABSTRACT

The main objective of this retrospective study was to evaluate the long-term functional outcome in patients treated for Volkmann's ischemic contracture. In this study, functional outcome (measured as mobility, grip strength, and sensibility) and arm length difference after treatment of Volkmann's ischemic contracture were analyzed and discussed. Twenty-five patients treated between 1969 and 2001 were evaluated. The method of treatment was related to the severity of the infarction, ranging from conservative to free vascularized muscle transplantation. Although the study population was small, we could observe a wide range of functional outcome. Substantial improvement of function was obtained in patients who had free vascularized muscle transplantation. Unfortunately in one patient with an occlusion of the distal brachial artery and an insufficient flow through the collateral circulation of the radial artery, the gracilis muscle was lost. Tendon lengthening had unsatisfactory results because of recurrence of the contracture. Excision of fibrotic muscle tissue, neurolysis and tenolysis sometimes combined with a tendon transfer gave good hand function results in patients with sufficient remaining muscle tissue. In most of the patients in whom the contracture developed during childhood, a difference in forearm length was observed.

INTRODUCTION

In 1881, Volkmann[25] described a condition of muscle ischemia, necrosis, and subsequent contracture of the forearm. He concluded that the contracture was a consequence of an interruption of the arterial blood supply caused by the application of tight, constricting bandages to the injured limb. In 1909, Thomas collected 107 cases that had been reported in the literature and among these were cases in which no splint or bandage had been applied, so extrinsic pressure could not be the sole cause of Volkmann's contracture.[23] We now recognize ischemic contractures can develop from many different injuries as long as the injuries cause swelling of the soft tissues that are contained in relatively nondistensible osseofascial compartments.[26] As a result of this swelling, intramuscular pressure is elevated at a magnitude sufficient to occlude capillary perfusion. The compartments with the least possibility to expand are the most likely to sustain ischemic injury. Because the deep flexor compartment of the forearm lies next to the bone with a tight surrounding fascia it will be the first to be damaged.[20] In addition, the flexor digitorum profundus lies most distant from the arterial anastomotic pathways that potentially are available to re-establish its circulation. The center of the muscle, which provides tendons to the middle and ring fingers, is particularly vulnerable.[11] However, the infarction also can extend to the superficial muscles, the extensor muscles, and the intrinsic hand musculature. In Volkmann's ischemia, at first there is often total paralysis of the forearm, but within 2 or 3 months, the extensor muscles recover well and also there may be some recovery in the flexors.[20,24] If the ischemia is not corrected, the muscles become necrotic and eventually are replaced by fibrous tissue. The nerve damage caused by the initial ischemia also can be aggravated by the subsequent muscle fibrosis. Volkmann's ischemic contracture is the result of an unrecognized or inadequately treated compartment syndrome (Fig 1).

Improved understanding of the pathogenesis of a compartment syndrome has resulted in more rapid diagnostic and therapeutic measures and reduced the incidence of Volkmann's ischemic contracture.[4,7,8,13,14,15,17] However, the fact that the condition still occurs indicates it is not always recognized or treated in time to prevent devastating effects. In North America, failure in diagnosis of an acute compartment syndrome is one of the most common causes of litigation against the medical profession.[13]

Fig 1. *This clinical photograph shows a severe case of a Volkmann's ischemic contracture.*

Because a fully developed contracture of the flexor muscles in the forearm is extremely disabling more data about identification of compartment syndrome and adequate treatment are needed.

The treatment of an established contracture is complicated and depends on the severity of the infarct and the affected muscle and nerve tissue. Although several methods of treatment are described in the literature, long-term results in different treatment regimes are unknown.[7,11,13,15,17,18,24,27] Considering the fact that most ischemic contractures develop during childhood, not only a disabled hand function but also a retardation of forearm growth can be expected. However, forearm growth retardation has hardly been mentioned in literature.[28] For both patient as attending physician knowledge about long term outcome of treatment of patients with Volkmann's ischemic contracture is indispensable.

The main objective of this study was to evaluate in a retrospective study the long term functional outcome in patients treated on Volkmann's ischemic contracture. In this study, functional outcome (measured as mobility, grip strength and sensibility) and arm length difference after treatment of Volkmann's ischemic contracture were analyzed and discussed.

Furthermore we aimed to identify retrospectively the initial symptoms of compartment syndrome. If symptoms related to compartment syndrome were present, therapeutic measurements were evaluated.

Finally we retrospectively analyzed motor and sensory recovery in the first months after the compartment syndrome.

MATERIALS AND METHODS

Between 1969 and 2001, 32 patients with Volkmann's ischemic contracture were treated; 25 were available for evaluation. Seven patients were not included. One patient did not want to participate, one patient moved abroad, and five patients could not be located. Treatment of patients varied, ranging from conservative through excision of fibrous tissue, neurolysis, tenolysis, proximal muscle slide, tendon lengthening, tendon transfers, and nerve grafting to free vascularized, innervated musculocutaneous flaps. The chosen method of treatment in this group was related to the severity of the infarction and the affected muscle and nerve tissue. In all patients treated operatively, we required a minimum follow-up of 2 years.

All patients (or their parents) were asked to describe the symptoms they had with compartment syndrome, the improvement of sensory and motor function in the first 3 months, and their opinion about the treatment result.

An independent physician (not the operating surgeon) postoperatively examined all patients. The arm length of each patient was measured. To determine the strength of power grip the Jamar dynamometer was used.[21] Three trials with each hand were done alternately, and the mean value was calculated for each hand. The end result was expressed as a percentage of the performance compared with the uninjured hand. Sensibility was scored by means of the pocket version of Semmes-Weinstein monofilaments test with five probes, scored 0 to 5, and done according to a procedure described by Bell-Krotoski et al [1] for assessment of perception of touch/pressure: 0 = untestable, 1 (filament marking 6.65) = perception of deep pressure, 2 (filament marking 4.56) = loss of protective sensation, 3 (filament marking 4.31) = diminished protective sensation, 4 (filament marking 3.61) =

diminished perception of light touch, and 5 (filament marking 2.83) = normal perception of touch/pressure. As recommended by Bell et al,1 three critical sites for the median and ulnar nerve and one site for the radial nerve were used in the analyses, so the maximum score for the median and the ulnar nerves was 15 and the maximum score for the radial nerve was 5. To classify postoperative motor function, a classification system was developed based on the classification of Buck-Gramcko et al,[2] designed for assessment of hands after tendon surgery. The total active range of motion (ROM) of the wrist, fingers, and thumb was measured and scored as good, reasonable, unsatisfactory, and poor as shown in Table 1. This classification made a comparison possible between preoperative hand mobility (data from the last preoperative screening) and postoperative hand mobility. Preoperative data were retrospectively collected from medical records. Unfortunately, preoperative Semmes Weinstein and grip strength scores were not always available.

RESULTS

Twenty-five patients were evaluated with a mean interval between treatment and evaluation of 10 years (median 7 years; range, 2–29 years). In 15 patients, the contracture developed after a supracondylar humerus fracture; in four patients, it developed after a lower arm fracture; in three patients, it developed after a crush injury; in one patient, it developed after a rotation trauma; and in two patients, it developed after a combined supracondylar and lower arm fracture. Only five of the 25 patients were adults at the time the contracture developed. The mean age of the patients was 13 years with a median of 8 years and a range from 2 to 60 years.

Table 1 *Hand function; Total active range of motion*

	Wrist	***Fingers***	***Thumb***
Good	> 90°	>160°	> 40°
Reasonable	> 70°	> 140°	> 30°
Unsatisfactory	> 25°	> 120°	> 20°
Poor	< 25°	< 120°	< 20°

Conservative treatment, which existed of physical therapy and application of a splint, was used in one patient with a very mild contracture with ischemia of a small part of the deep forearm muscles and resulted in good hand function. Although mobility of the fingers and wrist and sensation was absent the first few weeks after establishment of the contracture, there was a rapid improvement of function the first few months. The patient was referred to us 6 months after establishment of the contracture and then mobility of the fingers and the thumb was scored reasonable. The mobility of the wrist was unimpaired. Because of additional improvement to good hand mobility and normal sensibility, no operation was needed.

Excision of necrotic muscle, neurolysis, and tenolysis only (Group 2) resulted in good hand mobility and an improvement in sensibility in two patients with infarction of only a part of flexors of the forearm. In both patients there was sufficient residual viable muscle and nerve tissue for restoration of hand function. The interval between establishment of the contracture and operation was only 3 and 5 months, respectively. Movement of the wrist and movement of the fingers improved to a good hand function. Sensibility improved in Patient 2 to a normal light touch and in Patient 3 to a diminished protective sensation in the median nerve area and a normal light touch in the ulnar nerve area (Table 3).

Tendon lengthening (Group 3) had disappointing results at evaluation. Between 1974 and 1990 this technique was used in eight patients. Although initially the mobility of the hand improved after tendon lengthening, recurrence of the contracture was seen in all patients. Therefore, six patients remained in the initial category of the classification. In three patients (Patients 6, 8, and 10) mobility improved slightly. Two patients also complained of loss of grip strength after tendon lengthening (Patients 5 and 9). Only two patients had reasonable postoperative results and the other patients had unsatisfactory or poor results (Table 3).

Tendon transfer (Group 4) was done in three patients with infarction of the deep and superficial flexors. Tendon transfer resulted in good hand mobility only in one patient (Patient 14; Table 3). In this patient, tendon transfer was combined with excision of fibrotic tissue. Patient 12 had improvement of one category in finger mobility after surgery, going from unsatisfactory to reasonable. In this patient a tenolysis also was done. In Patient 13, motor function improved slightly but still was categorized as poor. During surgery an extensive volar infarction was seen. In two patients the flexor digitorum superficialis was connected with the flexor digitorum profundus and in one patient (because more suitable donors were missing) the extensor carpi ulnaris was connected with the flexor digitorum profundus.

A combination of operative techniques (Group 5) was performed in four patients with a severe ischemic contracture with disappointing results. Two patients had slight improvement after four operations (Patients 15 and 16); in two patients motor function did not improve (Patients 17 and 18). Patients 15 and 16 had a combination of tendon lengthening, tendon transfer, and neurolysis in four and two procedures, respectively. Patient 17 had three operations; in another hospital the carpal bones and the distal ulna were resected in two procedures. A tendon lengthening was done in our hospital. In Patient 18, a tenolysis, a tenotomy of the flexor digitorum profundus of digitorum IV and digitorum V, and a neurolysis was done in one procedure. Only in Patient 15 did sensory function improve from a loss of protective sensation to a diminished light touch in the median nerve area. In the other patients no improvement of sensory function could be observed (Table 3).

Good results in hand mobility, in sensibility, and in grip strength were obtained in the free vascularized muscle transplantation group (Group 6). This procedure was done in seven patients between 1993 and 2000 with a total volar infarction and poor wrist, finger, and thumb mobility. Surgery was done in two stages because of the long-standing contractures (Fig 2); the first stage consisted of excision, tenolysis, and neurolysis (patients from Group 6 were excluded from Group 2) (Figs 3, 4), in the second stage the muscle transplantation was done (Fig 5). In six patients muscle transplantation was combined with a nerve graft. In two patients, because of a limited excursion of the gracilis muscle as a result of adhesions in the wrist, a third operation lysis of adhesions for improvement of function was performed. In six patients there was a considerable improvement of motor function as shown in Table 3 (Figs 6, 7). Unfortunately in one patient with an occlusion of the distal brachial artery, the gracilis muscle was lost (Patient 23). In retrospect, there had been an insufficient flow through the collateral circulation of the radial artery. Grip strength improved in all patients after free microvascular muscle transfer from 0% (power grip not possible) up to 60%.

Fig 2. *Preoperative Volkmann's ischemic contracture with a flexion contracture of the fingers and a supination and extension block of the wrist is shown.*

In all patients there was a postoperative improvement of sensory function. In three patients sensibility improved from a diminished protective sensibility to a normal light touch (Patients 19, 20, and 21), in two patients it improved from a loss of protective sensibility to a diminished protective sensibility (Patients 22 and 25) and in one patient it improved from a loss of protective sensibility to a diminished light touch in the median and ulnar nerve area (Patient 24) according to the Semmes-Weinstein test (Table 3).

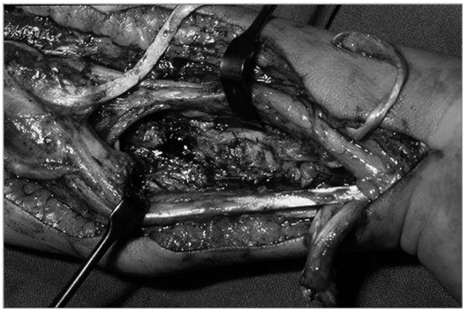

Fig 3. *The first phase of treatment is shown: excision of fibrotic tissue, tenotomy, and median and ulnar nerve neurolysis.*

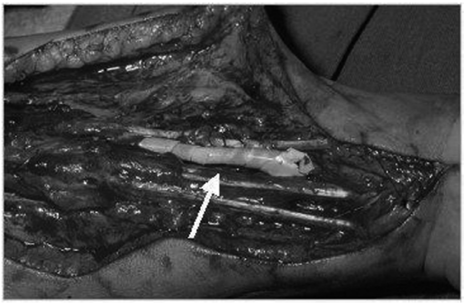

Fig 4. *The silastic sheet around the median nerve facilitates dissection in the secondary stage.*

All patients but one confirmed having one or more symptoms known to be related to compartment syndrome. As shown in Table 2, 22 patients had complaints of severe pain, 21 had reduced movement of the fingers, 20 had swelling of the hand, 20 had loss of sensation, and 15 patients had cyanotic fingers. Seven patients also had skin necrosis develop. All symptomatic patients reported their symptoms to their medical attendant; however, decompression was done only in three patients. The interval between the occurrence of symptoms and decompression in all of these patients ranged from 3 days to 3 weeks. In six patients, a plaster cast was split, in two patients the arm was elevated, and in one patient a drain was surgically inserted in the forearm musculature.

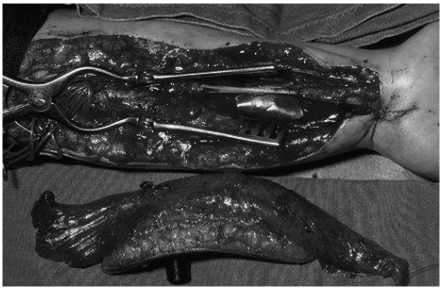

Fig 5. *The second phase of treatment is shown: intraoperative musculocotaneous gracilis flap.*

Fig 6A–B. *Postoperative flexion of fingers after free vascularised muscle transfer procedure is shown from the (A) side and (B) front views.*

In the majority of the patients in whom the contracture developed during childhood, a difference in forearm length was observed. In 16 of 18 patients a difference in forearm length that ranged from 75 to 92% (mean, 80%) was observed (Fig 8). One patient who did not have an arm length difference, was operated on 2 months after injury with an interval between operation and evaluation of only 2 years (Patient 3).

Fig 7A–B. *Postoperative extension of fingers after free vascularised muscle transfer procedure is shown from the (A) side and (B) front views.*

Symptoms	Present	Not present	Unknown
Pain	22	1	2
↓ Movement	21	2	2
Swelling	20	2	3
↓ Sensibility	20	2	3
Colour change	15	3	7
↓ Temperature	10	5	10
Blisters	7	16	2

Table 2. *Symptoms during Compartment Syndrome*

The other patient (Patient 1) was treated conservatively because of a strong improvement of hand function within a few months.

Sensibility was restored in five patients when the compartment syndrome just had subsided and the contracture had been established. According to the results of the questionnaire and the medical history, sensibility improved in the first 3 months in all other patients except five. Spontaneous improvement of strength and motion was reported in 17 patients.

DISCUSSION

Despite improved understanding of pathogenesis, diagnostics, and treatment methods of the compartment syndrome of the forearm, the extremely disabling Volkmann's ischemic contracture still occurs. The treatment of an established contracture is complicated and depends on the severity of the infarction and the affected muscle and nerve tissue. Although several methods of treatment are described in the literature, long-term results in different treatments are unknown.[6,10,12,18,15,17,24,27] Our main objective was to evaluate the long-term outcome in patients treated for Volkmann's ischemic contracture. For the patient and for the attending physician, knowledge about long-term outcome of treatment of patients with Volkmann's ischemic contracture is indispensable. Because of the fact that Volkmann's ischemic contracture is a relatively rare condition, our study population is too small to be able to provide statistically relevant correlations between method of treatment and functional outcome. However, our results do indicate some correlations between method of treatment and final outcome. In that respect, our study results can help in the decision making in future treatment of patients with Volkmann's ischemic contracture and can serve as a template for further research on this subject.

Because of the good outcome results in one patient with a mild contracture plus the considerable improvement in the first months after the establishment of the contracture in the majority of the patients in our study groups, we suggest initial conservative treatment in patients with good to reasonable hand function (Table 1).

	Wrist				Digitorum I				Digitorum II				Digitorum III				Digitorum IV				Digitorum V									
patientnr.	poor	unsatisfactory	reasonable	good	poor	unsatisfactory	reasonable	good	poor	unsatisfactory	reasonable	good	poor	unsatisfactory	reasonable	good	poor	unsatisfactory	reasonable	good	poor	unsatisfactory	reasonable	good	powergrip	ulnar[1]	median[1]	radial[1]	interval[2]	subj.result[3]
	Group 2 Excision, neurolysis, tenolysis																													
2		—	▶		—	—	▶		—	—	▶		—	—	▶		—	—	▶		—	—	▶		88	15	15	5	3	G
3	—	—	▶		—	—	▶		—	—	▶		—	—	▶		—	—	▶		—	—	▶		46	15	9	4	5	G
	Group 3 Tendon lengthening																													
4		■					■				■				■				■				■		62	12	12	4	10	U
5			■				■		■					■			■				■				38	13	14	4	132	P
6		■				■			■					■				—	▶			—	▶		73	12	12	4	10	U
7		■				■			■					■					■				■		42	12	12	5	132	U
8		■					■				■			—	▶			—	▶			■			76	12	12	4	10	R
9		■				■			■					■			■					■			44	9	11	4	216	P
10	■					—	▶		—	▶			—	▶			—	▶				■			34	7	8	3	60	R
11	■				■				■				■				■				■				24	15	15	5	24	U
	Group 4 Tendon transfer																													
12			■				■			—	▶			—	▶			—	▶			—	▶		11	10	12	5	12	P
13		■				■			■					■			■				■				23	15	15	5	18	U
14			■				■		—	—	▶		—	—	▶			—	▶				■		88	15	15	5	23	G
	Group 5 Mixed treatment																													
15	■				No Thumb				■				■				—	▶			—	▶			53	6	9	_	4	R
16	■					—	▶		■				■				■				■				20	9	12	4	24	P
17	■				■				■				■				■				■				0	12	10	4	84	P
18		■					■				■				■		■				■				92	12	12	4	11	P
	Group 6 Free micro vascular innervated muscle transfer																													
19	—	—	▶			■			—	—	▶		—	—	▶		—	—	▶		—	—	▶		60	15	15	5	5	G
20	—	▶			■				—	▶			—	▶			—	—	▶		—	—	▶		33	15	15	5	12	G
21	■				—	▶			—	▶			—	—	▶		—	▶			—	▶			10	15	15	5	60	R
22	—	—	▶		—	—	▶		—	—	▶		—	—	▶		—	—	▶		—	—	▶		10	9	9	5	7	G
23	■				■				■				■				■				■				X	X	X	X	12	P
24	—	▶					■		—	—	▶		—	—	▶		—	—	▶		—	—	▶		40	12	12	5	96	G
25		■			—	▶			—	▶			—	▶			—	▶			—	▶			8	9	9	5	72	R

Table 3. *Improvement of Wrist and Finger Mobility and Sensory Function after Treatment*

If after 3 months hand function deteriorates or does not improve, surgical intervention must be considered.

Excision of necrotic muscle, neurolysis, and tenolysis only resulted in good hand mobility and an improvement in sensibility in patients with infarction of only part of the flexors of

the forearm. This procedure is advised in patients who are diagnosed with unsatisfactory hand function with infarction of a considerable part of the deep and superficial flexors and neurologic signs (Table 1).[9] Even better results can be obtained if excision and neurolysis are combined with a tendon transfer (Table 3). Tendon transfers can best take place when nerves have recovered maximally, and contractures have been corrected with mobilization, splinting, and excision of fibrosis. The tendon transfers most often used, if muscles function, are the brachioradialis to the flexor pollicis longus and the extensor carpi radialis longus to the deep flexors of the fingers. After tendon transfer there should be adequate soft tissue coverage to facilitate tendon gliding.
Because our data show a high recurrence rate of the contractures and possible loss of power grip strength, tendon lengthening alone is not recommended (Table 3). If no suitable donors for tendon transfer are available, because of dorsal and palmar involvement, then free muscle transfer is indicated.

Fig 8. *This photograph, taken at long-term followup of a patient with Volkmann's ischemic contracture, shows the difference in forearm length.*

Because of the good outcome results in the free vascularized muscle transplantation group, we advise free vascularized muscle transplantation in patients with poor hand function and an extensive infarction diagnosed by magnetic resonance imaging (MRI; Table 1). Because MRI scan was not a standard procedure in treatment of patients with Volkmann's ischemic contracture until recently, results of MRI were not analyzed in the study results. In our experience, MRI serves as a very important diagnostic tool in patients with Volkmann's ischemic contracture. However, more research on this subject has to be done. In the majority of our patients, hand mobility and sensory function improved tremendously after free muscle transfer. A considerable increase of power grip strength also was seen; however, because of the contractile force of the gracilis muscle grip strength will stay limited. It should be mentioned that results might be different with an older study population.

Although not the subject of our study, we prefer a two-stage procedure with early excision followed by transplantation a few months later. If in the first stage the nerve is in continuity without deformity after neurolysis, a substantial recovery of sensory function often will occur. If nerve damaged classified as Grade 2 (hourglass deformity) or Grade 3 (total fibrosis) is observed (this is mostly the case when a substantial amount of forearm flexor muscles are fibrotic) a nerve graft combined with the free muscle transfer is planned in the second stage.[6,9] In most free muscle transfer cases in our series, sural cable grafts were necessary. At operation, the free muscle is connected proximally to the medial epicondyle and distally to the deep flexor tendons.

The exact moment of surgical intervention is important to consider in addition to the type of surgical procedure used. Although delay was advocated previously, our data also show that it is wise to operate on patients with poor or unsatisfactory hand function (Table 1) and severe muscle necrosis diagnosed by magnetic resonance imaging (MRI) in an early stage. In this stage, severe muscle necrosis easily is differentiated from viable muscle tissue and can be removed and prevent additional joint stiffness and nerve damage by fibrosis.[3,9,20,24] Early surgery also is necessary in patients with a so-called prolonged pain syndrome because prompt neurolysis and excision of fibrotic tissue will resolve the pain immediately.[9]

The difference of length of the forearm and hand observed in our patients has been described previously.[28] Reasons for this length difference may be impaired oxygenation of growth plates, remaining muscle, and nerve tissue. This hypothesis is supported by our results, although our study did not investigate mechanisms. Children with Volkmann's ischemic contractures and/or their parents should be informed about the possibility of having a length difference of the forearm.

A supracondylar fracture of the humerus is the most frequent cause for the development of a Volkmann contracture, followed by a fracture of the forearm. Therefore, especially in children, these fractures must be monitored carefully to facilitate early diagnosis of vascular injury or compartment syndrome.[8] Presence of symptoms such as extreme, poorly localized pain particularly with passive stretching of the muscle by manipulation of the digits and the wrist, a sensory deficit, and reduction of active movement requires aggressive treatment. Although pain and loss of sensibility are not universal findings,[5] in our survey only one of our patients was asymptomatic. In all other patients symptoms were present but unfortunately they were not recognized or treated adequately. As shown by the results of our study, measurements such as opening of the plaster cast and elevation of the arm are not sufficient. Decompression should be done immediately to restore the microcirculation of the forearm.[7] In cases of a suspected vascular injury, decompression must be combined with vascular exploration and restoration of blood flow.

The most opportune time for fasciotomy is during the acute phase of the compartment syndrome that is, within 24 hours. Sheridan and Matsen [22] reported that the frequency and severity of complications of the decompression was related directly to the promptness with which it was done. In our patient group, decompression was done in three patients; however, the interval between occurrence of symptoms and decompression in these patients was more than 48 hours, which is much too late.[4]

The occurrence of Volkmann's ischemic contracture can be reduced additionally by early detection and treatment of compartment syndromes. Patients with high-risk injuries such as a supracondylar humerus fracture and a fracture of the forearm should be monitored carefully to facilitate early diagnosis of vascular injury or a compartment syndrome. If symptoms of compartment syndrome are present, decompression should be done immediately to restore microcirculation and if vascular injury is suspected vascular exploration should be done.

In patients with infarction of only a part of the deep forearm muscles diagnosed by MRI who have reasonable to good hand function, conservative treatment can be initiated with physical therapy and application of a splint. If this treatment is not adequate or if the contracture is more severe, surgical intervention can be considered. Excision of fibrotic muscle tissue, neurolysis, and tenolysis is advised in patients diagnosed with unsatisfactory hand function with infarction of a considerable part of the deep and superficial flexors and neurologic signs. Good results can be obtained if excision and neurolysis is combined with tendon transfers, specifically in patients who are treated soon after injury. Because of the high recurrence rate of the contracture and possible loss of power grip strength, we do not recommend tendon lengthening alone. In patients with poor hand function and an extensive infarction, we do free vascularized muscle transplantation in two stages. In the majority of our patients, hand mobility and sensation improved tremendously after free muscle transfer. A considerable increase of power grip strength also was observed.

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CHAPTER 4

PROGNOSTIC FACTORS FOR OUTCOME AFTER MEDIAN, ULNAR AND COMBINED MEDIAN-ULNAR NERVE INJURIES: A PROSPECTIVE STUDY

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ABSTRACT

Introduction - A major problem in surgery of peripheral nerve injuries of the upper extremities is their unpredictable final outcome. Information on prognostic factors is needed to improve functional outcome after repair of peripheral nerves. A retrospective study design has important limitations and a lack of prospective data on this subject exists. Therefore potentially important prognostic factors for functional outcome were identified and analysed in a prospective study design.

Objective – Identification of prognostic factors of functional recovery of peripheral nerve injury of the forearm and their independent contribution in the outcome in the first year after repair.

Methods - In patients with a median, ulnar or combined median-ulnar nerve injury, age, level of injury, type of nerve injury, number of damaged structures, number of damaged arteries, education, smoking and posttraumatic stress were analysed as prognostic factors for functional outcome after repair of peripheral nerves. Outcome parameters were sensory recovery (Semmes Weinstein monofilament test) and motor recovery (MRC, power grip, pinch grip) and the ability to perform daily activities.

Results - Age group, education, location of injury, posttraumatic stress after one month, number of injured structures and number of injured arteries are found to be predictive of functional recovery after peripheral nerve injuries of the median and/or ulnar nerve of the forearm.

Conclusion – Our prospective analysis of prognostic factors shows several factors to be predictive of functional recovery after peripheral nerve injuries of the median and/or ulnar nerve of the forearm. Of these prognostic factors only posttraumatic stress can be influenced to optimize functional outcome.

INTRODUCTION

The hand is the most injured body part in humans and the leading body part treated in hospital emergency departments. In 30-40% of the injury events the upper extremity is involved. Hand injury generally takes place in a young and economical active population[34]. When cuts and lacerations of the fingers and hands are combined, the number of days-away-from work are second only to back strain and sprain frequency according to the US Bureau of Labor Statistics data.[1] Occupational hand injury rates varied from 0.33 to

11.0 per 100 worker-years according to four US and eight international industry specific studies.[2] An example of a hand injury with serious consequences for hand function and an unpredictable outcome is the peripheral nerve injury of the forearm. Few data are available to determine the incidence, but the estimated incidence of peripheral nerve trauma is 1/1000 in the population per year[3]. Nerve injuries are difficult for which there may be no satisfactory surgical solution. Recovery following these injuries is often disappointing. Even with a technically perfect microsurgical repair, sensory functions and strength cannot be expected to fully recover, although improvement generally occurs.[7-13,15,16, 29, 25,32,37, 38,41,42,44]

A major problem in surgery of peripheral nerve injuries is the unpredictable final outcome. More knowledge about prognostic factors is needed for further improvement of functional outcome after repair of peripheral nerves. Early intervention in patients with suboptimal sensory and motor recovery based on their individual profile of prognostic factors suspected for insufficient outcome, could improve overall outcome results of peripheral nerve injury. Furthermore information on prognostic factors is needed to inform patients about their functional and social prospects. Although several factors like age, type of injury, level of injury and delay have been described to influence outcome results of peripheral nerve injury[8,10,. 45,46,47,48,49,50,51,52], most of these studies are retrospective[8]. Besides, no conclusive agreement exists on indepent predictors for functional outcome of median and ulnar nerve injuries. Our aim was, because of limitations of retrospective study design and the lack of prospective data on this subject, to identify prognostic factors that may predict prospectively functional recovery of peripheral nerve injuries of the forearm. Furthermore the independent contribution of these prognostic factors in the outcome in the first year after repair was studied. In this prospective study, factors identified as prognostic in retrospective studies (age, level of injury, type of nerve injury, injured nerve, number of damaged structures and arteries, education, smoking and posttraumatic stress) were analysed. Outcome parameters were motor and sensory recovery and the ability to perform daily activities in the first year after injury.

MATERIAL EN METHODS

Study population

Between 2000 and 2003 patients with a peripheral nerve injury, operated in the University Medical Center Rotterdam, the University Medical Center Utrecht (UMCU), the MCRZ Rotterdam, the Isala Clinics Zwolle, the University Medical Center Nijmegen "St. Radboud" and the University Medical Center Amsterdam (VU) were asked to participate in this study. To meet the recruitment deadline of the study a multi center approach was needed. Inclusion criteria were a traumatic median and/or ulnar nerve injury between wrist and elbow crease (divided in 3 sections; proximal third, middle third (intermediate) and distal third). Patients under the age of 12, patients with amputations of hand and fingers and patients with insufficient knowledge of the Dutch language were excluded from participation. Also data of people with a partial lesion of the median or ulnar nerve were not used for statistical analysis. According to these criteria, 82 patients were asked for study participation. Three patients rejected participation. Eighteen patients initially included in the study were lost during follow up (Table I). Finally the data of 61 patients were used for evaluation. The majority of the patients lost from follow-up, injured themselves as a consequence of aggressive behavior or were under the influence of alcohol and difficult to motivate for follow-up. Comparable problems with recruitment can also be found in literature in studies where alcohol or drug addicts are approached for follow-up[43]. All participants provided informed consent. For this study purpose, patients were evaluated at 1, 3 and 12 months after injury. The Medical Ethical Committee of the University Medical Center Rotterdam approved the study.

Study population	
Number of patients with a peripheral nerve injury	98
Number of patients who did not want to participate	3
Number of patients who did not meet the inclusion criteria	16
Loss of follow-up	18
Number of patients used for evaluation	61

Table I *Study population*

Assessments

The assessments used are presented in Table II.

Sensory innervation	Semmes-Weinstein monofilament test
Motor innervation	Manual muscle strength testing according to MRC
Power grip strength	Jamar dynamometer
Tip-pinch grip strength	Jamar pinch gauge meter
Daily living	Questionnaire (DASH)
Psychological functioning	Questionnaire (IES)
Socio-demographic charact.	Questionnaire (own design)

Table II *test battery*

Sensory Innervation:

For sensory evaluation the pocket version of the Semmes-Weinstein monofilament test was used (monofilaments 2.83, 3.61, 4.32, 4.56 and 6.65; ranked 1-5) according to the procedure described by Bell-Krotoski[17]. For this study purpose the sum of assessments from 3 critical sites for each nerve was recorded, so scores ranged from 0 (anaesthetic) to 15 (normal sensation). For median nerve repair: distal phalanges of digits I and II and proximal phalanx of digit II and for ulnar nerve repair: distal phalanx of digit V, proximal phalanx of digit V, and proximal hypothenar were measured. The percentage of the maximum score was calculated for both the median and ulnar nerve areas. If a combined median-ulnar nerve transection was present, the combined percentage was calculated. The percentages were used for analysis.

Motor innervation:

For examination of motor function manual muscle strength testing according to Medical Research Council Muscle Power Grading 0 (no palpable contraction)-5 (normal) was used[20.32]. For median nerve injuries palmar abduction of digit I was examined, and for ulnar nerve injuries abduction of digits II and V, and adduction of digit V. The percentage of the maximum score was calculated for both the median and ulnar nerve function. If a combined median-ulnar nerve transection was present, the combined percentage was calculated. The percentages were used for analysis.

Power grip strength:

Grip strength was measured using a Jamar dynamometer according to Mathiowetz et al[30]. Three trials with each hand were carried out alternately (second handle position), and the mean value was calculated for each hand. In case the third measurement was the highest, a fourth measurement was performed. The results were expressed as a percentage of the performance compared to the uninjured hand, which was considered normal. Corrections for hand dominance were made[36].

Tip-pinch grip strength:

For assessment of tip pinch strength the Jamar pinch gauge meter was used according to Mathiowetz et al[30] . Three trials with each hand were carried out alternately, and the mean value was calculated for each hand. In case the third measurement was the highest, a fourth measurement was performed. The results were expressed as a percentage of the performance compared to the uninjured hand, which was considered normal. Corrections for hand dominance were made[36]

Questionnaires

Daily living:
For assessment of functional recovery, the DASH- questionnaire (Disabilities of Arm, Shoulder and Hand) version 2.0 (May 1997) was used after translation according to the criteria of the institute for Work& Health and the American Academy of Orthopaedic Surgeons[24, 31]. In this questionnaire patients were asked to score 30 items (each item scores 1-5 Likert scale) related to functional activities and injury related symptoms. The raw functional symptom score (FSS) was converted into a 0-100 scale, with 0 reflecting minimum and 100 maximum disability.

Psychological functioning:
To measure the current degree of subjective impact of peripheral nerve trauma experienced by a person, the IES (Impact of Event Scale) was used at 1 and 3 months after injury. The IES, designed by Horowitz in 1979, includes 15 items that refer to "the past seven days," across the subscales of avoidance and intrusion and taps dimensions that are similar to the defining symptoms of PTSD[25]. Each item has a scoring range of 0-5 on a 4-point scale (0 = not at all, 1 = rarely, 3 = sometimes, 5 = often). Total IES scores range from 0-75 (worst score).

Sociodemographic characteristic: Patients were asked to answer questions about their occupation, education level ranging from one (did not finish primary school) to seven (university degree) and whether they returned to work.

Procedure
Assessments were done in accordance with a standardised test procedure and were performed by a physician not involved in the patient's surgery or treatment following the injury.

Statistical analysis:
Predictive factors to be investigated were age, injured nerve, number of damaged structures, number of damaged arteries, location of injury (proximal, intermediate and distal), type of injury (sharp, crush), smoking, education level and posttraumatic psychological stress. For statistical analysis of post traumatic stress 1 and 3 months IES scores were analysed, for evaluation of functional outcome 12 months measurements were used. Data analyses were performed separately for sensory recovery, motor recovery and daily activities (DASH). The association between each predictor and recovery was first studied by univariate analysis of variance or correlation analysis. Variables that were

univariately associated with motor or sensory recovery (p<0.05) were then included in a multivariate regression model to evaluate the independent contribution in the prediction of a specific type of recovery.

RESULTS

Study population

Characteristics of study population	
Age child <16	5 (8%)
adolescent 16-25	18 (30%)
young adult 26-40	19 (31%)
adult > 40	19 (31%)
Sex Male (%)	51 (84 %)
Female (%)	10 (16 %)
Type of injury Median	22 (36%)
Ulnar	31 (51%)
Combined	8 (13%)

Table III. *Characteristics of study population*

For this study purpose 61 patients with median (n= 22), ulnar (n=31) and combined nerve injuries (n=8) that were surgically repaired in the participating hospitals were prospectively examined at 1, 3, and 12 months after injury. Study population characteristics are demonstrated in Table III. After one year seven patients (15.6%) had not yet returned to work, which involved 22% of all patients performing a job that specifically required hand function.

Outcome and predictive factors

First, the relationship to functional outcome of factors reflecting characteristics of the lesions as well as other patient characteristics that were found to have prognostic importance according to the literature was evaluated. In Table IV is indicated which factors were associated with the outcome measurement at 12 months after surgery, using correlation analysis for continuous variables and analyses of variance for categorized prognostic factors.

		Sens med	Sens uln	Sens hand	Power grip	Pinch grip	MRC med	MRC uln	MRC hand	DASH score
Age		+	-	+	+	-	-	-	-	+
Education		+	-	-	-	+	+	-	-	+
Smoking		-	-	-	-	-	-	-	-	-
Location	Dist./interm.	-	+	-	-	+	-	-	-	-
	Dist./proxim.	-	+	+	-	+	-	-	-	-
	Interm/proxim.	-	-	-	-	-	-	-	-	-
No of structures		+	-	+	+	+	+	+	+	-
Injur.nerve	Comb./median	-	X	X	+	-	-	X	-	-
	Comb./ulnar	X	-	X	+	-	X	-	-	-
	Ulnar/median	X	X	-	-	-	X	X	+	-
No of arteries		-	-	-	+	+	-	+	-	-
Type of injury	Sharp/crush	-	-	-	-	-	-	-	-	-
Posttraum. stress	1 month	-	-	-	+	+	-	-	-	+
	3 months	-	-	-	-	-	-	-	-	-

Table IV. *Univariate analysis using correlation analysis for continuous variables and analyses of variance for categorized prognostic factors*

X = Not applicable

+ = significant

- = not significant

Subsequently the variables that were found to be associated with the outcome measurements were analysed using backward stepwise multiple regression analyses to evaluate the most important factors. For location of injury and kind of nerve damage, dummy variables were used.

Ulnar sensibility

Univariate analysis of variance showed that only location of injury was significantly related with ulnar sensibility (F(2,58) 4.02, p=.023). Distal lesions are associated with better ulnar sensory recovery than intermediate (mean difference 3.8, p=0.029) or proximal lesions (mean difference 3.8, p=0.045).

Median sensibility

Number of structures involved (r =-.27,0.025) education (r =-.29, p =0.017) and age (r =-.25 p=0.048) were significantly correlated with median sensibility. Backward stepwise multivariate regression analysis of these 3 factors showed a significant model (F(3,48)=2.99, p=.040), that explained 16% of the variance, with a significant contribution of education, see Table V.

	Sens med	Sens uln	Sens hand	Power grip	Pinch grip	MRC med	MRC uln	MRC hand	DASH score
Age			-.34**	-.25*					
Education	.29*				.27*				
Location:									
Distal					.38**				
Intermediate									
Proximal			-.28**						
No of structures				-.30**	-.29*	-.29*		-.31*	
No of arteries							-.29*		
Damaged nerve									
Ulnar									
Median				.23*					
Combined									
Posttraum. Stress after 1 month				-.26*					.42**

Table V *Beta coefficients significantly related to outcome in multiple regression analyses*
**p<.05, **p<.01*

Sensibility of hand
Age (r =-.38, p=0.003), location of injury F (2,58) 4.17, p=.023 and number of structures (r =-.33, p=0.012) were significantly related with sensory recovery of the hand. Younger age was associated with better sensory recovery of the hand. Distal lesions were related to better sensory recovery of the hand than proximal lesions (mean difference 5.35, p=0.018). Intermediate lesions were not associated with less sensory recovery than distal lesions. When more structures were involved in the lesion the sensibility of the hand was less.
Multivariate regression analysis of these 3 factors showed a significant model [F (4,54)=5.85, p<.001], that explained 30% of the variance, with a significant contribution of age and location of injury, see Table V. Older age and proximal lesions were associated with less sensibility of hand.

Power grip
Univariate analysis showed that age (r = -.35, p=0.02), number of damaged structures (r =-.40, p=0.003), number of arteries (r =-.27, p=0.034),) and post traumatic stress 1 month

postoperative (IES1) (r =-.40, p=0.002) were significantly related with power grip. Older age group, more damaged structures, more arteries involved and a higher degree of posttraumatic stress one month postoperative were associated with lower power grip. In addition power grip differed according to the damaged nerve, i.e. combined lesions being associated with less power grip in comparison to median (mean difference = 31.6) or ulnar (mean difference= 23.5) nerve lesions only (F(2,58)7.20, p<0.01). Backward stepwise multivariate regression analysis of these 5 factors resulted in a significant model [F(6,52)5.46, p<.01] that explained 39% of the variance. Age group, number of damaged structures and kind of damaged nerve as well as posttraumatic stress 1 month postoperative (IES1) all contributed significantly to this outcome, see Table V .

Pinch grip

Pinch grip differed according to location [F (2,58)5.41, p<.01]; (mean difference of distal vs intermediate is 18.8, p=0.036 and mean difference of distal vs proximal is 23.9, p<.01). In addition lesion of more structures (r=-.42, p=0.002), more arteries (r= -.30, p=0.018) and less education (r=.29, 0.032) of the patients were significantly related to less pinch grip. Backward stepwise regression analysis of these factors showed a significant model [F (6,45)4.33, p<.01] that explained 37% of the variance, with a significant contribution of education, number of damaged structures and location of injury, see Table V. A distal location of injury, higher education and less structures involved was associated with a better pinch grip.

Median motor recovery

Univariate analysis showed that fewer structures involved in the lesion (r= -.30, p=0.023) and the type of damaged nerve [F(2,58)7.98, p<.01] were significantly related with a better median motor recovery measured by MRC. Backward stepwise multivariate regression analysis of these factors showed a significant model [F (3,55) 2.97, p=.04] explaining 14% of the variance with a significant contribution of the number of structures involved in the lesion, see Table V.

Ulnar motor recovery

First, number of structures (r= -.27, p=0.037) and number of arteries, (r =-.29, p=.035 0.) were found to be significantly related to a better ulnar motor recovery measured by MRC. Backward stepwise multivariate analysis of these factors showed a significant model [F (2,56)3.17, p=.05] that explained 10% of the variance, with a significant contribution of the number of arteries involved in relation to ulnar motor recovery, see Table V.

Motor recovery of whole hand

Univariate analysis showed that damage in fewer structures (r=-.31, p=0.016) and in fewer arteries (r=-.27, p=.038) was significantly related to better motor recovery of the whole hand measured by MRC. Backward stepwise multivariate regression analysis of these two factors showed a significant model [F (2,56)3.49, p=.037] that explained 11% of the variance, with a significant contribution of only the number of structures: a higher number of damaged structures was related to lower motor recovery of the hand, see Table V.

DASH

Univariate analysis showed that age (r=.25, P=.05), educational level (r=-.30, p=.012), and posttraumatic stress one month after injury (r=.46, p=<.01) were significantly related to the DASH results. Backward stepwise multivariate regression analysis of these factors showed a significant model [F (3,50)6.53, p<.01] that explained 28% of the variance, with a significant contribution of post traumatic stress one month after injury to DASH scores indicating more disability, see Table V.

	Sens Med	***Sens Uln***	***Sens Hand***	***Power Grip***	***Pinch Grip***	***MRC Med***	***MRC Uln***	***MRC Hand***	***DASH Score***
	M (SD)	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***
Distal	67.1 % (34.1)	83.5% (33.2)	76.4% (17.4)	67.6% (20.5)	65.3% (22.9)	82% (30.8)	79% (34.4)	61.1% (35.6)	15.9 (17.2)
Proximate	69.3% (40.1)	58.0% (38.2)	63.7% (21.1)	59.% (29.5)	41.4% (33.0)	70% (40.2)	80% (43.2)	40.3% (34.9)	10.9 10.1
Intermed.	86.7% (33.2)	58.4% (33.8)	72.2% (18.8)	62.8% (14.5)	46.4% (14.7)	86.6% (33.2)	62.2 % (38)	46.7% (33.17)	21.0 21.2

M =Mean SD = Standard deviation

Table VI *Location of injury in relation to outcome at 12 months*

	Sens Med	***Sens Uln***	***Sens Hand***	***Power Grip***	***Pinch Grip***	***MRC Med***	***MRC Uln***	***MRC Hand***	***DASH score***
	M (SD)	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***
Median	55.0% (33.1)	96.7% (11.3)	75.7% (15.1)	73.2% (19.3)	64.3% (22.7)	71.6% (38.6)	94.2% (21.6)	65.8% (40.2)	31.7 (17.6)
Ulnar	90.5% (25.9)	64.2% (33.3)	75.6% (18.4)	65.1% (21.1)	60.4% (23.9)	94.6% (15.8)	68% (39.8)	50.3% (30.1)	14.8 (14.4)
Combined	37.1% (24.6)	51.4% (33.1)	51.4% (20.3)	41.6% (8.6)	31.3% (28.1)	51.4% (38)	54.2% (39.6)	42.7% (36.9)	27.6 (21.8)

M =Mean SD = Standard deviation

Table VII *Injured nerve in relation to outcome at 12 months*

	Sens Med	Sens Uln	Sens Hand	Power Grip	Pinch Grip	MRC Med	MRC Uln	MRC Hand	DASH score
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Sharp	72.9% (33.7)	74.6% (31.8)	73.7% (19.9)	66.4% (20.0)	60.3% (25.9)	83.4% (31)	77.4% (35)	58.7% (34.7)	16.1 (17.5)
Crush	50.5% (41.9)	82.9% (31.5)	66.6% (13.9)	59.4% (31.0)	45.9% (20.1)	60% (40)	71.4% (48.8)	31.4% (36.3)	14.29 (11.44)

M =Mean SD = Standard deviation

Table VIII *Type of injury in relation to outcome at 12 months*

DISCUSSION

Our prospective study revealed that age, education, location of injury, number of structures involved and post traumatic stress 1 month after repair of a peripheral nerve injury were all significant predictors for different aspects of functional outcome 12 months after injury.

Prognostic factors:

Analysis of our prospective data showed a significant influence of age on sensory recovery and motor recovery (power grip). Several retrospective studies have identified age as an important factor for functional recovery after nerve repair [8,49,50,52,54]. It has generally been accepted that children exhibit a greater capacity for nerve regeneration than adults.[15,16,18,32, 57] Neuronal activity re-establishes rapidly in children, particularly in the very young, in whom the rate of axonal regeneration is thought to be as much as 5 mm per day[56.] Besides, it is well known that age delays axonal regeneration by slowing axonal degeneration, axon sprouting, and Schwann cell response. The end result is a regenerated nerve with fewer axons and less myelination in older patients. In addition Apel et al. found in aged rats an impaired neuro-musculair joint response to injury, which may contribute to poor neuromuscular recovery seen after nerve injury in this group of peripheral nerve injury patients[65]. Although experimental and histological studies indicate a better nerve re-growth in children, there are also some findings giving evidence for a superior cerebral adaption in children[16, 55]. This neural plasticity has been pointed out as the crucial factor for their better peripheral nerve regeneration[28,34,39]. Children are supposed to have a superior cerebral capacity to adapt and probably benefit from better cortical acquisition processes and are thus capable of putting the changes in the nerve messages to better use.[39] Lundborg and Rosen reported (n=19) an assocation between cognitive capacity and sensory recovery of tactile gnosis[39,53]. A study of a subgroup of our study population did not reveal an association between cognitive capacity and recovery of sensory function measured by Semmes Weinstein test. However, in this study population no children < 12 years were included and only 8% of the study population was < 16 years[61]. Although a relation between cognitive capacity and functional recovery could not be demonstrated, we did found level of education to be a predictor for recovery of median sensory function and for pinch grip. Higher level of education resulted in better functional outcome.

In our study, location of injury was a significant predictor for both motor as sensory recovery of peripheral nerve injury of the forearm. We found that distal lesions had better recovery of pinch grip 12 months postoperative than proximal or intermediate lesions at the forearm and both distal as intermediate lesions had better recovery of sensory function12 months postoperative than proximal lesions. However, as indicated by Rosen, recovery at 12 months is not supposed to have reached it's end point and in case of proximal forearm lesions. At the time of evaluation nerve fibers could not yet have reached the musculature of the hand[58]. Although pinch grip was correlated with location of injury, MRC scores and powergrip were not influenced by location. Location of injury[8] is known for its influence on outcome after nerve repair [18,57,44,45,49]. With restoration of nerve continuity, axons may regenerate and, thus, re-innervate the motor end plates and sensory receptors. When the nerve injury is very proximal, nerve regeneration may not occur in sufficient time for muscle reinnervation. Furthermore because of shorter distance between level of injury and final receptors and better organised sensory and motory fascicles in distal injuries there is less risk for mismatching. Ruijs described in her meta-analysis of predictors of functional outcome after median and ulnar nerve that intermediate or high lesions compared to low lesions gave an 54% lower change of motor recovery but had no inpact on sensory recovery[52].

Our study results did not show a correlation between median and/or ulnar nerves and sensory recovery. Concerning motor recovery we found a better power grip after median nerve injuries than after ulnar injuries. Better motor recovery of the median nerve as opposed to the ulnar nerve was already described in earlier studies. [52,59,60,64]. The meta analysis of Ruijs showed a 71% lower change of motor recovery in ulnar than in median nerve injuries[52]. This can be explained by the fact that especially distal ulnar lesions have a larger motor component than median lesions.

Our study revealed that the number of damaged structures, reflective of the seriousness of the lesions was predictive for motor recovery (power grip, pinch grip and MRC scores). Daily activities and sensory recovery were not influenced by the number of damaged structures. Although there are no precise data in the literature regarding the dependence of nerve repair outcomes on other injuries in the nerve repair region, it has been assumed that the presence of such injuries is certainly a significant variable of outcome of nerve repair[64]. However in the retrospective study of Vordemvenne accompanying artery and flexor tendon injuries were not identified as a predictive factor for outcome[60] and in our study only motor recovery was influenced by number of damaged structures.

In our prospective study posttraumatic stress proved also to be a predictor for functional outcome after peripheral nerve injury of the forearm. Multivariate regression analysis demonstrated an independent relation between posttraumatic stress 1 month postoperative and power grip: a higher degree of posttraumatic stress one month postoperative was associated with less power grip. In addition posttraumatic stress 1 month after injury was independently related to daily activities measured with daily activity of shoulder and hand (DASH). A higher degree of posttraumatic stress one month after injury was associated with greater motor disability. Early psychological stress symptoms after peripheral nerve injury, have been identified as a predictive factor for functional recovery after peripheral nerve injury and also contribute to this highly variable outcome. In a retrospective study 94% of the patients with peripheral nerve lesions demonstrated posttraumatic psychological stress. Psychological morbidity, measured with the impact of event scale was found in 36% of this retrospective study population. Multiple linear regression of results of the retrospective study showed a significant association between psychological stress and functional recovery and a delayed return to work [20]. In order to analyse the contribution of the different aspects of post traumatic stress disorder (PTSD) responsible for impaired functional recovery further study on early detection of and possible intervention in posttraumatic stress should be performed.

Because of the low incidence of crush injuries in our study group, owing to the strict inclusion criteria, we were not able to detect differences in the contribution of crush versus sharp lesions in functional outcome.

No relation between smoking and functional outcome was found. Currently, relatively little has been written regarding the specific effects of smoking on peripheral nerve function after injury or repair. In two retrospective studies healing after nerve transection appeared to be affected adversely by cigarette smoke[61,62]. However in an experimental study of the effects of tobacco smoke on nerve healing after crush injury in a rat model, no significant association between tobacco smoke exposure and delayed nerve recovery after a nerve crush injury was found[63].

Although we believe that absence of consensus about predictors for outcome after peripheral nerve injuries may be due to the retrospective nature of the majority of studies, another major factor inducing variation concerning predictive factors of functional outcome after peripheral nerve injuries is the complexity of postoperative assessment

[8,10, 45- 52]. Postoperative assessment of hand function after peripheral nerve injury is very complicated, as there are numerous tests to choose from and often tests are time consuming and difficult to administer[14, 45]. Literature suggests combined assessments, using both objective scoring systems and self-report questionnaires, but the choice of evaluating methods to minimize biases is not obvious and the definition of efficacy, or good outcome, is not always evident.

Because assessment methods used in different studies can vary considerably, an extensive comparison between different outcome studies is difficult and study results are not always representative for "true" functional outcome of hand function. A major step in post operative assessment of hand function after peripheral nerve injury was Rosen's thesis in 1996 about proper evaluation of median and ulnar nerve injuries[38,39,59]. This certainly contributed to improved understanding of functional testing. For that reason our test battery was based on her findings. To use all the tests she described in her thesis would have been too time consuming; therefore we had to make a selection based on factors like validity, reliability and administration time. Therefore the Semmes Weinstein Monofilament Test (SWMF) was incorporated in our test battery. Advantages of SWMF include the ability to assign numbers to sensory touch thresholds, regulation of force variations, and translation of forces obtained into functional levels. For evaluation of motor function we included manual muscle testing and for assessment of integrated function the Jamar dynamometer (pinch and power grip) [38]. Furthermore as suggested by Vordemvenne et al., we added the DASH questionnaire to our test battery in order to sufficiently estimate the patient's opinion about the impact on their activities in daily life after nerve reconstruction[60]. We believe our test battery (which had to be combined with the Impact of Event Scale and a questionnaire concerning socio-demographic characteristics) enabled us to obtain an accurate view of the results of nerve repair in terms of restoration of function and still was acceptable for participating patients in terms of administration time.

CONCLUSION AND FUTURE PERSPECTIVES

As confirmed by our prognostic study age, location of injury, number of injured structures and arteries and posttraumatic stress are strong predictors for functional recovery after peripheral injuries of the median and/or ulnar nerve of the forearm. These data may help us to inform patients about their expected recovery during the first year after injury. The information also enables us to optimize outcome of patients with peripheral nerve injuries of the forearm. Although our prospective analysis of prognostic factors shows several factors to be predictive of functional recovery after peripheral nerve injuries of the

median and/or ulnar nerve of the forearm, posttraumatic stress is the only factor which possibly can be influenced and to optimize functional outcome results.
To what extent the latter really improves outcome should be subject of further study.

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CHAPTER 5

COGNITIVE CAPACITY: AN ASSOCIATION WITH RECOVERY OF SENSIBILITY AFTER PERIPHERAL NERVE INJURY OF THE FOREARM?

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ABSTRACT

In the recovery process of sensibility after repair of a peripheral nerve injury of the forearm, not only age but also surgical repair techniques are of importance. If regenerating axons are misdirected, reorganisation or other adaptic processes are needed at the level of the somatosensory brain cortex. These processes are thought to be dependent on the patient's cognitive capacity. We conducted a prospective multicentre study to assess the association between cognitive capacity and recovery of sensibility after peripheral nerve damage of the forearm.

Patients with a traumatic peripheral nerve lesion of the forearm and consecutive surgical repair were included. After 12 months, the patients were assessed with respect to recovery of sensibility (Semmes–Weinstein monofilaments) and cognitive capacity, with four tests assessing different aspects of cognitive functioning.

Twenty-eight patients (25 male, three female; median age: 28.5 years; range: 15–79 years) with median and/or ulnar nerve injury of the forearm were included in the study. Younger age showed a positive association with sensory recovery ($\beta = -0.845$, 95% CI: −1.456 to −0.233; $p = 0.01$). No association was found between the cognitive-capacity tests used and sensory recovery.

The present prospective study did not reveal any association between recovery of sensibility measured by Semmes–Weinstein test score and cognitive capacity. Further studies should be performed to confirm these results.

In the Netherlands, each year approximately 400 patients are diagnosed with a traumatic lesion of the median or ulnar nerve.[1] Recovery after nerve repair often leads to reduced sensibility and motor function, despite improved results in refinements of surgical techniques and microenvironmental factors influencing nerve growth (mainly experimental results).[2, 3, 4 and 5] problems in daily life activities and at work occur due to the inadequate nerve repair resulting in a partial or total dysfunctional hand.[6, 7 and 8]

Besides peripheral factors such as level[9] and type of injury,[6] the central nervous system is thought to play an important role in the recovery process after nerve injury. Research in primates[10, 11, 12 and 13] demonstrated remarkable alterations in the somatosensory brain cortex after peripheral nerve injury of the forearm. Formerly well-defined finger representations in the somatosensory brain cortex changed into dispersed discontinuous patches[10, 14 and 15] due to misdirectional growth of regenerating axons in the hand. Such a phenomenon is thought to be the initiator of functional reorganisation of the somatosensory brain cortex.[4, 10, 13, 14, 15 and 16]

A more orderly cortical functional reorganisation, and thereby probably a better sensory recovery after nerve injury, can be accomplished by teaching the patient's central nervous system to adapt to a correct interpretation of the altered sensory impulses given by the hand. Children, not yet deprived of adaptic processes, show good recovery[17] without any sensory rehabilitation.[6 and 18] In adults, cognitive functioning, a reflection of a collection of mental processes and activities used to perceive and remember,[5] is thought to be responsible for the variety of sensory recovery. This variety of sensory recovery exists even after re-learning programmes.[19]

Earlier retrospective research suggested specific cognitive capacities, that is, verbal learning and visio-spatial ability, to be prognostic factors for the functional outcome after peripheral nerve transection of the forearm.[5] To evaluate this prospectively, we conducted a multicentre study to assess the association between cognitive capacity and recovery of sensibility after peripheral nerve injury of the forearm using Semmes–Weinstein monofilament (SWMF) testing.

MATERIAL AND METHODS

From 2000 through 2001, patients with a partial or total nerve transection of the median and/or ulnar nerve between wrist and elbow were included in a multicentre study with seven participating hospitals. Patients had to be 12 years or older, and in all cases, surgical repair had to be performed within 3 months after nerve trauma using epineural and fascicular microsurgical repair techniques.

Twelve months after the peripheral nerve injury, the touch/pressure perception sensibility status of the patients' hand was assessed by Semmes–Weinstein test score and cognitive capacity tests were performed. All tests were done by one member of the research team, not involved in any treatment of these patients. All patients did not participate in any sensory re-learning programmes. At baseline and at 12 months, specific demographic data were recorded (Table 1 and Table 2). The study was approved by the medical ethical committee of the Erasmus Medical Center, Rotterdam, and an informed consent was obtained from all participants.

Demographic data	Number (%)
Patients	28
Nerve injury	
Median	11 (39,3)
Ulnar	13 (46,4)
Combined	13 (46,4)
Type of injury	
Total	27 (96,4)
Partial	1 (3,6)
Dominant hand affected	16 (57,1)
Time to nerve repair	
< 1 day	26 (92,9)
> 1 day	2 (7,1)
Level of injury	
Proximal	6 (21,4)
Middle	5 (17,9)
Distal	17 (60,7)

Table 1. *Demographic data.*

Patient number	Nerve[1]	Touch/pressure threshold[2], % of max. score	Type of injury[3]	Level of injury[4]	Stroop part I, t-scores	Stroop part II, t-scores	Stroop part III, t-scores
1	M	53	T	D	41	46	51
2	U	60	T	M	29	34	40
3	M	60	T	D	32	41	52
4	M	73	P	D	37	31	43
5	M	43	T	D	38	48	44
6	M	7	T	D	32	27	35
7	C	60	T	M	53	44	34
8	U	70	T	D	50	41	51
9	U	15	T	D	67	71	74
10	M	0	T	D	37	38	46
11	U	0	T	P	40	47	42
12	U	80	T	D	40	41	41
13	U	30	T	M	38	37	44
14	U	100	T	M	39	40	40
15	M	60	T	D	36	39	37
16	U	55	T	P	22	34	31
17	C	58	T	D	62	78	79
18	U	70	T	M	32	38	47
19	U	5	T	P	53	45	38
20	C	26	T	D	40	47	46
21	C	26	T	P	55	41	43
22	U	95	T	D	42	41	40
23	M	57	T	D	53	57	61
24	M	27	T	D	43	40	40
25	U	55	T	P	69	59	60
26	M	37	T	P	48	46	49
27	M	80	T	D	52	54	49
28	U	70	T	D	58	66	51

Patient number	CLVT (-8 to +8)					Sum score CLVT (-40 to +40)	Fluency I, standard scores (0 to 50)	Fluency II, standard scores (0 to 50)	NART (55 to 145)
	Tot-A[5]	Lspeed[5]	Conso[5]	Recog[5]	F-pos[5]				
1	0	-1	0	-2	1	-2	21	22	90
2	-1	-4	1	0	-3	-7	25	26	70
3	2	2	-1	-1	0	2	30	35	10
4	-1	-2	1	-1	-2	-5	31	23	92
5	2	4	0	3	1	10	25	19	72
6	-2	-3	-5	1	6	-3	23	19	77
7	0	-2	-1	1	0	-2	26	19	79
8	-2	-1	-3	-1	4	-3	31	25	102
9	3	2	2	-1	-2	4	31	37	115
10	0	0	-2	-1	1	-2	29	23	72
11	-2	-2	2	0	1	-1	24	22	80
12	-1	-3	-2	2	-2	-6	22	28	80
13	-2	-3	1	1	0	-3	23	15	93
14	-1	-4	-1	0	0	-6	27	23	82
15	-2	-2	1	0	1	-2	20	22	64
16	2	2	1	-1	1	5	22	29	67
17	-2	-2	-2	0	1	-5	32	26	82
18	-2	-3	1	-1	2	-3	16	20	76
19	-2	-1	-2	-1	4	-2	23	23	75
20	-2	-4	0	0	-1	-7	24	29	79
21	-2	-2	-2	3	1	-2	30	34	73
22	0	0	2	0	-1	1	22	29	91
23	-2	-3	2	-4	2	-5	37	29	87
24	-2	-2	-1	0	1	-4	21	25	90
25	0	2	0	-1	2	3	30	33	104
26	0	0	1	-2	-1	-2	34	33	98
27	-2	1	-2	-1	5	1	28	27	102
28	0	1	-2	0	1	0	25	25	99

Table 2 *Demographic information, functional sensibility and cognitive capacity tests*

[1] M=median, u=ulnar, c=combined median-ulnar; [2] Expressed as % of maximum score in 6 (median nerve) respectively 4 (ulnar nerve) zones in the hand measured with Semmes-Weinstein monofilaments. 5= normal, 4= light diminished touch, 3= diminished protective sensation, 2= loss of protective sensation, 1= deep pressure and 0= untestable. ; [3] T= total; P= partial nerve lesion. [4] D= distal, m= middle and p= proximal level of the forearm; [5] Tot-A= performance level on list A; Lspeed= learning speed, Conso= consolidation; Recog= recognition; F-pos= false-positives.

Measurement of sensory function

Cutaneous touch/pressure threshold of the palmar side of the hand was assessed with the mini-kit SWMFs (thickness: 2.83; 3.61; 4.31; 4.56 and 6.65).[20] A score of 5 was given when the thinnest filament was felt, and a zero score when the thickest filament was not perceived. A six-point measurement for the median nerve (distal phalanx of thumb, index and middle finger; basis and proximal phalanx of index finger and thenar) and a four-point measurement for the ulnar nerve (distal and proximal phalanx and basis of the little finger and hypothenar) were used.

The percentage of the maximum score was calculated for both the median (6 measurements × 5 = maximum of 30) and ulnar (4 measurements × 5 = maximum of 20) nerve areas. If a combined median–ulnar nerve transection was present, the combined percentage was calculated. The percentages were used for analysis.

Measurement of cognitive capacity

Cognitive capacity was examined with neuropsychological tests assessing selective attention and cognitive flexibility, verbal learning capacity, learning strategies and intellectual ability.

The Stroop colour word test assesses selective attention and cognitive flexibility. The test consists of three sheets containing the colours: blue, green, red and yellow. The first sheet presents 100 colour words printed in black ink, followed by a sheet of 100 coloured patches. The last sheet shows 100 printed colour names with the print ink in a colour other than the name of the colour word written. Words, patches and ink colours, respectively, have to be read as fast and correctly as possible. Colour factor and interference factor deciles were calculated.[21]

Dutch translation of the Californian Verbal Learning Test (CVLT), version I, assesses verbal learning capacity and verbal learning strategies. The test involves learning and recalling a verbally presented list of 16 items (comprising four categories) over five trials, with free and category-cued recall assessed after an interference list and again after a 20-mins break. Recognition of list A is tested with a list of 44 items which have to be answered as being a content of list A or not. The following indices, corrected for age and sex, are used for analysis: The index 'performance level on list A' (*Tot-A*) denotes the complete level of performance in the learning phase. The index 'learning speed' (*Lspeed*) is calculated on the basis of the number of correct answers at each of the five presentations of list A. This index shows the relation of newly remembered words on a trial. The index 'consolidation' (*Conso*) corresponds to how well the information learned will be remembered during a longer period in which interference takes place. The index 'Recognition' (*Recog*) determines if the recognition performance is better than the 'long-term free recall'. The index 'False-Positives' (*F-pos*) shows how many times the test person says 'yes' wrongly during the recognition procedure.[22] The overall performance level on the CVLT was assessed by the calculation of sum scores of the five test parts.

Word fluency test assesses 'strategy-making' capacity. Fluency of speech is measured by the quantity of words produced, adjusted for sex and age, within a restricted category and within a time limit of 1 min. Patients were tested for two semantic categories, that is, animals and occupations.[23]

Dutch version of the 'National adult reading test' (DART) assesses intellectual ability. The DART consists of 50 phonetically irregular words, which have to be read out loud. Each correctly pronounced word receives two points. One point is scored if the pronunciation of the word remains unclear. The test came with an instruction tape on which the correctly spoken words together with common pronunciation mistakes were recorded. Deviated IQ scores, adjusted for age and sex, are calculated and analysed.[24] According to the rules of the DART, only patients between 17 and 75 years old were used for analysis.

Educational level ranged from one (did not finish primary school) to seven (university degree).[25]

Statistical analysis

Univariate general linear-model analysis was used to investigate the association between recovery of sensibility and cognitive capacity tests. We used the general linear model univariate procedure providing regression analysis for one dependent variable.

For analysis, we used the percentages of sensory recovery as the dependent variable and height of the lesion as a fixed factor. Other variables were used as covariates. All cognitive capacity tests were adjusted for age and sex, except the results of the Stroop test.

Analyses were performed controlling for sex, age, site of lesion and education level using SPSS statistical software version 9.0 (SPSS, Inc., Chicago, IL). A p-value of <0.05 was considered statistically significant.

RESULTS

Thirty-seven patients were identified as having a traumatic peripheral nerve injury of the forearm who met the inclusion criteria. Eight patients were lost to follow-up, and one patient was excluded due to inability to understand the Dutch language. They had comparable lesions to the others. Of the remaining 28 patients, 25 were male and three female. The median age was 28.5 years (range: 15–79 years). Other demographic data are shown in Table 1.

Table 2 shows the individual scores of the sensibility test and of each of the cognitive capacity tests.

Analysis showed a significant inversed influence of age, corrected for level of injury, on the recovery of sensibility ($\beta = -0.845$, 95% confidence interval (CI): −1.456 to −0.233; $p = 0.01$). No association was found between any of the cognitive capacity tests and recovery of sensibility (data not shown). These results were not affected by analysis with exclusion of the one patient with partial nerve injury of those with delayed nerve injury repair ($n = 2$) (data not shown).

DISCUSSION

This prospective multicentre study shows an inverse association between age and recovery of sensibility ($p = 0.01$), indicating that younger persons show better recovery. There was no positive association between any of the cognitive capacity tests and recovery of sensibility after peripheral nerve injury and repair of the forearm.

Cognitive functioning reflects a collection of mental processes and activities used in perceiving, remembering and thinking, and the act of using those processes not only in understanding a sentence, for example, but also in recognising objects and touch perception. Those processes may also be of importance for sensory recovery after peripheral nerve damage. Peripheral nerve injury and repair is associated with alterations in the recognition of objects and touch perception due to abnormal reinnervation. This is a result of misdirection of axonal growth into distal sensory targets that are different in location, and due to misdirection of axonal growth into different sensory end organs as well. Loss of functional nerve fibres occurs due to entrapment in scar tissue at the repair site.[26] After regeneration, the stimuli given by the hand alters and the person has difficulty interpreting those signals into known associations. Some new signals cannot be interpreted at all and no or altered perception takes place. Probably, various cognitive processes ought to be stimulated for active learning and adapting to new situations.

In childhood, the altered sensory impulses given by the hand are much easily interpreted by the somatosensory brain cortex than in adult age. It is thought that this is the result of reduced brain plasticity with age or the other way around, due to the active learning processes and not yet static schemes of interpretation in young children.[27] Research with fetal monkeys led to the conclusion that this active sensory rehabilitation by children is of more importance than the accuracy of nerve realignment.[11] Children who recover without any guidance show excellent results compared to adults in sensory functioning.[5, 9, 11, 17, 18, 19 and 28] Adults can improve their recovery results by participating in a formal programme of sensory re-learning.[2] and [4] However, evidence for this improvement of outcome is limited.[29]

Most sensory re-education programmes assume that sensory retraining begins at the start of reinnervation of the hand at a point when cortical reorganisation becomes manifest (phase two).[30] Phase one training (before reinnervation has started) might prohibit reorganisation of that specific part in the brain after nerve damage by visuo-tactile and audio-tactile interactions. Others mention the 'mirror-neuron-system'[31 and 32] in which motoneurons (in)directly are connected to the somatosensory cortex. The latter is activated during visual observation of a hand being touched.[33, 34] Our study was performed prior to these hypothesis and publications and the absence of a re-education programme in our study might have influenced outcome. On the other hand, if cognitive capacities were of importance as being suggested in prior studies, the cognitive tests in our study should have presented some correlation with sensory recovery.

To test the hypothesis that there may be an association between sensory recovery and cognitive capacity, we selected four cognitive capacity tests for assessing the variance seen in interpreting the altered sensory impulses given by the hand after peripheral nerve injury and repair. Those tests assessed selective attention and cognitive flexibility, which might be used for suppressing irrelevant sensory information, thereby creating a known association. In addition, verbal learning capacity and learning strategy tests were performed to see if verbal learning is of importance in interpreting the altered sensory impulses. A test for intellectual ability was also included. These cognitive capacities are thought to be of importance in the process of brain plasticity.

We used the SWMFs to assess sensibility of the hand. First, application of a touch/pressure stimulus with SWMF is the most commonly used method for sensibility analysis due to its objectivity, high reproducibility and hand-held form.[35] Second, the touch/pressure thresholds of detection do not change with sensory re-education. If thresholds would become better, then this is more dependent upon cognition than sensation.[36] Third, normal touch/pressure threshold is relatively constant with ageing and, furthermore, due to heterogeneity of our study population with regards to different levels of nerve injury and medical centres, we had to choose a sensory test applicable to all patients. An interpretation test, like an object recognition test, was not performed.

In the vast majority of individuals, language functions are processed in the left hemisphere (dominant). Evidence of this is seen by the fact that brain lesions that adversely affect language are found in the left hemisphere in about 95% of the cases. Almost all right-handed individuals and about half of all left-handed individuals are left-cerebral dominant. In the cognitive tests used in this study, language was used frequently. Since most of our study population was right handed (25 patients) and only three patients were left handed, we think our cognitive tests were valid measurement methods.

This study was performed prospectively with a reasonable number of patients. All cognitive capacity tests were performed by one researcher according to the highest standards, and our follow-up period was set at 1 year. However, it is not known whether this period of time is sufficient for the somatosensory brain cortex to adjust to altered sensory impulses given by the hand.[37] On the other hand, this study did identify an inverse association between age and recovery of sensibility. Therefore, the association between cognitive capacity and sensory recovery, if any present at all, is probably not as strong as suggested in earlier retrospective studies.

In conclusion, this study is the first prospective study to investigate the association between cognitive capacity and sensory recovery after peripheral nerve injury and repair of the forearm. In line with earlier reports, we found an inverse association between age and level of recovery of sensibility. However, in contrast with earlier retrospective reports, we did not find any association between cognitive capacity and recovery of sensibility as measured by Semmes–Weinstein test score. We recommend that further studies with a larger number of patients and longer follow-up periods should be performed.

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CHAPTER 6

EVALUATION OF COLD INTOLERANCE IN PATIENTS WITH PERIPHERAL NERVE INJURIES

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ABSTRACT

Introduction – Cold intolerance develops in the majority of patients who sustain peripheral nerve injury of the forearm. Very little is known about pathogenesis, aetiology and treatment of cold intolerance. For thorough analysis of all aspects of cold intolerance a reliable and validated questionnaire is indispensable.

Objective – Evaluation of existing questionnaires for analysis of cold intolerance and introduction of a renewed cold injury questionnaire.

Methods-

I. Twenty-eight peripheral nerve patients were asked to fill in a Cold Induced Sensitivity Scale (CISS) and were thereafter physically examined and questioned for symptoms of cold intolerance. Results of the CISS and actual complaints/ symptoms were compared.

II. Sixty CISS scores of randomly assigned people of the normal population were analysed and compared with CISS scores from peripheral nerve patients in literature.

III. A new questionnaire for the evaluation of cold intolerance was designed based on the questions of the CISS.

Results –

I. In the peripheral nerve injury group 18 out of 28 patients had difficulties with understanding of the items of the CISS questionnaire.

II. Forty eight out of 60 people without hand trauma or operation in their history had cold intolerance according to the CISS score.

III. The newly designed questionnaire appeared to be able to distinguish cold intolerance in patients with a previous nerve injury operation of the hand or forearm (secondary Raynaud phenomenon) from cold intolerance in the normal population (primary Raynaud phenomenon).

Conclusion – existing questionnaires are not precise enough for thorough analysis of different aspects of cold intolerance. Therefore a renewed questionnaire was introduced.

INTRODUCTION

Although exact incidence is unknown, cold intolerance (skin colour changes, numbness, weakness, stiffness, swelling, paresthesias, aching and pain in the fingers and hand after cold exposure) is a common problem in patients who sustain peripheral nerve injury. Figures in literature vary between 50% and 83% (1,3,4). The consequences of this condition for the patient can be serious and debilitating, as illustrated by the study of Koman (4). In this study cold intolerance was found to be associated with more functional limitations and a reduced health-related quality of life (HRQL) in hand injury patients. Unfortunately despite high incidence and severity of this condition very little is known about the pathogenesis, aetiology and treatment of cold intolerance (1). Research on this topic is complicated by subjectivity of the condition and factors like method and timing of questioning can largely influence study outcome. Although technologies like Laser Doppler Fluxmetry, isolated cold stress testing and thermography can assist in the initial evaluation of cold intolerance (5,6,7), they cannot replace questionnaires due to their low specificity as demonstrated by studies of Suominen, Freedlander, Gelberman and Backman (6,8,9,10). For a thorough analysis of the phenomena of cold intolerance as well as for implementation of new diagnostic devices, a reliable and validated questionnaire is indispensable. Although in the past the McCabe and the modified Cold Induced Sensitivity Scale (CISS) were introduced in literature (1,11), in most studies a validated questionnaire for data gathering was absent. In the majority of reports the method of questioning was not described at all. A disadvantage of the existing questionnaires for cold intolerance is the sometimes confusing nature of some questions for patients with peripheral nerve injury complaints. Another major drawback of the CISS Questionnaire (and the McCabe) is that symptoms of cold intolerance as a consequence of hand injuries are not easily distinguished from already existing cold intolerance symptoms. A substantial percentage of the population suffers from cold intolerance complaints as a result of a condition named idiopathic Raynaud (primary Raynaud phenomenon). In literature the incidence of primary Raynaud phenomenon in the normal population varies between 5 and 20 % (21). If cold intolerance symptoms have a predisposing factor it is called secondary Raynaud's phenomenon. Secondary means that patients have an underlying disease or condition that causes Raynaud's phenomenon. This is the case in people having cold intolerance symptoms after hand injuries. Primary Raynaud's phenomenon has no predisposing factor, is more mild, and causes fewer complications than non-idiopathic Raynaud (secondary Raynaud phenomenon). Because the CISS questionnaire does not relate cold intolerance symptoms to the non injured hand or to the situation before injury of the hand reported incidence of cold intolerance after hand injury might be higher than in reality.

For that reason Ruijs suggested a threshold for pathological cold intolerance measured with CISS of 30. Although this is a method to identify people with pathological cold intolerance, for thorough analysis of the phenomena of cold intolerance a more detailed questionnaire is indispensable. In this paper we analyze and discuss problems encountered with former questionnaires used for analysis of cold intolerance and a renewed questionnaire will be introduced.

MATERIAL AND METHODS

The study consisted of three different parts.

I Evaluation of the CISS questionnaire in patients with peripheral nerve injury of the upper arm

The CISS questionnaire was sent to 28 patients operated between 1999 and 2001 with a peripheral nerve injury of the upper arm 12 months after operation. All patients had a traumatic nerve transection of the median and/or ulnar nerve between wrist and elbow fold and were older than 12 years. In all cases, nerve suturing was performed within 3 months after nerve trauma. At baseline and at 12 months specific demographic data was recorded. All patients were invited for physical examination. Sensibility (Semmes-Weinstein monofilaments) and power grip measurements were performed (Jamar dynamometer) (12,13). The physician elucidated and went over all questions with the patient. Both CISS questionnaires were analyzed and compared for identification of indistinct questions.

II Evaluation of the CISS in the normal population

Sixty randomly assigned people of the normal population were asked to fill in the CISS questionnaire. People with a previous hand injury or hand operation and people with autoimmune diseases were excluded from study. Also people under the age of 12 were excluded. As in the majority of the studies after cold intolerance in hand injury, patients working with vibrating tools, patients who smoke, patient with pulmonary hypertension, and patients using vasoconstricting medication were not excluded from study participation. The CISS scores were analyzed and compared with CISS scores from peripheral nerve patients in literature.

III Evaluation of a newly designed questionnaire for cold intolerance.

A new questionnaire was designed based on the questions of the CISS questionnaire. Care was given to prevent a high reading level (reading skills beyond 12 year old), ambiguity, double-barrelled questions, value-laden words and positive and negative wording. To ensure that all conditions were met, the questionnaire was pre-tested on a population of sixty people without previous hand injury or hand operation (a different study population than the population described in part II of this study) . By asking each participant to rephrase the question in his own words, trying to keep the meaning as close to the original as possible (Nuckols method), it was checked if all questions were understood and correctly answered (14). Items which did not meet these criteria were eliminated or rewritten and pretested again. Subsequently, the modified questionnaire was sent twice with a two week interval to fifty people with a previous nerve injury operation of the hand or forearm. The purpose was to identify questions with a very high or low endorsement rate (the proportion of people who give each response alternative to an item; >0.95 or under 0.05) and a low reliability coefficient (< 0.85)

RESULTS

I. Twenty-eight patients were included in this study of which 25 were male and 3 female. Their median age was 28.5 years (range 15 to 79). Of this 28 patients 24 patients were identified as having cold intolerance as calculated with the CISS questionnaire based on a score of zero on question one, as defined by Irwin et al (1). Four patients were identified as not having cold intolerance with the CISS questionnaire (question one was scored zero). Seven patients scored < 25 (defined by Irwin as mild cold intolerance), 11 patients scored between 26 and 50 (moderate cold intolerance), 5 patients scored between 51 and 70 (severe cold intolerance) and 1 patient scored > 70 extreme cold intolerance. Of the people scored as having cold intolerance mean score was 29.7 with a range from 4-79. When applying the threshold of 30 suggested by Ruijs et al. (2) for defining pathological cold intolerance, 37.5% of the patients were identified as having cold intolerance.

In a personal interview all four patients scoring zero confirmed the absence of symptoms of cold intolerance. Three of which had a close to normal sensibility and power grip (17, 22). It appeared that a total of 18 out of 28 patients experienced difficulties with answering the questions of the CISS questionnaire. Of these 18 patients nine patients could not perform the requested tasks of question 5 with the injured hand due to functional impairment. Four patients with a diminished protective sensation were unable to answer question 1 and 2 which concerned the experience of numbness on exposure to cold in the injured hand. Five patients incorrectly answered question 1 and 2 of the CISS (Table 4) because they forgot to correlate the frequency of the symptoms of pain, numbness, stiffness, loss of grip strength, aching, swelling and skin colour change to the exposure of cold. Because of that two patients appeared not to have cold intolerance although they had moderate cold intolerance according to the CISS. Three patients mentioned in the interview that due to the variation of symptoms with temperature and humidity the term "cold" used in the questionnaire was too general and had to be specified more. (see Table 2)

Study population I- Demographic data	
Peripheral nerve injury population	
Patients	28
Male: female	25:3
Age (in years)	28.5 (range: 15–79)
Nerve injury	
Median	11
Ulnar	13
Combined	4
Type of injury	
Total	27
Partial	1
Dominant hand affected	16
Time to nerve repair	
<1 day	26
>1 day	2
Level of injury	
Proximal	6
Middle	5
Distal	17
Smoking vs non smoking	16:12

Table 1

Study population I – CISS scores		
Peripheral nerve injury population		
CISS Questionnaire	24 cold intolerance	4 no cold intolerance
Mild cold intolerance	7	
Moderate cold intolerance	11	
Severe cold intolerance	5	
Extreme cold intolerance	1	
CISS score > 30	9 (37.5%)	
Mean CISS score	29,7 (SD 19.1 range 4-76)	
Interview	22 cold intolerance	6 no cold intolerance
Difficulties answering CISS due to:	18	
Inability to perform tasks	9	
Unsuitable questions	4	
Ambigious questions	5	

Table 2

II. Sixty people without previous hand trauma or operation were asked to fill in the CISS questionnaire. Twenty-seven (45%) of them were female and thirty-three (55%) were male. Twelve (20%) scored 0 at question one of the CISS questionnaire and were identified as not having cold intolerance; 80% had a positive CISS. Of these sixty people 30 persons scored < 25 (defined by Irwin as mild cold intolerance), fourteen persons scored between 26 and 50 (moderate cold intolerance), three persons scored between 51 and 75 (severe cold intolerance) and one scored > 75 (extreme cold intolerance) . The mean score was 23.1 (SD 16.5) with a range from 4-90 and a median of 16.4. (Figures displayed in Table 3). 12% of the control subjects scored 30 or higher on the CISS questionnaire, defined by Ruijs et al.(2) as a threshold for pathological cold intolerance.

Study population II	**60 patients**
Healthy population	*27 (45%) male 33 (55%) female*
CISS Questionnaire Cold intolerance:	12 (20%) no cold intolerance 48(80%) cold intolerance 22 male; 82% of male study population 26 female; 79% of female study population
Mild cold intolerance	30 (62.5%)
Moderate cold intolerance	14 (29.2%)
Severe cold intolerance	3(6.3)
Extreme cold intolerance	1(2%)
Mean CISS score	23.1 (SD 16.5 range 4-90 median 16.4)
Mean CISS score female	19
Mean CISS score male	18.8

Table 3

III. Four items in the newly developed questionnaire appeared to be incomprehensible to the target population. Of these four items, one was eliminated and three of them were rewritten. The newly developed questionnaire appeared to be able to distinguish cold intolerance symptoms as a consequence from hand injury from primary cold intolerance symptoms; all people without previous hand injury or hand operation had a score of zero. To investigate test-retest reliability the modified questionnaire was sent twice to 50 patients with a previous nerve injury operation of the hand or forearm, both questionnaires were returned by 45 patients. Two questions with a very high endorsement rate (>0.95) and three questions with a low endorsement rate (< 0.05) were modified. One questions with a low reliability coefficient (< 0.85) was eliminated.

DISCUSSION

Complaints like skin color changes, numbness, weakness, stiffness, swelling, paresthesias, aching and pain in the fingers and hand after cold exposure are very common peripheral nerve injuries of the forearm (15, 16, 17). In general these type of symptoms can be summarized as cold intolerance. Several definitions are proposed to describe this condition (18,19,20). This abundance of definitions emphasizes the complexity of the condition. This might be due to the high diversity of symptoms. What makes it even more confusing is that considerable amount of peripheral nerve injury patients will experience symptoms like skin color changes, numbness, weakness, stiffness, swelling, paresthesias, aching and pain in the fingers and hand as a consequence of the initial injury, and not specifically evoked by cold. In addition, if evoked by cold the above mentioned symptoms can also be pre-existent. If cold intolerance symptoms have no predisposing factor it is called primary Raynaud phenomenon. Primary Raynaud phenomenon, stemming from Raynaud disease, is an exaggeration of vasomotor responses to cold or emotional stress. More specifically, it is a hyperactivation of the sympathetic system causing extreme vasoconstriction of the peripheral blood vessels, leading to tissue hypoxia. Primary Raynaud's disease is more mild and causes fewer complications than secondary Raynaud's disease. About half of all cases of Raynaud's disease are of this type.

Because of abundance of definitions, variety of intensity and diversity of symptoms as well as the confusing nature of existing questionnaires there is a wide variation of reported incidence of cold intolerance after peripheral nerve injury (50-83%) (1). In addition knowledge about course, pathogenesis, and predictive factors of cold intolerance after upper peripheral nerve injury is lacking. As a consequence no valuable therapy is available.

Cold intolerance can be severely disabling. Patients who work outdoors may have to change their occupations. Associations with functional limitations, pain and reduced Health-Related Quality of Life (HRQL) have also been found. Even migration to warmer countries due to cold intolerance has been reported (19). More knowledge of cold intolerance can determine how to inform, prepare and treat these patients with cold intolerance. For thorough analysis of the phenomena of cold intolerance, a reliable and validated questionnaire is mandatory. Most of the time the CISS (11) is used to identify and evaluate patients who suffer from cold intolerance after upper extremity nerve injury (2,3), however this questionnaire seems not precise enough to analyze the different aspects of cold intolerance. In our study 18 out of 28 patients with a peripheral nerve injury had in some degree difficulties with correct understanding of the questions of the CISS questionnaire. Most important the hypothesis that in the CISS questionnaire idiopathic complaints of cold intolerance were not distinguished from cold intolerance symptoms as a consequence of former hand injury, appeared to be true after analysis of CISS scores in a healthy population. Sixty people without hand trauma or operation in the history were asked to fill in the CISS questionnaire, only 20% of this study population scored zero. Eighty percent of the patients claimed to have symptoms of cold intolerance. Surprisingly, the number of people claiming to have cold intolerance measured by CISS was only 3% lower in our population (people without nerve injury) compared to the number of peripheral nerve patients claiming to have cold intolerance in the study of Irwin (83%) (1). Because in literature the incidence of primary Raynaud phenomenon in the normal population varies between 5 and 20%, this high incidence of people identified as having cold intolerance complaints by means of the CISS score is likely due to incorrect interpretation of the questions. Although cold intolerance in our normative population was comparable with incidences of cold intolerance after hand injury in literature, mean CISS score was lower. Ruijs who also detected a high incidence of cold intolerance in the normal population suggested the threshold for pathological cold intolerance of 30 and higher (2SD). Although this is an excellent method to identify people with pathological cold intolerance, in our study still 11 people (23%) of the normal population had a score above this threshold. So for thorough analysis of the phenomena of cold intolerance after peripheral nerve injury as well as for implementation of new diagnostic devices, a questionnaire which is able to distinguish primary from secondary cold intolerance complaints is indispensable. Improving the CISS questionnaire by relating cold intolerance symptoms to the non injured hand would not be sufficient. Unilateral idiopathic cold intolerance symptoms in patients with primary Raynaud phenomenon are quite common. Besides, as illustrated by our study results, there were two other reasons for an impaired reliability of the CISS questionnaire. In the first place some patients could not perform the requested tasks with the injured hand due to functional impairment. In the second place patients with a diminished protective sensation were unable to answer questions about loss of sensation as a consequence of cold exposure and at last a considerable part of the patients forgot to correlate the frequency of pain, numbness, stiffness, loss of grip strength, aching, swelling and skin color change to the exposure of cold which incorrectly resulted in higher scores.

For that reasons with help of the key informant interviews of study-step I and the information acquired from study-step II a new questionnaire for cold intolerance was designed and validated. In order to diminish the risk of incorrect answering by patients who experience cold intolerance symptoms as a consequence of their initial injury and not specifically evoked by cold, it was emphasized in every question that cold intolerance symptoms like the frequency of pain, numbness, stiffness, loss of grip strength, aching, swelling and skin color change had to be related to cold exposure.

In the new questionnaire symptoms of cold intolerance in the injured hand were related to possible pre-existing cold intolerance symptoms. Relating cold intolerance symptoms to the non injured hand (as primary cold intolerance gives symptoms in both hands) would not be sufficient as unilateral idiopathic cold intolerance symptoms in patients with primary Raynaud phenomenon are quite common.

Because incidence and intensity of cold intolerance symptoms are largely dependent on weather conditions in our new questionnaire symptoms of cold intolerance were related to two weather conditions; 0 and 10 degrees Celsius.

For further inventarisation of severity of the condition, cold intolerance symptoms were separately scored for frequency and prolongation of the complaints.

In the last part of the new questionnaire implications of existing cold intolerance symptoms for the patient were analyzed. In addition questions which patients found difficult to answer because they were not able to perform the requested tasks with the injured hand were eliminated from the questionnaire.

Although this questionnaire proved to be reliable both in the normal population as in the target population, its qualities have to be proven in larger study populations. Further studies should concern sensibility and specificity, exact incidence of cold intolerance after different types of hand and peripheral nerve injury, prevalence of various symptoms of cold intolerance and their provocative moments. Furthermore, impact of cold intolerance complaints on quality of living and the identification of predictive factors have to be studied . If we want to optimize treatment results in peripheral nerve injury patients more exact data are indispensable.

Table 4: *CISS Questionnaire [Irwin et al.,1997 (1)].*

Question	Score
1. Which of the following symptoms of cold intolerance do you experience in your injured limb on **exposure to cold? (Please give each symptom a score between 0 and 10, where 0+ no symptoms at all and 10= the most severe symptoms you can possibly imagine.)**	
Pain	
numbness	
stiffness	
weakness (loss of grip strength)	
aching	
swelling, skin colour change (white/ bluish white/ blue)	
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 30 minutes	**10**
4. What do you do to ease or prevent your symptoms from 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 wintry 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	
Domestic chores	**4**
Hobbies and interests	**4**
Dressing and undressing	**4**
Tying your shoe laces	**4**
Your job	**4**

The scoring system is illustrated in bold and allows a maximum of 100 points. In cases where more than one option was ticked the points of the highest scoring choice were awarded

Table 5: *Rotterdam Cold Intolerance Questionnaire - RCIQ*

1a. How often do you experience the following symptoms as a consequence of cold if you walk outside without gloves in a temperature of about 10 degrees?

	Non of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
pain	□0	□2	□4	□6	□8	□10
ice cold feeling	□0	□2	□4	□6	□8	□10
numbness	□0	□2	□4	□6	□8	□10
stiffness	□0	□2	□4	□6	□8	□10
weakness	□0	□2	□4	□6	□8	□10
swelling	□0	□2	□4	□6	□8	□10
tingling sensation	□0	□2	□4	□6	□8	□10
skin colour change	□0	□2	□4	□6	□8	□10

Max score 80

1b. How often do you experience the following symptoms as a consequence of cold if you walk outside without gloves in a temperature of about 0 degrees

	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
pain	□0	□1	□2	□3	□4	□5
ice cold feeling	□0	□1	□2	□3	□4	□5
numbness	□0	□1	□2	□3	□4	□5
stiffness	□0	□1	□2	□3	□4	□5
weakness	□0	□1	□2	□3	□4	□5
swelling	□0	□1	□2	□3	□4	□5
tingling sensation	□0	□1	□2	□3	□4	□5
skin colour change	□0	□1	□2	□3	□4	□5

Max score 40

If you have answered all the questions of 1a en 1b with none of the time you can stop here.

2a.How often did you experience the following symptoms as a consequence of cold before injury if you walked outside without gloves in a temperature of about 10 degrees

	Non of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
pain	□0	□2	□4	□6	□8	□10
ice cold feeling	□0	□2	□4	□6	□8	□10
numbness	□0	□2	□4	□6	□8	□10
stiffness	□0	□2	□4	□6	□8	□10
weakness	□0	□2	□4	□6	□8	□10
swelling	□0	□2	□4	□6	□8	□10
tingling sensation	□0	□2	□4	□6	□8	□10
skin colour change	□0	□2	□4	□6	□8	□10

Max score 80

2b.How often did you experience the symptoms as a consequence of cold before injury if you walked outside without gloves in a temperature of about 0 degrees

	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
pain	□0	□1	□2	□3	□4	□5
ice cold feeling	□0	□1	□2	□3	□4	□5
numbness	□0	□1	□2	□3	□4	□5
stiffness	□0	□1	□2	□3	□4	□5
weakness	□0	□1	□2	□3	□4	□5
swelling	□0	□1	□2	□3	□4	□5
tingling sensation	□0	□1	□2	□3	□4	□5
skin colour change	□0	□1	□2	□3	□4	□5

Max score 40

Score (1a + 1b) – score (2a + 2b)

If symptoms as a consequence of cold after injury did not appear or increase after injury you can stop here.

3.How much do the following symptoms bother you?

	I don't experience it	Hardly	A little bit	Moderately	Quite a bit	Extremely
pain	□0	□1	□2	□3	□4	□5
ice cold feeling	□0	□1	□2	□3	□4	□5
numbness	□0	□1	□2	□3	□4	□5
stiffness	□0	□1	□2	□3	□4	□5
weakness	□0	□1	□2	□3	□4	□5
swelling	□0	□1	□2	□3	□4	□5
tingling sensation	□0	□1	□2	□3	□4	□5
skin colour change	□0	□1	□2	□3	□4	□5

Max score 40

4. When you develop cold induced symptoms, on you return to a warm environment are the symptoms releaved:

□0 within a few minutes
□5 within 30 minutes
□10 after 30 minutes

Max score 10

5a. Do the cold induced symptoms limit your work activities

Yes, limits a lot	Yes, limits a little	No, not limited at all
□ 10	□5	□0

If answered with yes, which activities?

…………………………………………………………………………………………

Max score 10

5b. Do the cold induced symptoms limit your hobbies/ activities outside ?

Yes, limits a lot	Yes, limits a little	No, not limited at all
□ 10	□5	□0

If answered with yes, which activities?

…………………………………………………………………………………………

Max score 10

5c. Do the cold induced symptoms limit your activities outside ?

Yes, limites a lot	Yes, limites a little	No, not limited at all
□ 10	□5	□0

If answered with yes, which activities?
……………………………………………………………………………………

Max score 10

Total max score/2 = final outcome

Total score is converted into a 1-100 scale, whereby 1 reflects minimum and 100 maximum cold intolerance.

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CHAPTER 7

EARLY POSTTRAUMATIC PSYCHOLOGICAL STRESS FOLLOWING PERIPHERAL NERVE INJURY: A PROSPECTIVE STUDY.

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ABSTRACT

Introduction - Psychological symptoms frequently accompany severe injuries of upper extremities and are described to influence functional outcome. As yet little knowledge is available about occurrence of posttraumatic psychological stress and the predictive factors of such psychological symptoms in relation to peripheral nerve injuries of the upper extremity.

Objective - In this prospective study different aspects of early posttraumatic stress in patients with peripheral nerve injury of the forearm were analysed. Our main objectives were to assess the incidence and intensity of post-traumatic psychological stress symptoms and to identify risk factors for early psychological stress.

Methods - In a prospective study design patients with a median, ulnar or combined median-ulnar nerve injury were monitored for posttraumatic psychological stress symptoms with the Impact of Event Scale questionnaire (IES).

Results - Psychological stress within the first month after surgery occurred in 91.8% of the population (IES mean=22.0, SD=17.3). Three months post operatively 83.3% (IES mean=13.3, SD=4.1) experienced psychological stress. One month postoperative 24.6 % of the patients and three months postoperative 13.3% of the patients had IES scores indicative of need for psychological treatment. Female gender, adult age and combined nerve injuries were related to occurrence of psychological stress symptoms one month post operative.

Conclusion – In the majority of patients, peripheral nerve injury of the forearm is accompanied by early posttraumatic psychological stress, especially in female adults who suffered from combined nerve injuries.

INTRODUCTION

Severe injuries of the upper extremities are frequently accompanied by psychological symptoms like persistent, distressing recollections of trauma as flashbacks and nightmares, disturbed affect and anxiety, conditioned arousal to reminders of the trauma, and avoidance of stimuli reminiscent of the accident [1]. When such symptoms last for more than one month, these are representative of posttraumatic stress disorder (PTSD). Posttraumatic stress disorder is a strongly disabling condition, impairing functionality and physical health of sufferers and it is associated with a high level of suicidal behavior (19%)[15]. Epidemiological studies indicate that posttraumatic stress disorder is becoming a major health concern; approximately one third of the population will be exposed to severe trauma during their lifetime and 10-20% of these individuals will develop posttraumatic stress disorder. The incidence of posttraumatic stress disorder in injured adults admitted to hospital is between 14-46%[16]. It has been estimated that the prevalence of posttraumatic stress disorder in the general population will range from 3 -6%[8,9,11]. The symptoms of posttraumatic stress disorder reflect a psychological disturbance that often requires medication or psychotherapy like cognitive-behavioral therapy, relexation training, imagery techniques and systematic desensitization to return the patient to a productive every day life[3,4,8,14,15]. Although we know early post traumatic stress disorder has a relationship with functional outcome after peripheral nerve injury still little knowledge is available about the incidence and predictive factors for posttraumatic stress symptoms [1-4,22]. Our main objective were to assess incidence and intensity of post-traumatic psychological stress symptoms and to identify risk factors for early psychological stress.

MATERIAL EN METHODS

Study population Between 2000 and 2003 patients with a peripheral nerve injury, operated in the University Medical Center Rotterdam, the University Medical Center Utrecht, "UMCU", the MCRZ Rotterdam, the Isala Clinics Zwolle, the University Medical Center Nijmegen "St.Radboud", the University Medical Center Amsterdam "VU" were asked to participate in this study. Exclusion criteria were age under 12 years old, amputations of hand and fingers and insufficient knowledge of the Dutch language. According to these criteria 82 patients were asked for study participation. Three patients rejected participation and 16 patients initially included in the study were lost during follow up. Finally data of 61 patients were used for evaluation. Informed consent was provided by all participants. For this study, patients were evaluated at one, three and 12 months after injury.

Assessments

To measure the current degree of subjective impact of peripheral nerve trauma experienced by a person, the Impact of Event Scale-revised (IES) was used at 1 and 3 months after injury. The IES, designed by Horowitz in 1979, includes 15 items that refer to the "the past seven days," across the subscales of avoidance and intrusion and taps dimensions that are similar to defining symptoms of PTSD[15]. Each item is scored on a 5-point scale. These scores were reduced, weighed and labelled as follows: (0) not at all (1) rarely (3) sometimes (5) often. Total IES scores range from 0-75 (75= worst score). As a general rule patients displaying scores above 30, have symptoms serious enough to be in need for psychological treatment.

Statistical analysis:

The relationship between type of injury, number of damaged structures, presence of arterial damage, age, gender, education level and posttraumatic psychological stress 1 and 3 months after injury (measured with the IES) was studied with oneway analyses of variance or pearson product moment correlational analyses. Variables that were found to be associated with early posttraumatic stress were then included in a multivariate regression model to evaluate their independent contribution in the prediction of posttraumatic psychological stress.

RESULTS

Study population

For this study 61 patients with median (n= 22; 36%), ulnar (n=31; 51%) and combined nerve injuries (n=8; 13%) that were repaired in the participating hospitals, were prospectively examined at 1, 3 and 12 months after injury. The study group consisted of 23 children and adolescents (38% < 26 years) and 38 adults (62% >25 years). Most patients, 84% (n=51), were male and 16% (n=10) were female.

Psychological impact

Incidence of psychological posttraumatic stress symptoms:

The results from the IES revealed that 91.8% (mean = 22.0, SD = 17.3) of the study population experienced psychological stress within the first month after surgery. Three months post operatively psychological stress was experienced by 83.3% (mean = 13.3, SD = 14.1). A score greater than 30 which indicates need for psychological treatment was found in 24.6 % of the patients at one month postoperative and in 13.3% at three months postoperative. Scores above 40, which is the threshold for severe psychological stress were found in 14.8% of the patients with the measurement at one month postoperative. At 3 months 10% of the patients still had scores above 40. A minor response (<18) was reported by 44.3% (1 month) and 73.3% (3 months). A moderate response (18-39) by 40.9% (1 month) and 16.7% (3 months) of the patients. Psychological stress symptoms at one month and three months showed a strong correlation (r=.75).

Predictors for early post-traumatic psychological stress:

Significant independent predictors of early post-traumatic psychological stress one month post operative were gender (F(1,59) 5.45, p=.023) and age (F(1,59) 6.53, p=.013). At three months post operative only age differed (F(1,58) 7.68, p=.007). Females had significantly more psychological stress symptoms at one month than males and adults had more symptoms than adolescents both at one and three months postoperative. The one-way analysis of variance for stress symptoms according to type of nerve injury showed a non significant difference (F(2,58) 2.70, p=.075), but post hoc comparisons indicated that combined nerve injuries differed from median nerve lesions (mean difference=16.8, SE=7.24, p=.024).

These relationships were not found for the measurements at three months postoperative. The mean scores for the psychological stress symptoms in relation to these predictors are presented in Table 1. Education, number of damaged structures, presence of arterial damage and location of injury were not associated with the amount of psychological stress symptoms at one and three months postoperatively.

Next a multivariate backward regression analysis was done, using psychological stress symptom score at one month postoperative as dependent variable and age, gender and type of nerve injury as predictors. This resulted in a significant model (F(4,10) 4.56, p=.006) that explained 23% of the variance. Both age (β=.34, p=.013) and gender (β=.24, p=.047) contributed significantly, whereas type of injury (specifically median nerve injury that was least associated with psychological stress symptoms of the different kinds of injury) did not contribute significantly (β=-.23, p=.063).

	IES 1 month			IES 3 months		
	Mean	SD	N	Mean	SD	N
Gender*						
Males	19,80	14,913	51	12,08	12,979	50
Females	33,30	24,413	10	19,10	18,375	10
Total	22,02	17,324	61	13,25	14,084	60
Age*[a]						
Adolescents	15,04	13,851	23	7,13	8,880	23
Adults	26,24	18,002	38	17,05	15,431	37
Total	22,02	17,324	61	13,25	14,084	60
Injury						
Median	18,042	15,407	30	15,09	16,876	30
Ulnar	22,07	18,042	24	11,57	12,199	23
Combined*[b]	35,00	16,186	7	14,43	12,581	7
Total	22,02	17,324	61	13,25	14,084	60

Table 1 *Psychological stress symptoms by gender, age, injury*
**p<.05*

DISCUSSION

Psychological stress symptoms within the first month after surgery, occurr in most patients after peripheral nerve injuries of the upper extremities. Our prospective study showed that almost all patients (92%) experienced psychological stress symptoms and 83% still experienced psychological stress three months post operatively. Psychological treatment was indicated in 25% one month postoperative and still in 13% at three months postoperative, according to the IES.

In medical practice attention after hand trauma is primarily focused on functional recovery. However posttraumatic stress disorder has been found to contribute more to patient's perceived general health than degree of physical functioning or injury severity[17]. Results of hand injuries are immediately apparent, there is fear of potential further injury and the injured hand acts as a constant reminder. An example of a handinjury with serious functional consequences and often a disappointing recovery is peripheral nerve injury of the forearm. Earlier studies demonstrated a mean time of returning to work of 31.9 weeks and 41% of patients even do not return to work in the first year after peripheral nerve injury[18,19].

In the current prospective study the majority of the patients with peripheral nerve injuries of the upper extremities experienced psychological stress symptoms within the first three months after surgery. One month postoperative a quarter of all patients displayed psychological stress indicative of psychological treatment. These findings are in agreement with earlier study results. In a retrospective study of Jaquet et al. 94% of the patients with peripheral nerve lesions demonstrated additional posttraumatic psychological stress. In this retrospective study psychological morbidity, measured with the impact of event scale, was found in 36% of the cases.

Not only the incidence of posttraumatic psychological stress after peripheral nerve injury is high, and important in it self. Data from a part of a bigger prospective study also indicate early psychological stress after peripheral nerve injury as a predictive factor for power grip and daily activities measured with the daily activity of shoulder and hand questionnaire (DASH) twelve months after injury. A higher degree of posttraumatic stress one month after injury was associated with greater motor disability. Psychological stress symptoms at one month postoperative were found to predict power grip as well as daily functioning at 12 months post operative.

Early identification of patients with psychological stress symptoms and appropriate treatment could improve functional outcome and facilitate earlier return to work in patients with severe hand trauma. Grunert et al. already demonstrated (1991) that early intervention reduced the effects of litigation on stress symptoms[3]. Van der Kolk et al (1994) suggest that patients with more recent stress symptoms have better response to treatment[10]. Besides, early detection and support and treatment of people with emotional problems, costs less than the long-term societal costs associated with failure to provide early and effective treatment[11]. Once actual PTSD has developed, it is often a chronic and recurring condition[15]. Although effects of therapy in patients with PTSD and peripheral nerve injuries need further study, our results indicate that early support and intervention could optimize surgical treatment results. Earlier research has demonstrated effectiveness of cognitive- behaviour therapy, group therapy, and exposure therapy, in which the patients repeatedly relives the frightening experience under controlled conditions to help him or her to think through the trauma[3]. In 80% of people with PTSD, depression, or anxiety disorders, alcohol or other substance abuse occurs[12,15]. The likelihood of treatment success of peripheral nerve injuries of the upper extremities is increased when these other conditions are appropriately diagnosed and treated as well.

Identification of risk factors that may lead to psychological stress symptoms is needed for optimal treatment of patients. Previous exposure to trauma and a personal or family history of psychiatric disorders, particularly depressive disorders were found to be predictors of PTSD. In our study, significant independent predictors of early post-traumatic psychological stress were female gender, adult age and a combined nerve injury. Education, concomitant arterial bleeding and number of damaged structures and location of injury were not significantly associated with amount of psychological stress at one and three months postoperatively.

In our study female gender was found to be predictive for early posttraumatic stress. Multiple research studies have demonstrated that, in general, women have higher rates of PTSD than men[6,7,16] however findings are mixed regarding the prevalence of PTSD in males or females among individuals who have experienced an injury or disability. Perry et al (1987)[23] found that individuals who had severe burns and PTSD were more likely to be male than those with burns and without PTSD. Roca et al (1992)[26] found that gender did not significantly predict posttraumatic stress levels among individuals with burn injuries.

Another factor predictive for early posttraumatic stress in our study was age; Adult age over 25 years was associated with a higher degree of early post-traumatic psychological stress one month post operative. In several studies younger age on different diseases was indicated as a predictor of PTSD. Cordova et al. (1995)[24] found that among women who had received treatment for breast cancer, age was the only significant predictor of posttraumatic stress levels, with a younger age related to higher levels of posttraumatic stress. Thompson (1999)[25] found that among individuals who had experienced a myocardial infarction, age was significantly related to posttraumatic stress levels, with a younger age related to higher levels of PTSD. In a recent study where the role of physical, psychosocial and compensation-related factors in the development of 129 patients of an adult population with PTSD following major trauma were examined, it was found that PTSD was significantly associated with younger age ($P < 0.0001$)[22]. However note that in our study children above 12 years and adolescents were included, however the other studies concerned adults.

Combined nerve injuries were associated with a higher degree of early psychological stress one month post operative than median or ulnar injury. The relatively small number of patients that were diagnosed with this type of injury weakened our analysis and the power of our study. However further study on the type of injury in relation to psychological stress symptoms seems indicated. Severity of injury does not appear to be a strong predictor of the disorder. Feinstein in 1991[5]and Michaels in 1999[17,18] were unable to find a relationship between severity of injury and PTSD[5]. The major risk is conveyed by the experience of the fear, horror and helplessness and the ongoing pain and uncertainty caused by the injury[27]. In peripheral nerve injury patients and especially in patients with combined nerve injuries helplessness and uncertainty caused by the injury is substantial.

The remaining question is what mechanism is responsible for impaired functional outcome in peripheral nerve patients with psychological stress symptoms or early PTSD? Research has demonstrated that PTSD clearly alters a number of fundamental brain mechanisms[8]. Neurobiological studies indicate that this disorder involves fundamental hyperresponsivity within the amygdala, deficient hippocampal function and inadequate function of the anterior cingulated cortex. Besides glucocorticoid hypersensitivity and/or serotonergic and noradrenergic dysregulation represent possible neurochemical substrates for an unbalanced modulation of the limbic circuit[8,13]. Abnormalities or dysfunctional processes in brain chemicals may result in problems with coping, behaviour, learning and memory among people with the disorder. These skills are particularly important in patients with peripheral nerve injuries, who have to adapt to alterations in recognition of objects and touch perception, due to abnormal innervation and misdirection of nerves.

The accompanying symptoms of PTSD like depression, sleeping disorders and loss of motivation could also be responsible for impaired functional recovery and a late return to work. Furthermore there is evidence that psychological stress adversely affects the immune system and could influence and delay woundhealing[8].

In conclusion this study demonstrates a high incidence of early posttraumatic psychological stress following peripheral nerve injury of the forearm. Early detection of posttraumatic psychological stress symptoms and subsequent support and intervention in peripheral nerve patients might improve their functional outcome.

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CHAPTER 8

DIFFICULTIES IN CONDUCTING A PROSPECTIVE OUTCOME STUDY

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INTRODUCTION

The current emphasis on quality of healthcare, cost effectiveness, and consumer satisfaction increasingly requires objective analysis of treatments and interventions. Traditionally the parametrics for evaluating healthcare interventions were the five Ds: death, disability, dissatisfaction, disease, and discomfort. As patients become more active in defining healthcare quality, outcome measures are becoming increasingly patient-focused and are aimed more at quality of life and functional status[1]. The concept of the ideal outcome as perceived by doctors, however, may differ significantly from that of the patients. To meet these new demands for understanding the process–outcome relationship, there exists a tremendous need for physician involvement in developing outcomes assessment programs. Clinicians are being forced to evaluate what they do and how they do it, and evidence from personal case series is no longer sufficient[2]. Accurately measuring patient outcomes, however, demands expertise. Not only is theoretical knowledge about the subject of study required, but also management, statistical, and social skills are indispensable for good results. For the most part this can be learned from books; nevertheless, much can only be learned by experience. This article is presented as a short manual for the conduct of a clinical outcome study in upper extremity surgery. Not only data from literature but also the authors' own experiences are described and discussed. It is the authors' hope that solutions that originated from encountered problems and difficulties can provide a helpful template for the setup and conduct of an outcome study in hand surgery.

OUTCOME STUDIES IN HAND SURGERY

The human hand is a miracle of creation. The hand plays a dual role of supplying sensation and performing motor function. These motor functions can range from movements requiring great strength and coordination to fine and delicate detail. In 1843, Sir Charles Bell expressed the importance of the hand by stating:
We ought to define a hand as belonging exclusively to man—corresponding in sensibility and motion with that ingenuity which converts the being who is weakest in natural defense, to the ruler over animate and inanimate nature. With the hands the laborer supports a family, the parent loves and cares for a baby, the musician plays a sonata, the blind read, and the deaf talk[3].
Unfortunately the hand is also man's most frequently injured body part. In 30%–40% of injury events the hand is involved. The incidence rate of hand injuries is 5–11 per 100 workers per year (data from Liberty Mutual–Harvard University Hand Injury Study). In

addition, hand injuries generally take place in a young and economically active patient population. In the United States, hand injury results in 3–4 million missed working days, and total cost of upper extremity disorders is estimated to be almost $19 billion. Studies have shown that the indirect costs of lost productivity were nearly twice the direct healthcare costs[4-6]. This makes hand injuries for patient and society a real burden.

In general, the outcome of severe hand trauma is unpredictable. For the patient, this unpredictable outcome produces insecurity about the future that can result in demotivation, long-term unemployment, and psychological problems. Currently the amount of psychological symptoms after severe hand injuries is strongly underestimated by medical society. In literature, however, several studies have emphasized the high incidence of occurrences of posttraumatic stress disorder after severe work-related trauma and its potentially debilitating consequences. In a study of 170 patients with severe hand trauma, 81% initially had flashbacks that persisted at 18 months in 39% of patients[7]. In another study of 57 children with severe hand injuries, posttraumatic stress disorder was present in 84% after 1 month and in 20% after 12 months[8]. As illustrated by these frequencies, there is a need to include the psychological side effects in the evaluation of outcome after severe hand trauma. The high incidence of hand injuries, the unpredictable outcome, and the extensive physical and psychological consequences for the patient therefore calls for more outcome research on this subject.

FUNCTIONAL RECOVERY AFTER PERIPHERAL NERVE INJURY: AN EXAMPLE OF AN OUTCOME STUDY

An example of a hand injury with serious consequences and an unpredictable outcome is the peripheral nerve injury of the lower arm. In 1999, a prospective multicentered study was initiated in the University Hospital Rotterdam. The decision to use a prospective approach was based on the fact that, although the prospective controlled study is the most valid form of a clinical outcome study, in the literature only retrospective studies on peripheral nerve injuries were presented. A multicentered approach was needed because after estimation of the required patient population the number of patients treated at our hospital seemed too low to meet the recruitment deadline of the study. The aim of the study was to identify the predictive factors responsible for functional recovery of peripheral nerve injury of the forearm in the first year after repair. To accomplish a valid prognostic model, patients with a median or ulnar nerve injury between wrist and elbow needed to be evaluated at 1, 3, 6, and 12 months after nerve repair. For evaluation, physical examination and questionnaires were used. For reasons of patient convenience, evaluation took place in the referring hospital. Evaluation was performed by the study coordinator, who was stationed in Rotterdam. Despite thorough examination of literature, the multicentered approach and the prospective character of the study created several difficulties. These difficulties and the solutions that came from them are now further described and discussed.

HOW TO INITIATE AN OUTCOME STUDY

What to measure

The first step in the setup of an outcome study is defining the research question and selecting the methods of evaluation. The research question determines which kind of outcome study to choose. Outcome studies can be divided into three types: the physiological outcome study, the functional outcome study, and the quality of life outcome study. Physiological measures are the most easily quantifiable and do not require the perception of the patient. This is the most traditional form of an outcome study. The outcome is usually one of efficacy, for example, did the replanted finger survive or not and what where the predictive factors of failure. The most valid clinical outcome study is the randomized, prospective controlled study. Retrospective studies, however, are the most common type of outcome study still published today.

The functional outcome study is of particular interest for plastic and reconstructive surgery and for orthopedics. An objective measurement, like the range of motion of the joints of the fingers or the power or pinch grip of the hand, can be used to assess whether the patient benefited from a certain operation or therapy. Objective measurements however, are not able to give a complete image of patient functioning. Additional assessments of the patient’s capacity to perform daily activities and work after an intervention procedure are needed.

Another type of outcome study is the quality-of-life study. Interpreting the results of this kind of study is complex because of its subjective nature. However, it is certainly important to assess whether an operation or therapy is linked to an alteration in the patient’s quality of life, whether work related or in relation to hobbies. With increasing frequency, new and validated tests are appearing that make general or disease-specific analysis of quality of life easier and more reliable. Use of objective measurements only is insufficient for a comprehensive evaluation of hand function, different types of study should be combined for a complete picture of the patients recovery. To assess motor recovery, range of motion, grip strength, and tip-pinch grip strength were measured[9]. Sensory recovery was tested with Semmes-Weinstein monofilaments[10]. The DASH[11] (Disabilities of Arm, Shoulder, and Hand) and Impact of Event scale[12] (IES) were used to measure quality of life of the patients.

Study design

After the clinical question is formulated and the primary outcome measures are specified, one has to calculate sample size for the most important outcome measures[13]. The size of clinically important differences between outcome measures also has to be determined.
An important factor in determining the sample size is the estimation of the dropout rate. If dropout rates are not considered in sample size, the validity of the study decreases. Reasons for dropping out are, for example, patients who move to a different area and patients who cannot be traced. The dropout rate is influenced by several study-related factors that result in a wide variation in dropout rate from study to study. Perhaps the most important factor is the type of intervention used. It can be expected that in studies in which the intervention is painful and intrusive the dropout rate will be high. Other factors are length and frequency of follow-up, the study population, and possible gain for the patient. To estimate dropout rates it is useful to study relevant literature in advance for dropout rates of comparable studies. Also, a pilot study can be used to estimate loss of follow-up. Muench and Ederer stated that the number of patients promised for a clinical study divided by a factor of at least 10 rarely represents a gross exaggeration[14,15]. Possible reasons for these unrealistic estimations are the stringent inclusion and exclusion criteria used in most studies. Because of the expected dropout rate and the limited number of patients treated at the authors' hospital, a multicentered approach was needed to meet the recruitment deadline of the study. In general a multicentered approach heavily increases the workload. For participating medical centers, screening patients for entry into the study is time consuming. If doctors in the participating hospitals have to do the recruitment by themselves, especially when recruitment concerns extensive data gathering, fewer patients will be entered in the study.

The negotiation phase

When a multicentered approach is needed to meet the recruitment deadline of the study, access to research settings or subjects has to be initiated. Such negotiating may be complex and demanding. Ill informed participants may result in withdrawal or lack of commitment, or may compromise the quality of the data obtained. Before contacts are made with the parties concerned, the research proposal has to be finished. The research question, methods of screening, and the inclusion and exclusion criteria have to be determined and shouldn't be modified during the negotiating phase. Murphy proposed a strategy that can be of help in the negotiation process[16]. In her strategy, the first step of the negotiation phase consists of identification of all possible stakeholders. This includes not only the doctors of the participating hospitals, but also individuals like hand therapists, nurses, and the secretarial staff. After completing the list with all stakeholders in the participating hospitals, an estimation has to be made of the individual response to the project. Involvement of "opinion leaders" and powerful members of the community is indispensable for the success of the project. Negotiating the support of such people and organizations at the outset often eases access to individual research settings. Individuals interested in research and enthusiastic and motivated enough to promote the study also have to be selected. In several articles this person is described as "the local champion" [17,18,19]. The local champion can be helpful in obtaining negotiating access for the researcher with the individual participants. The local champions need adequate information about the proposed research before being asked to decide about their participation. This information has to summarize all the practical aspects of the study and the implications the study has for all participants. It is advisable to send a summary of the project information to the most important participants before the first meeting takes place. In the authors' study, local champions were identified, special brochures were designed, and a web page with an e-mail link was created to supply participants with all the necessary information for the project.

INCREASING PATIENT RECRUITMENT

Doctors

Even if doctors have consented to participate, actual patient recruitment may fall short of expectations. When all involved individuals in the study are adequately and accurately informed about the project, patient recruitment can commence. From the authors' own experience, we advise handing out reminders to all people involved with the inclusion of patients. These reminders have to contain all necessary information like inclusion and exclusion criteria; telephone numbers, e-mail, and fax numbers of the coordination center should be placed on the desk of the participants. We asked the participating physician to provide name and date of birth of the patient and completed the missing data ourselves with the help of the medical record. Another problem the authors encountered during the project was that in the course of time a lot of doctors changed their place of work or just forgot about the study. Unfortunately that also resulted in missed inclusions. The authors experienced that the best way to solve this is by asking one doctor to accept responsibility for the inclusion of patients. This individual should be mailed or called regularly. In addition, it is advisable to ask, for example, hand therapists to act as a "safety net." Writing newsletters, paying regular visits to the participating departments, and providing consistent feedback also increases the inclusion of patients.

Patients

It is not only ignorance or negligence on the part of the individuals in the participating hospitals that results in missed inclusions. Probably the most missed inclusions are caused by loss of patients. The authors' study population, which consisted of people with a lesion of the peripheral nerve of the lower arm, was difficult to motivate for followup. The group consisted mostly of patients who attempted suicide or slammed through a window, either out of aggression or following alcohol abuse. Comparable problems with recruitment also can be found in studies in which alcohol or drug addicts who are approached for followup. During the course of the authors' project, we came to a new method of approach of patients. At first when a patient was reported to the coordination center, contact was made with the patient by one of the researchers. After informed consent was obtained, patients received a letter with the dates of all followup appointments at once. All the appointments were scheduled at the participating hospital and performed by more than one physician. This resulted in missed inclusions; patients forgot about their dates or did not show up because they had other appointments or engagements. In addition the fact they were examined by different researchers on the succeeding appointments diminished their sense of commitment to the study. The authors' solution was to use a more patient-tailored approach. In the progress of this study only one appointment was made at a time, appointments were scheduled at the patient's home, and followup was done by only one physician. Although this logistic change of protocol increased the workload tremendously, it was rewarding in the end. Despite the use of the described measurements, however, there still remained patients who did not show up for their appointments, for example, patients who moved or became unmotivated. To minimize this group of patients it is recommended to ask the patient for a mobile phone number or e-mail address, always contact the patient the day before the appointment, and call immediately if a patient does not show up. Extensive explanation by the researcher during the examination and screening at home also increases the chance of successful attendance of followup appointments.

Although our measurements for patient recruitment may seem obvious, only in the course of time and as a result of missed inclusions and loss of followup we started to use them. Fortunately this resulted in an increase in our inclusions rate, and loss of followup declined dramatically.

Postal questionnaire response rate

Studies have been reported in which additional measurements to increase rates of postal questionnaires are surveyed. Postal questionnaires are used widely to collect data in health research and are often the only financially viable option when collecting information from large, geographically dispersed populations. In the authors' study, postal questionnaires were used to complete the information received by physical examination. In our case, the authors had to ask the patient to complete the questionnaire at home because going through the questionnaires during the appointment would be too demanding for patient and researcher and would impair the viability of the obtained data. As with loss of followup, however, nonresponse to postal questionnaires also occurred and reduced the effective sample size and possibly introduced bias. Because of budgetary considerations, the authors decided not to use monetary incentives. In a study by Edwards et al, who reviewed 292 randomized controlled trials including 258,315 participants, the odds of response were more than doubled when a monetary incentive was used[20,21]. The use of short questionnaires, questionnaires originating from universities, questionnaires designed to be of more interest for participants, personalized questions, and letters also increased the response. Even the color of the ink on the letters and questionnaires could influence the response rate; colored ink increased the chance of response 1.39 times. Methods the authors used in our study, such as stamped return envelopes, contacting participants before sending, and providing nonrespondents with a second copy, proved successful in increasing the number of returned questionnaires (Table 1).

SUMMARY

The success of an outcome study depends largely on the number of recruited patients, the loss of followup, and the response rate to postal questionnaires. In this article, different strategies were described to increase the aforementioned items. Most strategies were developed because of failure of measures used earlier. In the authors' study concerning hand surgery, this resulted in missed inclusions and loss of followup. It is hoped that by reading and using the strategies discussed, future researchers will start at the end of the learning curve and will shed a bright light on the obscurity of recovery after hand injury.

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CHAPTER 9

DISCUSSION

INTRODUCTION

The main rationale for this thesis is the need for a better understanding of impaired restoration of function after peripheral nerve injury. With a mean time of return to work of 31.9 weeks and 41% of the patients not returning to work in the first year, injury of peripheral nerves of the forearm has serious consequences[1,2]. Although functional outcome after peripheral nerve injury is highly unpredictable, patients can experience considerable loss of muscle function, impaired sensation and/or painful neuropathies and neuroma's. Several factors have been indicated to influence outcome results of median and ulnar nerve injuries, but no conclusive agreement exists on indepent predictors[2-11]. However, more knowledge about prognostic factors is essential to inform patients about their functional and social prospects and is indispensable for obtaining optimal treatment results. In this thesis peripheral nerve injury following compression injury as peripheral nerve injury following penetrating nerve injury are studied.

HOW CAN WE IMPROVE FUNCTIONAL OUTCOME AFTER PERIPHERAL NERVE INJURY?

In order to answer this crucial question the following sub-questions, as argumented in the introduction have to be addressed.

WHAT MAKES THE OUTCOME OF PERIPHERAL NERVE INJURIES SO UNPREDICTABLE/ I.E WHY DOES THE OUTCOME AND PROGNOSIS OF ACUTE NERVE INJURY VARY WIDELY?

Multiple studies regarding prognostic factors for functional recovery after peripheral nerve lesions have been published, however the results of various clinical studies of outcome after peripheral nerve injuries were highly variable. Three main reasons for unpredictable outcome and prognosis of acute nerve injury can be indicated:

1. Retrospective study design

Most studies concerning recovery after peripheral nerve lesions used a retrospective design.

The absence in literature of a conclusive agreement on indepent predictors for functional outcome, is supposedly at least partly due to confounding bias of the retrospective study material available. Therefore in this thesis we have chosen a prospective design to evaluate factors identified as prognostic in earlier retrospective studies for functional recovery of penetrating peripheral nerve injury of the forearm (as age, level of injury, type of nerve injury, number of damaged structures, education, smoking, posttraumatic stress, cognitive capacity) and evaluated their independent contribution in the first year after repair. The results of these studies are discussed on page 55-87 and 107-118.

Although in general a prospective study design is preferred, in chapter 3 a retrospective study design was chosen. In this chapter the effect of different treatment modalities on the outcome of compression nerve injury (compartment syndrome) was studied. Because this is a relative rare condition a retrospective study design allowed us to examine a larger study population over a longer observation period. In literature long term outcome studies of different treatment modalities after compression nerve injury (compartment syndrome) are almost nonexistent. The results of these studies are discussed on page 51-72.

2. Difficulties in post-operative assessment

Another factor contributing to unpredictable outcome and prognosis of acute nerve injury is the complexity of post-operative assessment of hand function. There are numerous tests to choose from and often tests are time consuming and complex to administer. Literature suggests combined assessments, scoring systems and questionnaires, but there is still today only limited clinical documentation concerning applicability in the clinical trial setting. The general notion seems to be that a battery of methods encompassing all the above domains, including the estimation of pain/discomfort, should be used[12,13,14,17,24]. However, the choice of evaluating methods to minimise biases is not obvious and the definition of efficacy, or good outcome, is not always evident.
Because used assessment methods in the literature vary considerably, an extensive comparison between different outcome studies is difficult and study results are not always representative for "true" functional outcome of hand function. Even in a prospective study design the specific function and complexity of peripheral nerve injury makes it difficult to reach an accurate view of the results of nerve repair in terms of restoration of function, or to isolate the effect of the variables that may influence the outcome. Besides, there is a controversy between clinical tests and functional capacity of the injured hand. In addition the degree of outcome of hand function is also highly individual and correlated with factors as for example daily occupation, function of the bilateral hand and secondary complaints as cold intolerance or pain.

Test methods are basically used to analyze:

- Sensory recovery
- Motor recovery
- Integrated sensory/motor functioning
- Daily activities and degree of pain and discomfort

Sensory tests
Despite the plethora of sensory tests, there is little consensus which ones should be used in outcome studies. Quantitative sensory tests are techniques employed to measure the intensity of stimuli needed to produce specific sensory perceptions. They are used to evaluate a sensory detection threshold or other sensory responses from supra-threshold stimulation. In the clinical setting sensory function has long been estimated by means of the two-point discrimination test (2PD), described originally by Weber in 1835[15,16]. This test measures the distance (in millimeters) between two points necessary for the individual to feel two distinct contacts, indicating peripheral innervation density. This also means there has to be cerebral integration, for it makes a different test than the Semmes Weinstein. Despite concerns regarding standardization of 2PD equipment and protocols, particularly with regard to application of pressure with the prongs, 2PD has been demonstrated to be a valid measure of chronic nerve compromise. However as the Semmes-Weinstein filament test provided greater standardization in sensation and pressure perception, this test has become one of the most commonly used quantitative measures in hand therapy practice[17,18]. Advantages of SWMF include the ability to assign numbers to sensory touch thresholds, regulation of force variations, and translation of forces obtained into functional levels. For that reason we incorporated the Semmes Weinstein monofilament test in our test battery. Unfortunately, there are also several limitations of this method of clinical assessment, such as fragility of the instruments, variations in forces applied between devices obtained from different manufacturers, and limitations associated with the use of an ordinal (logarithmic) scale [20]. Because the STI (shape texture identity) test at the time we composed our test battery was not validated yet, we did not include it in our test battery[21]. Combining the Semmes Weinstein test with other test methods like vibration tests or intergraded test as for example the pick-up test were too time consuming.

Motor tests

Manual Muscle Testing
Manual muscle testing (MMT) is routinely used in assessment of motor nerve recovery. It can be extremely valuable in determining the level of a nerve laceration or extent of nerve reinnervation. Muscles are isolated by providing resistance that is as specific as possible to the actions of the targeted muscle, but this can be difficult. The contraction obtained is graded on a scale from 0 to 5. This scale has been termed the Medical Research Council Scale or the Oxford Grading Scale[22,23]. However, it has been demonstrated that even low levels of innervation can produce grade 4 contraction. Therefore, once reinnervation permits a grade 3 (full antigravity) contraction, quantitative measures of muscle strength,

obtained using dynamometers, are required to effectively monitor further improvement. It has been suggested that measurement of abduction of digit 5 (D5), abduction D2 and intrinsic positioning of all four fingers can be used to assess ulnar nerve injuries in the hand. Rosen and Lundborg suggest adduction of D5 instead of the intrinsic position, which is meritorious on the basis of technical aspects alone. Median nerve injuries require assessment of abduction and opposition of the thumb[24].

Muscle Dynamometry

Grip strength is arguably the most studied of all physical impairments used by hand therapists. Clinical assessment recommendations distributed through the American Society of Hand Therapists describe a standardized test protocol with the elbow flexed 90 degrees, the forearm in neutral, and the patient gripping the Jamar dynamometer at the second handle position[25]. The reliability of grip strength testing has been well-established. However, the level of injury and nerves involved will impact on the overall loss of grip strength, as well as the distribution of this loss between the radial and ulnar digits. Although measurements of grip strength can very well be used to establish the impact of tendon or nerve injury on the hand, they are not precise enough to give appropriate information of individual intrinsic muscle strength after peripheral nerve injury[62,63]. For that reason the Rotterdam Intrinsic Hand Myometer (RIHM) was introduced by T.A.R. Schreuders[64]. Unfortunately, because the RIHM test at the time we composed our test battery was not validated yet, we could not include it in our test battery. However in our believe the Jamar dynamometer was an adequate tool to compare muscle strength between groups of patients and detect changes in muscle strength in our studygroup. For assessment of tip pinch strength the Jamar pinch gauge meter was used according to Mathiowetz et al[30]. For muscle dynamometrie three trials with each hand have to be carried out alternately, and the mean value has to be calculated for each hand. In case the third measurement is the highest, a fourth measurement has to be performed. Corrections for hand dominance have to be made[36].

Daily activities and degree of pain and discomfort

As patients become more active in defining healthcare quality, self-report disability measures that incorporate aspects of activity and participation should also be included in studies to provide a broader understanding of health outcomes after nerve injury. For that reason we added in our prospective study the Daily activities of shoulder and hand (DASH) test[26,27], the Impact of Event scale (IES)[28], the Cold Intolerance sensitivity scale (CISS)[29,30] questionnaire and a questionnaire concerning return to work to our test battery. Unfortunately during the course of the study we experienced several difficulties in the evaluation of cold intolerance with the CISS, which is a common problem in peripheral nerve injury patients. This questionnaire proved to be not precise enough for thorough analysis of different aspects of cold intolerance of peripheral nerve patients. Because for thorough analysis of all aspects of cold intolerance a reliable and validated questionnaire is needed, a renewed questionnaire for the evaluation of cold intolerance was introduced in chapter 6.

3. Heterogeneity of the study group.

A third reason for unpredictable outcome and prognosis of acute nerve injury is the heterogeneity of the studied group. Peripheral nerve lesions are generally accompanied by tendon and/or arterial injury which makes examination of causal relationships complicated. Also there is a large variety in localization of the injury; the more proximal the nerve lesion the longer it takes for the newly regenerated nerve fibers to reach the hand. In addition a considerable part of patients with penetrating peripheral nerve lesions of the fore arm are injured because of a suicide attempt or as a result of alcohol abuse. In general people with severe psychological problems are difficult to motivate to attend post-operative revalidation programs and outcome measurements may be modified by their mental state[31]. At last factors like age, injured hand (dominant or non dominant) and profession have a substantial influence on individual perception of outcome. As a consequence, if we really want to identify prospective factors for functional recovery after peripheral nerve injury large study populations are needed. For that reason a multicentre study design was used to evaluate the outcome of penetrating nerve injuries[32].

CAN WE IDENTIFY PROGNOSTIC FACTORS FOR FUNCTIONAL RECOVERY AFTER PERIPHERAL NERVE INJURY IN A PROSPECTIVE STUDY?

Identified prognostic factors for functional recovery after penetrating peripheral nerve injury in this thesis:

		Sens med	Sens uln	Sens hand	Power grip	Pinch grip	MRC med	MRC uln	MRC hand	DASH score
Age		-	-	+	+	-	-	-	-	-
Education		+	-	-	-	+	-	-	-	-
Smoking		-	-	-	-	-	-	-	-	-
Location	distal	-	-	-	-	+	-	-	-	-
	intermediate	-	-	-	-	-	-	-	-	-
	proximal	-	-	+	-	-	-	-	-	-
No structures		-	-	-	+	+	+	-	+	-
Injur.nerve	ulnar	-	X	X	-	-	-	X	-	-
	median	X	-	X	+	-	X	-	-	-
	combined	X	X	-	-	-	X	X	-	-
Type of injury	Sharp/crush	-	-	-	-	-	-	-	-	-
Post .tr. stress	1 month	-	-	-	+	-	-	-	-	+
Cogn.cap.		-	-	-	-	-	-	-	-	-

Age:

Analysis of our prospective data showed a significant influence of age on sensory recovery and motor recovery (power grip). Several retrospective studies have identified age as an important factor for functional recovery after nerve repair[33-36]. It has generally been accepted that children exhibit a greater capacity for nerve regeneration than adults[37-41]. Neuronal activity re-establishes rapidly in children, particularly in the very young, in whom the rate of axonal regeneration is thought to be as much as 5 mm per day[42]. Besides, it is well known that old age delays axonal regeneration by slowing axonal degeneration, axon sprouting, and Schwann cell response. The end result is a regenerated nerve with fewer axons and less myelination in older patients. In addition Peter Apel et al found in aged rats an impaired neuro-musculair joint response to injury, which may contribute to poor neuromuscular recovery seen after nerve injury in this group of peripheral nerve injury patients[43]. Although experimental and histological studies indicate a better nerve re-growth in children, there are also some findings giving evidence for a superior cerebral adaptation in children[38,44]. By some authors this neural plasticity has been pointed out as the crucial factor for their better peripheral nerve regeneration[45-47].

Level of injury:

In our study, location of injury was a significant predictor for both motor as well as sensory recovery of peripheral nerve injury of the forearm[49]. We found that distal lesions had better recovery of pinch grip 12 months postoperative, than proximal or intermediate lesions at the forearm. Although pinch grip was correlated with location of injury, MRC scores and powergrip were not influenced by location. Both distal as intermediate lesions had better recovery of sensory function 12 months postoperative than proximal lesions. However, in our study at the time of evaluation nerve fibers could not yet have reached the musculature of the hand. As indicated by Rosen, recovery at 12 months is not supposed to have reached it's end point in case of proximal forearm lesions[50]. Location of injury is known for its influence on outcome after nerve repair[2,4,33,39,51,]. With restoration of nerve continuity, axons may regenerate and, thus, re-innervate the motor end plates and sensory receptors. When the nerve injury is very proximal, nerve regeneration may not occur in sufficient time for muscle reinnervation. Furthermore because of shorter distance between level of injury and final receptors and better organised sensory and motory fascicles in distal injuries, there is less risk for mismatching. Ruijs described in her meta-analysis of predictors of functional outcome after median and ulnar nerve injury that intermediate or high lesions compared to low lesions gave an 54% lower change of motor recovery but had no impact on sensory recovery[52].

Type:

Because of the low incidence of crush injuries in our study group, we were not able to statistically analyse the contribution of crush versus sharp lesions in functional outcome.

Number of damaged structures:

Our study revealed that the number of damaged structures, reflecting the seriousness of the lesions was predictive for motor recovery (power grip, pinch grip and MRC scores). Daily activities and sensory recovery were not influenced by the number of damaged structures. Although there are no precise data in the literature regarding the dependence of nerve repair outcomes on other injuries in the nerve repair region, it has been assumed that the presence of such injuries is certainly a significant variable of outcome of nerve repair[53]. However in the retrospective study of Vordemvenne accompanying artery and flexor tendon injuries were not identified as a predictive factor for outcome and in our study only motor recovery was influenced by number of damaged structures[14].

Early psychological stress:

Although not earlier identified, Jaquet at al. indicated early psychological stress in patients after peripheral nerve injury, as a predictive factor for functional recovery after peripheral nerve injury. In this study 94% of the patients with peripheral nerve lesions demonstrated posttraumatic psychological stress. Psychological morbidity, measured with the impact of event scale was found to be 36% in this retrospective study population. Multiple lineair and logistic regression of results of this retrospective study showed an significant association between psychological stress and functional recovery (Beta=.51, p<.001) and an delayed return to work (Beta=.44, p<.001) . Patients who suffered severe early posttraumatic stress were six times more likely not to return to work within one year, compared to the group that reported a minor psychological response[54]. In the current prospective study 91.8% of the study population (mean score 22.0 SD 17.3) experienced psychological stress within the first month after surgery and 83.3% (mean score13.3 SD 14.1) experienced psychological stress 3 months post operatively, with 24.6 % (one month postoperative) and 13.3% (3 months postoperative) displaying scores indicating need for psychological treatment. Our study results reveal that early psychological stress, measured with the impact of event scale (IES) was associated with functional outcome. Multiple linear regression demonstrated significant relationships of IES (used to measure early posttraumatic stress) one month postoperative in relation with daily activity of shoulder and hand scores (DASH) and power grip 12 months postoperatively. Although we have not clarified which mechanism is responsible for impaired function outcome in peripheral nerve patients with early PTSD, it was found that PTSD alters a number of fundamental brain mechanisms which may result in problems with restoration of function[55,56].

Cognitive capacity

Cognitive capacity has been pointed out as the crucial factor for their better peripheral nerve regeneration. Cognition is a collection of mental processes and activities used in perceiving, remembering, and thinking, and the act of using those processes in understanding a sentence for example, but also in recognizing objects and touch perception. Those processes may also be of importance for sensory recovery after peripheral nerve damage. Peripheral nerve injury and repair is associated with alterations in the recognition of objects and touch perception due to abnormal reinnervation. This is a result of misdirection of axonal growth into distal sensory targets that are different in location, but also due to misdirection of axonal growth into different sensory end-organs[57]. Loss of functional nerve fibres occurs due to entrapment in scar tissue at the repair site. After regeneration the stimuli given by the hand have been altered and the brain has difficulty interpreting those signals into known associations. Some new signals cannot be interpreted at all and no perception takes place[58]. Children are supposed to have a superior cerebral capacity for adaptation processes. Hence they probably benefit from better cortical acquisition processes and are capable of putting the changes in the nerve messages to better use. Both Jaquet et al as Lundborg and Rosen found an assocation between cognitive capacity and sensory recovery of tactile gnosis in their retrospective studies. However, analysis of our prospective data did not reveal an association between cognitive capacity and recovery of sensory function measured by Semmes Weinstein test despite a significant influence of age on sensory recovery and motorrecovery (power grip) [45-48]. Although a relation between cognitive capacity and functional recovery could not be demonstrated, we did found level of education to be a predictor for recovery of median sensory function and for pinch grip. Higher level of education resulted in better functional outcome.

HOW CAN WE IMPROVE FUNCTIONAL OUTCOME AFTER PERIPHERAL NERVE INJURY?

Our study results indicate that early posttraumatic stress (PTSD) is a prognostic factor for functional outcome after penetrating peripheral nerve injury. Contrary to factors as age, location of injury and number of damaged structures, PTSD may a prognostic factor which might be influenced in an early stage. What is the mechanism responsible for impaired functional outcome in peripheral nerve patients with early PTSD? Research has demonstrated that PTSD clearly alters a number of fundamental brain chemicals and mechanisms that may result in problems with coping, behaviour, learning and memory among people with the disorder. These skills are particularly important in patients with peripheral nerve injuries, who have to adapt to alterations in recognition of objects and touch perception due to abnormal innervation and misdirection of nerves. The accompanying symptoms of PTSD like depression, sleeping disorders and loss of motivation could also be responsible for impaired functional recovery and a late return to work. Furthermore, there is evidence that psychological stress adversely affects the immune system and could influence wound healing[55,56].
Earlier research has demonstrated effectiveness of cognitive- behavioural therapy, group therapy exposure therapy and medical therapy in patients with PTSD. In addition Grunert et al demonstrated in 1991 that with early intervention of PTSD the effects of litigation on symptom maintenance were minimal[61]. Van der Kolk et al (1994) suggested that patients with more recent PTSD had better response to treatment[62]. Once PTSD has developed, it is often a chronic and recurring condition.

So would it be possible with early identification of patients with PTSD after severe hand trauma, to improve functional outcome and return to work? We believe it might. Although effects of therapy in patients with PTSD and peripheral nerve injuries yet have to be studied, according to our study results of early support and intervention could optimize treatment results. Intense emotional responses are normally seen during the first two

weeks following trauma of upper extremities. In this period the physician should provide the patient with psychosocial support. Stress symptoms like anxiety or sleep problems should improve during this period. If there is no improvement during this period, the physician should consider instituting psychological treatment.
Identification of risk factors that may lead to PTSD is needed for optimal treatment of patients. In literature previous exposure to trauma and a personal or family history of psychiatric disorders, particularly depressive disorders were found to be predictors of PTSD. In our study, significant independent predictors of early post-traumatic psychological stress were age, with older patients more frequently showing stress symptoms and presence of combined nerve injuries.

As opposed to penetrating nerve injury, functional outcome of nerve injuries after compression (compartment syndrome) can largely be optimized by prevention of long term ischemia. As confirmed by our study results, a supracondylar fracture of the humerus is the most frequent cause for a compartment syndrome, followed by a fracture of the forearm[59,60]. Therefore, especially in children, these fractures must be monitored carefully to facilitate early diagnosis of vascular injury or compartment syndrome. Presence of symptoms such as extreme, poorly localized pain, particularly with passive stretching of the muscle by manipulation of the digits and the wrist, a sensory deficit and reduction of active movement requires aggressive treatment. As shown by the results of our study, measurements such as opening of the plaster cast and elevation of the arm are not sufficient to prevent Volkmann's ischemic contracture. Decompression should be done immediately, to restore the microcirculation of the forearm. In cases of a suspected vascular injury, decompression must be combined with vascular exploration and restoration of blood flow.

In compression nerve injuries a lot of different treatment modalities can be performed. In this thesis we have demonstrated that method and timing of treatment largely influences outcome in this type of lesion. Our retrospective study evaluated the effect of timing and method of treatment of an established ischemic contracture of the forearm on functional outcome. In literature not only type of surgical procedure, but also exact moment of intervention is a subject of discussion. Based on our long term study results we came to the following advice regarding treatment of Volkmann's ischemic contracture.

- Although delay was advocated previously, it seems wise to operate on patients with poor or unsatisfactory hand function (Table 2). Excision of severe muscle necrosis diagnosed by magnetic resonance imaging (MRI) and neurological signs in an earlier stage prevent additional joint stiffness and nerve damage by fibrosis. Early surgery also is necessary in patients with a so-called prolonged pain syndrome, because prompt neurolysis and excision of fibrotic tissue will resolve the pain immediately.

- In patients with good to reasonable hand function (Table 2) we suggest initial conservative treatment and then wait for spontaneous improvement of sensibility and motor function. If after 3 months hand function deteriorates or does not improve, surgical intervention must be considered.
- In patients with poor hand function (Table 2) and an extensive infarction diagnosed by MRI, we advise doing free vascularized muscle transplantation. We prefer a two-stage procedure with early excision followed by transplantation a few months later. If in the first stage the nerve is in continuity without deformity after neurolysis, a substantial recovery of sensory function often will occur. If the nerve is damaged by the ischemia, this is mostly the case when a substantial amount of forearm flexor muscles are fibrotic, a nerve graft is planned in the second stage, combined with the free muscle transfer. In the majority of our patients both hand mobility and sensory function improved tremendously after free muscle transfer. A considerable increase of power grip strength can be seen; however, because of the contractile force of the gracilis muscle grip, strength will stay limited.

	Wrist	***Fingers***	***Thumb***
Good	> 90°	>160°	> 40°
Reasonable	> 70°	> 140°	> 30°
Unsatisfactory	> 25°	> 120°	> 20°
Poor	< 25°	< 120°	< 20°

Table 2. *Hand Function: Total Active Range of Motion*

- Excision of fibrotic muscle tissue, neurolysis, and tenolysis is advised in patients who are diagnosed with unsatisfactory hand function (Table 2) with infarction of a considerable part of the deep and superficial flexors and neurological signs.
- Good results can be obtained if excision and neurolysis is combined with a tendon transfer, specifically in patients who are treated early after injury.
- Because of the high recurrence rate of the contractures and possible loss of power grip strength, tendon lengthening only is not recommended.

FUTURE PERSPECTIVES

Treatment of patients with injured peripheral nerves still belongs to one of the most challenging reconstructive surgical problems. The primary aim of this thesis was to analyse and discuss functional outcome after peripheral nerve injuries of the forearm. Retrospective evaluation of long term functional outcome of different treatment modalities of peripheral compression injuries (compartment syndrome) resulting in Volkmann's Ischemic Contracture and prospective identification of prognostic factors for functional outcome in penetrating median or ulnar nerve injuries will contribute to a better understanding of recovery after peripheral nerve trauma.

Why are prognostic factors so important for us? Our main rationale for this thesis was optimization of treatment results. We demonstrated that in patients with compression nerve injury (Volkmann's ischemic contracture) functional outcome can be largely improved by choosing the appropriate treatment procedure at the right moment. Optimal treatment of an established ischemic contracture requires a thorough examination of the extent of damage of the ischemia, followed by conservative therapy or operation. The most important measures concerning Volkmann's ischemic contracture, however, involve measures to prevent the contracture. Very simple measures, such as monitoring high-risk injuries and immediate vascular repair or decompression if symptoms of a compartment syndrome are present, should minimize the incidence of this disabling condition in future. A penetrating nerve injury has standardized timing- and a uniform method of treatment and this type of injury cannot be easily prevented. Measurements regarding improvement of functional outcome are mainly postoperative interventions. With help of prognostic factors identified in this thesis, patients categorized as "high risk" for suboptimal recovery of either sensory or motor hand function, might improve by early intervention. Intervention can range from surgical procedures (such as tendon transfers, secondary microsurgical nerve repair, nerve grafting, neurolysis) to sensory reeducation, hand therapy, reintegration or even psychological counseling. However to what extent this really improves outcome we don't know yet and should be further studied. For evaluation of intervention methods, reference intervals for patients the first year after periferal nerve repair considering motor recovery, sensory recovery, daily activities and pain/discomfort are needed. In order to create reference intervals for recovery during first year after injury, we need large quantities of peripheral nerve patients. Considering the relatively low incidence of peripheral nerve injury a multicenter approach is needed.

In this thesis recommendations considering study and evaluation methods were made and the neccesity of a reliable and solid testbattery was emphasized. Unfortunately the perfect test battery for evaluation of different domains of functional recovery doesn't exist yet. In order to improve the contemporary testbattery for functional outcome we introduced a new questionnaire for cold intolerance. Although this questionnaire proved to be reliable both in the normal population as in the target population, its qualities still have to be proven in larger study populations. In addition further studies should be done on the exact incidence of cold intolerance after different types of hand and peripheral nerve injury, the prevalence of various symptoms of cold intolerance and their provocative moments, the impact of Cold Intolerance complaints on quality of living and on detailed identification of predictive factors.

Prognostic factors are indispensable for identification of patients at high risk for impaired functional outcome. Subject of further study should be the evaluation of intervention on different levels, both concerning surgical procedures, as well as psychological counseling in high risk patients. For such purposes we are in need of improvement of our evaluation methods and reference intervals considering motor recovery, sensory recovery, daily activities and complaints of pain/discomfort.

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CHAPTER 10

SUMMARY

SUMMARY

Chapter 1, the introduction of this thesis, describes both history as recent advances in treatment of peripheral nerve injury. The unpredictable nature of outcome after peripheral nerve injuries is discussed. With better understanding of prognostic factors we could be able to evaluate and optimize our methods of treatment and improve outcome. For a reliable evaluation of the influence of prognostic factors on outcome a proper study design is indispensable.

In **Chapter 2** Volkmann's ischemic contracture, a specific peripheral nerve injury, is described**.** Volkmann's ischemic contracture is a tragic result of a neglected compartment syndrome. In humans, compartment syndromes can be induced by direct muscle trauma, bleeding and localized pressure by casts or by circular dressings. When diagnosed early and treated properly, the development of Volkmann's ischemic contracture can be prevented. When symptoms of a compartment syndrome are present, superficial and deep fasciotomy should be performed as well as vascular repair if necessary. When a contracture is established, optimal treatment requires a thorough examination of the extent of damage of the ischemia, followed by conservative therapy in mild cases. The moderate or severe cases require surgery, ranging from tendon transfers to free innervated vascularised muscle transfers.

In **Chapter 3** a long-term follow up study of functional results after treatment of Volkmann's Ischemic Contracture is performed. The main objective was to evaluate the long-term functional outcome in patients treated for Volkmann's ischemic contracture. By means of a retrospective study, functional outcome (measured as mobility, grip strength, and sensibility) and arm length difference after treatment of Volkmann's ischemic contracture were analyzed and discussed. Twenty-five patients treated between 1969 and 2001 were evaluated. The method of treatment was related to the severity of the infarction, ranging from conservative to free vascularized muscle transplantation. Although the study population was small, we could observe a wide range of functional outcome. Substantial improvement of function was obtained in patients who had free vascularized muscle transplantation. Tendon lengthening had unsatisfactory results, because of recurrence of the contracture. Excision of fibrotic muscle tissue, neurolysis and tenolysis sometimes combined with a tendon transfer gave good hand function results in patients with sufficient remaining muscle tissue. In most of the patients in whom the contracture developed during childhood, a difference in forearm length was observed.

As nerve injuries can have severe sequelae, as described above, in **Chapter 4** a prospective study was performed to determine prognostic factors for outcome after median, ulnar and combined median-ulnar nerve injuries. Even after microsurgical nerve repair of the median or ulnar nerve, sensory recovery and strength cannot be expected to fully recover and most patients experience considerable loss of muscle function, impaired sensation and/or painful neuropathies or neuroma's. As peripheral nerve repair techniques cannot easily be further refined, there is a need for understanding the prognostic factors which influence the final outcome. What makes the outcome of peripheral nerve injuries so unpredictable? The prospective outcome study was performed in patients with a repaired median, ulnar or combined median-ulnar nerve injury. Investigated factors were age, level of injury, type of nerve injury, number of damaged structures, number of damaged arteries, education, smoking and posttraumatic stress. Age group, education, location of injury, posttraumatic stress after one month, number of injured structures and number of injured arteries were found to be predictive of functional recovery after peripheral nerve injuries of the median and/or ulnar nerve of the forearm. Of these prognostic factors only posttraumatic stress can be influenced to optimize functional outcome.

In **Chapter 5** a study was performed concerning cognitive capacity. In this study cognitive tests were positively related to recovery of sensibility by the Semmes Weinstein test score after peripheral nerve repair in the forearm.
In the recovery process of sensibility after repair of a peripheral nerve injury misdirected axons can result in disappointing outcome results when reorganisation or other adaptic processes at the level of the somatosensory cortex of the brain are impaired. These processes are thought to be dependent on the patient's cognitive capacity. It has generally been accepted that children exhibit a greater capacity for nerve regeneration than adults. The neural plasticity has been pointed out as the crucial factor for their better peripheral nerve regeneration. Children are supposed to have a superior cerebral capacity for adaptation. They probably benefit from better cortical acquisition processes and are capable of putting the changes in the nerve messages to better use. Lundborg and Rosen were the first to report (n=19) an assocation between cognitive capacity and sensory recovery of tactile gnosis. In this chapter a prospective multicentre study was conducted to assess the association between cognitive capacity and recovery of sensibility after peripheral nerve damage of the forearm. Patients with a traumatic peripheral nerve lesion of the forearm and consecutive surgical repair were included. After 12 months, the patients were assessed with respect to recovery of sensibility (Semmes Weinstein monofilaments) and cognitive capacity, with four tests assessing different aspects of cognitive functioning. Twenty-eight patients (25 male, three female; median age: 28.5 years; range: 15-79 years) with median and/or ulnar nerve injury of the forearm were included in the study. Although younger age showed a positive association with sensory recovery, no association was found between the cognitive-capacity tests used and sensory

recovery. The present prospective study did not reveal any association between recovery of sensibility measured by Semmes Weinstein test score and cognitive capacity. Further studies should be performed to confirm these results.

In Chapter 6 patients with peripheral nerve injuries were evaluated for Cold Intolerance.

Cold intolerance develops in the majority of patients who sustain peripheral nerve injury of the forearm. However, very little is known about pathogenesis, etiology and treatment of cold intolerance. For thorough analysis of all aspects of cold intolerance a reliable and validated questionnaire is indispensable. Although in the past cold intolerance questionnaires like the McCabe and the modified Cold Induced Sensitivity Scale (CISS) were introduced in literature, in most studies a validated questionnaire for data gathering was absent. A disadvantage of the CISS Questionnaire (and the McCabe) for cold intolerance is the sometimes confusing nature of some questions for patients with complaints following a peripheral nerve injury. Another major drawback of these questionnaires is that symptoms of cold intolerance as a consequence of hand injuries are not easily distinguished from already existing cold intolerance symptoms. In this chapter the CISS Questionnaire and the McCabe Questionnaire were evaluated and a renewed cold injury questionnaire was introduced. The study comprised three parts:

I. Twenty-eight peripheral nerve patients were asked to fill in a Cold Induced Sensitivity Scale (CISS) and were thereafter physically examined and questioned for symptoms of cold intolerance. Results of the CISS and actual complaints/ symptoms were compared.

II. Sixty CISS scores of randomly assigned people of the normal population were analyzed and compared with CISS scores from peripheral nerve patients in literature.

III. A new questionnaire for the evaluation of cold intolerance was designed based on the questions of the CISS.

The results were:

I. In the peripheral nerve injury group 18 out of 28 patients had difficulties with understanding the items of the CISS questionnaire.

II. Forty-eight out of 60 people without hand trauma or operation in their history had cold intolerance according to the CISS score.

III. The newly designed questionnaire appeared to be able to distinguish cold intolerance in patients with a previous nerve injury operation of the hand or forearm (secondary Raynaud phenomenon) from cold intolerance in the normal population (primary Raynaud phenomenon).

It can be concluded that existing questionnaires are not precise enough for thorough analysis of different aspects of cold intolerance. A renewed questionnaire was introduced, which showed promising and satisfactory results.

In **Chapter 7** a prospective study on early posttraumatic psychological stress following peripheral nerve injury is described. Psychological symptoms frequently accompany severe injuries of upper extremities and are described to influence functional outcome. As yet little knowledge is available about occurrence of posttraumatic psychological stress and the predictive factors of such psychological symptoms in relation to peripheral nerve injuries of the upper extremity. In this chapter a prospective study design was used to analyze different aspects of early posttraumatic stress in patients with peripheral nerve injury of the forearm. Our main objectives were to assess the incidence and intensity of post-traumatic psychological stress symptoms and to identify risk factors for early psychological stress. Patients with a median, ulnar or combined median-ulnar nerve injury were monitored for posttraumatic psychological stress symptoms with the Impact of Event Scale questionnaire (IES). Psychological stress within the first month after surgery occurred in 91.8% of the population (mean=22.0, SD=17.3). Three months post operatively 83.3% (mean=13.3, SD=4.1) experienced psychological stress. One month postoperative 24.6 % of the patients and three months postoperative 13.3% of the patients had IES scores indicating a need for psychological treatment. Female gender, adult age and combined nerve injuries were related to occurrence of psychological stress symptoms one month post operative. It was concluded that in the majority of patients, peripheral nerve injury of the forearm is accompanied by early posttraumatic psychological stress.

In **Chapter 8** difficulties in conducting a prospective outcome study are described. The current emphasis on quality of healthcare, cost effectiveness, and consumer satisfaction, increasingly requires objective analysis of treatments and interventions. Traditionally the parameters for evaluating healthcare interventions reflected the five Ds: death, disability, dissatisfaction, disease, and discomfort. As patients become more active in defining healthcare quality, outcome measures are becoming increasingly patient-focused and are aimed more at quality of life and functional status. Our concept of the optimal outcome, however, may differ significantly from that of our patients. To meet these new demands for understanding the process–outcome relationship, there exists a tremendous need for physician involvement in developing outcome assessment programs. Clinicians are being forced to evaluate what they do and how they do it, and evidence from personal case series is no longer acceptable. Accurately measuring patient outcomes, however, demands expertise. Not only is theoretical knowledge about the subject of study required, but also management, statistical, and social skills are indispensable for appropriate results. For some part this can be learned from books; nevertheless, much can only be learned by experience. This chapter is presented as a short manual for the conduct of a clinical prospective outcome study in upper extremity surgery.

SAMENVATTING

In **hoofdstuk 1**, de introductie van dit proefschrift, wordt aandacht besteed aan zowel de geschiedenis als de meer recente ontwikkelingen op het gebied van de behandeling van perifere zenuwletsels van de onderarm. In dit hoofdstuk wordt de onzekere uitkomst van dergelijke letsels besproken. Door meer kennis te vergaren over factoren die van invloed zijn op het uiteindelijk herstel na een zenuwletsel, zijn we niet alleen in staat patiënten beter in te lichten over het te verwachten herstel; we kunnen ook in een eerder stadium ingrijpen als het herstel niet verloopt zoals gehoopt. Om het uiteindelijk functioneel herstel na zenuwletsels te optimaliseren, is het verder van belang prognostische factoren te identificeren die te beïnvloeden zijn. Om het bovenstaande te kunnen doen is een goede testbatterij en een gedegen onderzoeksaanpak essentieel.

Hoofdstuk 2 is gewijd aan de ischemische contractuur van Volkmann. De ischemische contractuur van Volkmann is een ernstige handaandoening die veroorzaakt wordt door een niet onderkend compartimentsyndroom van de arm. Dit kan ontstaan na een letsel van de arm; vaak zijn het de combinatie van een sterke zwelling in de onderarm en de aanwezigheid van gips die uiteindelijk het compartimentsyndroom veroorzaken. Indien een compartimentsyndroom op tijd wordt ontdekt en behandeld kan het ontstaan van de ischemische contractuur van Volkmann voorkomen worden. Gebeurt dit niet zullen zenuwen en spieren van de hand en onderarm hun functie verliezen en een contractuur stand aannemen. Er zijn verschillende mogelijkheden om het (zenuw)letsel bij deze aandoening te behandelen. Behandelmethoden variëren van conservatieve therapie tot vrij geinnerveerde spiertransplantaten.

In **hoofdstuk 3** wordt een follow-up studie gepresenteerd waarin de lange termijn resultaten van de verschillende behandelingsmodaliteiten van de ischemische contractuur van Volkmann geanalyseerd zijn. Vijfentwintig patiënten behandeld tussen 1969 en 2001 werden opnieuw geëvalueerd door middel van uitgebreid handfunctie onderzoek. De resultaten van de verschillende behandelmethoden bleken sterk te variëren. Tevens kwam naar voren dat patiënten bij wie de contractuur in de kindertijd was ontstaan een aanzienlijk arm lengte verschil hadden ontwikkeld.

In **hoofdstuk 4** wordt ingegaan op prognostische factoren voor functioneel herstel na een traumatisch medianus en/of ulnaris letsel. De consequenties van een zenuwletsel van de onderam zijn over het algemeen groot; helaas valt vaak niet goed te voorspellen hoe de uiteindelijke uitkomst na chirurgisch herstel zal zijn. In het verleden zijn verschillende factoren geïdentificeerd die van invloed zijn op het herstel, maar resultaten spreken elkaar tegen. In dit onderzoek zijn factoren die retrospectief prognostisch voor het functionele herstel bleken te zijn in een prospectieve multi center trial geanalyseerd. Leeftijd, educatie, locatie van het letsel, posttraumatische stress en het aantal aangedane structuren en - arteriën bleken van invloed te zijn op het uiteindelijk herstel. Van deze factoren kan posttraumatische stress als enige beïnvloed worden.

In **hoofdstuk 5** wordt de invloed van cognitieve capaciteit op functioneel herstel na perifeer zenuwletsel van de onderarm geanalyseerd. In eerder uitgevoerd retrospectief onderzoek werd cognitieve capaciteit aangewezen als een belangrijke prognostische factor voor functioneel herstel. Onze prospectieve onderzoeksresultaten laten echter geen relatie zien tussen cognitieve capaciteit en functioneel herstel.

In **hoofdstuk 6** staan koude intolerantie klachten centraal. De meerderheid van mensen met een perifeer zenuwletsel van de onderarm krijgt te maken met koude intolerantie. Koude intolerantie klachten kunnen het functioneren van de patiënt sterk beperken. Er is uit onderzoek weinig bekend over het voorkomen, pathogenese en de behandeling van koude intolerantie. Voor onderzoek op dit gebied is het essentieel gebruik te kunnen maken van een betrouwbare en gevalideerde vragenlijst. Hoewel er in het verleden vragenlijsten ontworpen zijn om koude intolerantie klachten bij handletsel patiënten te kunnen evalueren, leveren deze vragen in praktijk bij zenuwletsel patiënten nogal wat problemen op. Een aantal vragen zijn verwarrend voor patiënten met een perifeer zenuwletsel en bovendien zijn primaire koude intolerantie klachten niet goed te onderscheiden van klachten ten gevolge van het zenuwletsel. Dat maakt deze vragenlijst minder geschikt voor uitgebreide analyse van de verschillende aspecten van koude intolerantie. In dit hoofdstuk wordt het voorkomen van koude intolerantie bij zenuwletsel patiënten besproken en wordt een nieuwe koude intolerantie vragenlijst geïntroduceerd.

In **hoofdstuk 7** wordt verder ingegaan op aanwezigheid van vroege post traumatische stress bij zenuwletsel patiënten. Post traumatische stress komt vaak voor bij patiënten met handletsels. Recent retrospectief onderzoek als ook onze eigen prospectieve studieresultaten (zie hoofdstuk 4) laten een relatie zien tussen de aanwezigheid van posttraumatische stress en functioneel herstel. Dat zou kunnen betekenen dat preventie of behandeling van posttraumatische stress in een vroeg stadium functioneel herstel bij zenuwletsel patiënten zou kunnen verbeteren. Daarvoor is het noodzakelijk te weten hoe vaak het voorkomt en welke mensen een hoog risico lopen op het krijgen van post traumatische stress. Uit ons onderzoek kwam naar voren dat 91.8% van de studiepopulatie in enige mate post traumatische stress heeft. Na drie maanden was dit nog 83.3%. Verder bleek dat na 1 maand bij 24.6% van de patiënten en na 3 maanden bij 13.3% van de patiënten de klachten dusdanig erg waren dat ze mogelijk in aanmerking zouden komen voor psychologische begeleiding. Vrouwen, patiënten met een gecombineerd zenuwletsel en patiënten met een hogere leeftijd bleken een groter risico te lopen op posttraumatische stress verschijnselen.

In **hoofdstuk 8** en tevens het laatste inhoudelijke hoofdstuk van dit proefschrift wordt aandacht besteed aan het opzetten en uitvoeren van prognostisch onderzoek bij handletsel patiënten. Handletsels komen zeer vaak voor en de consequenties kunnen groot zijn. Om resultaten op het gebied van de behandeling van handletsels te kunnen vergroten is goed prognostisch "outcome" onderzoek noodzakelijk, zeker ook gezien de huidige nadruk op de kwaliteit van gezondheidszorg, kosten effectiviteit en tevredenheid. Door de relatief lage incidentie van bepaalde handletsels kan voor een uitgebreide analyse een multicenter aanpak noodzakelijk zijn. Het opzetten en uitvoeren van een prospectief multicenter outcome onderzoek is echter gecompliceerd. Naast kennis over het onderwerp zijn de aanwezigheid van een goede testbatterij, management- en sociale vaardigheden onontbeerlijk voor een goed studie verloop. Voor een groot gedeelte is dit "boekenwijsheid", een aanzienlijk deel van de kennis over het uitvoeren van prospectief outcome onderzoek wordt verkregen door ervaring. In dit hoofdstuk worden zowel de resultaten uit wetenschappelijke studies als eigen ervaringen op het gebied van prospectief onderzoek naar zenuwletsels gepresenteerd. Beide kunnen helpen bij een gedegen studie opzet, succesvol verloop en betrouwbare resultaten van klinisch prospectief onderzoek binnen de handchirurgie.

CHAPTER 11

PUBLICATIONS

LIST OF PUBLICATIONS INCLUDED IN THE PRESENT THESIS

Volkmann's ischemic contracture. Prevention and treatment.
S.E.R. Hovius, J. Ultee.
Hand Clin. 2000 Nov;16(4):647-57.

Functional results after treatment of Volkmann's ischemic contracture: a long-term followup study.
J. Ultee, S.E.R Hovius.
Clin Orthop Relat Res. 2005 Feb;(431):42-9.

Prognostic factors for outcome after median, ulnar and combined median-ulnar nerve injuries: A prospective study.
J. Ultee, A.L. van Baar, J.B. Jaquet, P. Haupt, P.H.M. Spauwen, M. Ritt, M. Kon, S.E.R Hovius.
Submitted to New England Journal of Medicine.

Cognitive capacity: No association with recovery of sensibility by Semmes Weinstein test score after peripheral nerve injury of the forearm.
Z.J. Boender, J. Ultee ,S.E.R. Hovius.
J Plast Reconstr Aesthet Surg. 2010 Feb;63(2):354-9.

Evaluation of cold intolerance in patients with peripheral nerve injuries.
J. Ultee, S.E.R. Hovius.
J Plast Reconstr Aesthet Surg. Accepted for publication

Early posttraumatic psychological stress following peripheral nerve injury: a prospective study.
J. Ultee, A.L. van Baar, S.E.R Hovius.
Submitted to J Plast Reconstr Aesthet Surg.

Difficulties in conducting a prospective outcome study.
J. Ultee, J.W. van Neck, J.B. Jaquet, S.E.R. Hovius.
Hand Clin. 2003 Aug;19(3):457-62.2003 Aug;19(3):457-62.

CHAPTER 12

CURRICULUM VITAE

Jetske Ultee werd op 4 juni 1972 geboren te Woerden. Na het behalen van het VWO diploma (Vossius gymnasium Amsterdam gevolgd door Geert Grootte College in Deventer), startte zij na het staatsexamen natuur- en scheikunde afgelegd te hebben in 1994 met de opleiding Geneeskunde aan de Universiteit van Rotterdam. Tijdens haar afstudeeronderzoek naar de Ischemische contractuur van Volkmann, uitgevoerd voorafgaand aan de co-assistentschappen, raakte zij geïnteresseerd in de Plastische en Reconstructieve Chirurgie. Tevens werd met het afstudeeronderzoek onder leiding van Prof. S.E.R. Hovius de basis gelegd voor wat later dit proefschrift zou worden. Na het behalen van het doctoraal liep ze in 1997-1998 een stage van 6 maanden in Great Ormond Street Hospital in Londen bij dr. P. J. Smith om kennis te maken met de chirurgie van congenitale hand afwijkingen. Gedurende de co-schappen voorafgaand aan het behalen van het artsexamen werd het haar duidelijk dat ze zich wilde specialiseren tot Plastisch Chirurg. Eerst werkte zij een jaar als niet-opleidingsassistent in het Erasmus MC in Rotterdam (Prof. S.E.R.Hovius) om in 2000 de toezegging tot een opleidingsplaats Plastische Chirurgie te verkrijgen. Alvorens te starten met de vooropleiding Algemene Heelkunde werkte zij van 2001 tot 2003 als arts assistent en -onderzoeker aan het prognostisch multicenter onderzoek naar de uitkomst van perifere zenuwletsels, zoals in dit proefschrift verder uitgewerkt. In 2001 verhuisde ze met haar man Frits Berends naar Oosterbeek waar hij in het Rijnstate Ziekenhuis in Arnhem deel ging uitmaken van de maatschap Algemene Chirurgie. In Oosterbeek werd ook haar eerste dochter Noa geboren. Dit gecombineerd met de wens een groot gezin te stichten deden haar in 2004 beslissen de opleiding tot Plastisch Chirurg in Rotterdam niet voort te zetten maar naar een functie te zoeken die beter te combineren was met een gezinsleven in Oosterbeek. Inmiddels is het gezin dan ook uitgebreid met dochter India (2005), gevolgd door zoon Senna (2006) en zoon Bo in (2008) . Vanaf 2004 is ze gaan werken bij de Velthuiskliniek onder leiding van dr. P. Velthuis en J. Dekker. In de hierop volgende jaren heeft zij samen met dr. P. Velthuis de afdeling huidtherapie binnen de verschillende klinieken opgezet. Momenteel heeft ze naast het superviseren van de huidtherapie en het doen van onderzoek op het gebied van cosmetische huidbehandelingen samen met J. Dekker en P. Velthuis een bedrijf opgezet gericht op ontwikkeling en research van cosmeceuticals.

PORTFOLIO

Name PhD student: J. Ultee Erasmus MC Department: Plastic, Reconstructive and Hand surgery Research School: MUSC	PhD period: from 1999 onwards Promotor: Prof. Dr. S.E.R. Hovius	
1. PhD training	**Year**	**Workload (Hours/ECTS)**
General academic skills		
- English Writing and Communication: Internship Great Ormond Street Hospital London	1997-1998	-
- Conducting a Clinical Retrospective Study: *Volkmann's Ischemic contracture*	1997-2001	-
- Conducting a Clinical Prognostic Multicenter Study: *Outcome of peripheral nerve injury*	1999-2003	-
Research skills		
- Inclusion of patients, sampling, analyses	1999-2003	-
- Interpretation of results and writing	2001-2009	-
In-depth courses (e.g. Research school, Medical Training)		
- Internship Great Ormond Street Hospital London	1997-1998	Full time
- Internship Department of Plastic, Reconstructive and Hand surgery Erasmus MC	2000-2001	Full time
- Micro Surgery Course Erasmus MC	2000	5 days

Presentations		
- Nederlandse Vereninging Orthopaedie en Traumatologie *Volkmann's Ischemic Contracture*	1998	60
- Najaarsvergadering Nederlandse Vereniging Handchirurgie *Volkmann's Ischemic Contracture*	1998	60
- Voorjaarsvergadering Nederlandse Vereniging voor Plastische Chirurgie *Volkmann's Ischemic Contracture*	1999	60
- Precongres Fessh *Volkmann's Ischemic Contracture*	2000	100
- Capita Selecta Erasmus MC Rotterdam *Hand injury*	2002	100
- Najaarssymposium Nederlands gezelschap voor Handtherapie *Functional results following periph. nerve injury*	2002	60
International conferences	2000	100
- FESSH Barcelona *Functional results following periph.. nerve injury*		
- FESSH Amsterdam *Difficulties in conducting a prosp. outcome study*	2002	100
Seminars and workshops		
- Fysiotherapists Academical Hospital Nijmegen (AZN) *Treatment of Peripheral nerve injuries*	2002	50
Didactic skills		
- Education medical students Plastic Surgery department EMCR on hand injuries	2001-2003	3 days

Other		
- Organisation Wound Congress; " *Wondgenezing & Wondbehandeling 2001", Rotterdam*	2001	20 days
- Organisation Wound Congress; " *Wondgenezing & Wondbehandeling 2002", Rotterdam*	2002	20 days

2. Teaching activities	**Year**	**Workload (Hours/ECTS)**
Lecturing		
- Teacher Microsurgery course Erasmus MC	2001	5 days
- Teacher Microsurgery course Erasmus MC	2002	5 days
- Teacher Nerve repair course Erasmus MC	2002	5 days
Supervising students		
- Auke Tinselboer, Post traumatic stress in hand injury patients, graduate examination medicine	2000	12 days
- Pearl Landberg, Cold intolerance, graduate examination medicine	2001-2002	12 days
- Janine Boender, Cognitive capacity, master degree epidemiology	2001-2003	25 days
Comités		
- Dutch Wound Management Education Comite Nederland	2001/2003	25 days

CHAPTER 12

Dankwoord

Het dankwoord, het sluitstuk, en in mijn geval ook het laatste loodje. Na al die jaren ben ik dan toch eindelijk zo ver dat ik dit kan gaan schrijven. Niet iets om gemakkelijk over te denken want ik weet (uit ervaring) dat dit ook het meest gelezen hoofdstuk van het hele proefschrift is. En dan vooral die laatste alinea! Nog meer dan in de voorgaande hoofdstukken zal ik moeten wikken en wegen om de juiste woorden te vinden en om niemand te vergeten. En dan moet het ook nog uit het hart komen… En al is het dankwoord dan misschien niet te vergelijken met een wetenschappelijke publicatie, het is er wel onlosmakelijk mee verbonden. Want hoe exact ook, wetenschap staat en valt bij contacten tussen mensen!

Enkelen verdienen een speciaal woord van dank.

Professor Hovius, mijn promotor. Je hebt me geleerd niet voor de weg van de minste weerstand te kiezen. Het is meerdere malen gebeurd dat ik dacht een artikel helemaal klaar te hebben en door een enkele kritische vraag weer overnieuw kon beginnen. Uiteindelijk werd het er altijd beter van!

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