

The Treatment of Peripheral Nerve Injuries

Leila Harhaus*, Nora F. Dengler*, Karsten Schwerdtfeger, Annette Stolle

*These authors share first authorship

Department of Handsurgery, Peripheral Nerve Surgery and Rehabilitation, Department of Hand- and Plastic Surgery of Heidelberg University, BG-Trauma Center Ludwigshafen, Germany: Prof. Dr. Leila Harhaus

Department of Neurosurgery, Charité Universitätsmedizin Berlin, Germany: PD Dr. med. Nora F. Dengler

Faculty of Health Sciences, Brandenburg Medical School Theodor Fontane (MHB), Department of Neurosurgery, HELIOS Klinikum Bad Saarow, Germany: PD Dr. med. Nora F. Dengler

Saarland University Medical Center and Saarland University Faculty of Medicine, Neurosurgery, Homburg/Saar, Germany: Prof. Dr. med. Karsten Schwerdtfeger

Andreas Wentzensen
Research Institute,
BG Klinik Ludwigshafen,
Germany: Dr. phil. Annette Stolle

Summary

Background: Nerve lesions often heal incompletely, leading to lifelong functional impairment and high costs for the health care system. The updated German clinical practice guideline is intended to promote the early recognition of nerve lesions and the timely initiation of proper treatment for optimal restoration of function.

Methods: The recommendations are based on an assessment of all the evidence revealed by a systematic search of the literature, as well as on the expertise of the multiprofessional guideline group.

Results: Only a few publications contain high-quality evidence. This version of the guideline contains a more detailed discussion of war injuries, iatrogenic injuries, MR neurography, and specific treatments than the previous version. As for the different methods of nerve replacement, a comparison of autologous transplantation versus the use of conduits and tubes revealed no significant difference between these two methods on the mBMRC scale, and minimal superiority of autologous transplantation with respect to two-point discrimination. As for the use of nerve transfers when nerve reconstruction is not feasible or unlikely to succeed, nerve transfer yielded slightly better results than proximal reconstruction

for elbow flexion, but the difference did not reach statistical significance (mBMRC ≥ 3 : RR 1.16, 95% confidence interval [1.02; 1.32]). The treatment of neuromas with targeted muscle reinnervation was superior to the classic approach in decreasing both stump pain (MD 2.0 +/- 2.8) and phantom limb pain (MD 3.4 +/- 4.03).

Conclusion: The delayed or improper treatment of peripheral nerve lesions can lead to severe impairment. Timely diagnosis, the use of appropriate treatments in conformity with the guidelines, and interdisciplinary collaboration among specialists are all essential for optimizing the outcome.

Cite this as:

Harhaus L, Dengler NF, Schwerdtfeger K, Stolle A: Clinical practice guideline: The treatment of peripheral nerve injuries. Dtsch Arztebl Int 2024; 121: 534–8. DOI: 10.3238/arztebl.m2024.0071

Nerve lesions often heal incompletely, leading to lifelong functional impairment, chronic pain, and high costs for the health care system (1, 2). This is due to the pathophysiology of nerve regeneration. After a nerve is transected, the distal nerve end is subject to Wallerian degeneration with loss of axonal structures and the myelin sheath. The axons sprout from the proximal nerve end and grow distally through the remaining basal lamina tubes at a regeneration rate of approximately 1–3 mm/day. If motor axons reach their muscle end organ within 12–18 months, good function can return. Thereafter, the motor end plate degenerates completely, meaning that the possibility of reinneravation is lost. Therefore, the right timing for nerve reconstruction plays a particularly important role in motor nerve damage. Furthermore, since nerve injuries often go unrecognized or are recognized too late, this guideline is intended to promote the early recognition of nerve lesions and the timely initiation of proper treatment for optimal restoration of function.

In terms of diagnosis, advances in imaging using magnetic resonance neurography (MRN) have brought about relevant changes with regard to establishing the indication. From a treatment perspective, nerve transfers, which were not yet available in this form when the previous version of the guideline was developed, have

become a firmly established technique for restoring function and treating pain. The major importance of what is often long-term follow-up with occupational therapy and physiotherapy underlines the interdisciplinary aspect here.

The diagnosis and treatment of peripheral nerve injuries are topics much talked about in the literature. However, the numerous publications mostly have low-quality evidence, due to the heterogeneous injury picture, the resulting small number of cases, and ethical problems regarding randomization in health care research, among other factors.

Materials and methods

For the update of the German clinical practice (S3) guideline (*eBox 1*), areas in which relevant developments have taken place since the publication of the previous version were identified in a first step. In all, seven subject areas were defined, for which a systematic literature search and analysis according to GRADE criteria should be carried out with the aim of presenting aggregated results (*eBox 2*).

The cutoff date for the literature search was 31.07.2023, whereas no start date was specified.

The methodology was in line with the “Cochrane handbook for systematic reviews of interventions.” The literature search was carried out in MEDLINE with pre-defined medical subject headings (MeSH) terms (3) and in the Cochrane Central Register of Controlled Trials using the terms “nerve trauma” and “nerve injury” (*eFigure*). The inclusion criteria are presented in the *eMethods*.

For all other statements and recommendations, the Oxford levels of evidence used in the previous version (4) have been retained.

Results

Epidemiology

From a collective of 110,667 trauma patients at a European trauma center between 2012 and 2020, 5026 (4.54%) nerve lesions were identified (1). Despite their relative rarity, nerve lesions are of significant medical, social, and health economic relevance, since they predominantly affect people of working age (39.9 years) (1) and the recovery is long and associated with sick leave of 11–109 days (2). It is not uncommon for complete recovery not to be achieved—30% of affected individuals with work-related nerve injuries receive a work disability pension of at least 20% (2).

Nerve injuries in fractures

Peripheral nerve injuries are more common in certain fractures. According to their anatomical course and critical vascular supply, one sees in particular lesions of the axillary nerve, the radial nerve, and the peroneal nerve resulting directly from fractures (5).

Iatrogenic nerve injuries

In a large case series, 17.4% of peripheral nerve lesions were of iatrogenic origin. In 94% of the cases, a surgical procedure was the cause (6). Major procedures, such as osteosynthesis, herniotomy as well as knee, hip, and shoulder surgery bear the highest risk at 45%. Minor procedures, such as lymph node biopsies from the triangle of the neck and varicose vein surgery, were the cause of nerve lesions in 27% and neurosurgical procedures in 15% of cases. Non-surgical measures such as injections, puncture, positioning, and dressings were responsible for 4% of iatrogenic lesions (7).

Iatrogenic injury is the most common cause of lesions in some nerves. In large collectives of patients, 25.2% of treated sciatic nerve lesions (8), 60% of femoral nerve lesions (9, 10), and 94% of accessory nerve lesions were of iatrogenic origin (11).

Some nerves are more at risk during surgery than others due to their course (12). A large case series showed that the median (21.3%), accessory (18%), radial (15.6%), and peroneal (11.5%) nerves are those most frequently affected (13). The largest German case series to date revealed similar findings (1, 7). Radial nerve palsy is particularly common in humeral osteosynthesis (14). The incidence of radial nerve damage as a result of plate osteosynthesis of the distal humeral shaft was between 5.1 and 16% (15–18). Iatrogenic nerve injuries are often not noticed immediately (19) (*Table*).

Table

Risk of iatrogenic nerve injuries in relation to the nerve and type of procedure

Type of procedure	Nerve	Frequency
LNB in the lateral triangle of the neck	Accessory nerve	13–18%
Repositioning and osteosynthesis for humeral fractures	Radial nerve	5.1–16%
Kirschner wire osteosynthesis of elbow fractures in children	Ulnar nerve	1.1–4%
Open and endoscopic carpal tunnel release, shunt procedures, treatment of supracondylar humeral fractures in children and distal radial fractures in adults	Median nerve	16–21.3%
Artificial hip joint, dorsal approach for acetabulum fractures, intragluteal injections	Sciatic nerve	0.09–9%
Knee procedures, positioning injuries	Peroneal nerve	0.2–26.2%
Vascular interventions in the inguinal and pelvic region	Femoral nerve	0.21–2.6%

LNB, lymph node biopsy

Nerve lesions in children

Common causes of nerve injuries in childhood include cuts or lacerations (68.1%), followed by falls (14.6%), road traffic accidents (5.6%), and iatrogenic nerve injuries (1.4%) (1, 20). In the case of traumatic injuries, the finger nerves are most frequently affected at almost 50% (1), followed by the median nerve (14.8%)—mostly as a result of cuts, and less frequently due to supracondylar fractures or elbow dislocation (20, 21). Injuries to the ulnar and radial nerves are also common, usually caused by direct trauma, fractures, or elbow dislocation. Injuries to the lower extremity nerves are significantly less common (20, 22).

Nerve lesions due to combat injuries and gunshot wounds

The extent of an injury from a projectile depends on the body region affected and the kinetic energy delivered to the tissue, which derives from the velocity of the projectile. Therefore, a distinction is made between low- and high-velocity projectiles. On the upper extremity, one can assume that gunshot wounds that cause fractures and vascular injury also cause nerve lesions. Soft tissue damage and tissue contamination are relevant issues in the case of high-speed projectiles. Splintered bone fragments can cause additional nerve damage. Fragment dislocation, swelling, and scarring also contribute to the pattern of injury and are frequently found in the area of the radial nerve on the humerus or the peroneal nerve on the fibula (23–28). The risk of infection is particularly high in the case of high-velocity projectiles. Infection management involving repeated procedures to clean the wound usually precludes nerve reconstruction in the first instance. The defects caused by debridement may require extensive soft tissue reconstruction—only after this is secondary nerve reconstruction possible (25, 28–31).

Recommendations on the diagnosis of peripheral nerve injuries

The number of studies on diagnostic issues is largely inadequate and the level of evidence of low. Only for instrument-based diagnostic methods is there a larger number of publications.

Careful history-taking (grade A recommendation) and the earliest possible clinical examination (grade A recommendation) are crucial to distinguishing a peripheral nerve injury from spinal, cerebral, or other functional disorders. The lesion should be comprehensively described (in terms of functional sensitivity, motor function, anatomy/morphology, etiology) and reference made to the current classifications (British Medical Research Council [BMRC] and Seddon/Sunderland) (grade B recommendation). With regard to instrument-based diagnostic methods, neurography yields important information on the pathomechanism (neurapraxia without structural damage to the axons versus axonotmesis involving axonal damage but intact sheath structures) after as little as 1 week and shall be carried out in the first few weeks if there is diagnostic uncertainty (grade A recommendation). To differentiate between neurapraxia and axonotmesis, needle electromyography shall be performed at 2 weeks in the case of uncertainty (grade A recommendation).

Imaging techniques are gaining in importance. In cases of diagnostic uncertainty, neurosonography should be used preoperatively in order to more precisely define the location and severity of a nerve lesion and to ease decision-making regarding the further surgical procedure (grade B recommendation). MRN is able to visualize nerve lesions at the fascicular level and should be used in equivocal cases to localize and assess cause and severity (grade B recommendation). Compared to sonography, it can show deep and proximal nerve structures as well as patterns of muscular denervation, while nerve structures can also be identified in hematomas and soft tissue injuries. This enables treatment decisions to be made with significant time savings (22) (avoiding disadvantageous watch-and-wait intervals).

Recommendations on the treatment of peripheral nerve injuries

The time aspect takes highest priority in the treatment of peripheral nerve injuries. This is supported not only by a handful of studies with moderate quality of evidence but also, and most importantly, by clinical experience (32, 33). Nerve damage requiring surgical treatment should undergo appropriate microsurgery as soon as possible in order to achieve early and optimal reinnervation (grade B recommendation). Open injuries require immediate treatment, while closed injuries with proven discontinuity should be reconstructed within 1–2 weeks. Closed injuries without discontinuity and for which neurolysis is indicated, as well as adjuvant procedures if necessary, should be operated within 2–6 weeks.

Technical aspects

For all nerve suture or nerve reconstruction procedures, sufficient optical magnification devices and appropriate illumination should be available (microscope or loupes),

as well as microsurgical instruments and suture material. Devices for intraoperative neurophysiological testing, such as nerve stimulators to test muscle response to stimuli or to record nerve action potentials, are recommended (grade A recommendation). In the case of primary and secondary nerve sutures, tension-free coaptation of the nerve ends shall be ensured.

If tension-free coaptation is not possible, nerve reconstruction must be performed. In addition to classical autologous transplants, a variety of autologous or alternative conduits are also available. An analysis of the quantitative data (*eResults*) shows a trend towards autologous transplants, particularly in the case of mixed nerves. For pure sensory nerves, alternative transplants are available as an option.

In the case of partial nerve transection, split repair should be performed under certain conditions and based on strict indication criteria (grade B recommendation).

Various clinical situations

If a nerve shows clinical signs of dysfunction and has an open injury along its course, one can assume in the first instance that it is involved, and immediate exploration shall be undertaken (grade A recommendation). If primary treatment cannot be performed, for example, in the case of gunshot wounds, insufficient experience and equipment, or there are concomitant injuries, secondary treatment (delayed repair) should be carried out within 3–6 weeks, once a non-irritated, non-infected revision area has been achieved and assuming blood supply is good and the diagnosis has been confirmed—if follow-up checks are needed, these should be at the earliest possible time, but within 6 months at the latest (grade B recommendation). In the case of closed/blunt injuries or stretch injuries, a detailed neurological assessment should be carried out if nerve dysfunction is present and, where necessary, nerve exploration performed depending on the clinical, electrophysiological, and/or imaging findings and course (grade B recommendation). In the event that osteosynthesis is required for bony injuries close to the nerve, reliable nerve visualization with corresponding documentation of the findings should be undertaken (grade B recommendation). If regeneration does not occur, the further treatment concept should be determined within 6 months of the trauma, but as early as possible, and surgical nerve exploration should be considered (recommendation grade B). In cases of intraoperative nerve injury, reconstruction shall be performed by an experienced surgeon, ideally during the same procedure or after a few days (grade A recommendation).

The role of the distal nerve transfer

Nerve transfer enables the reinnervation of the affected musculature by transferring sacrificable motor fascicles from a healthy donor nerve near the target muscle to the motor branches of the damaged nerve, thereby converting a proximal lesion into a distal lesion.

The advantages of this method include a shorter reinnervation distance and reduced reinnervation times, while at the same time clearly defining which donor motor (more rarely, sensory) fascicles are assigned to which recipient fascicles. Nerve transfers should be used

when nerve reconstruction is not feasible or unlikely to succeed. They can also be used as a complementary end-to-side technique (grade B recommendation). Nerve transfers should be planned in such way that the coaptation site is as close as possible to the target muscle, and timed so that reinnervation of the target muscles—taking into account the time elapsed since the trauma and the distance that still needs to be grown through—can take place within 12 to at most 18 months (grade B recommendation). The donor nerve must be a sacrificable branch and have a largely suitable number of motor axons and function that is as synergistic with the recipient nerve as possible (grade B recommendation). Anatomically narrow areas in the recipient nerve can be decompressed in order to improve reinnervation (grade 0 recommendation). The quality of the evidence is greatly reduced by the quality of the included studies, the considerable variability in follow-up times, and the widely varying group sizes. Therefore, a trend towards better outcomes following nerve transfer can only be reported for the reconstruction of elbow flexion (muscle strength according to the British Medical Research Council [mBMRC] ≥ 3 , relative risk [RR] 1.16 [1.02; 1.32] (*eResults*)).

Salvage options

Motor replacement surgery by means of tendon transfer can be performed if reinnervation of the affected muscle is not feasible or has been unsuccessful (grade B recommendation) (*see eResults*).

Neuromas: prevention and treatment

Symptomatic neuromas can be treated surgically using various reconstructive or ablative strategies. Decisions in this regard need to be made on a case-by-case basis (grade 0 recommendation).

For macro-amputations, a special form of nerve transfer has been established whereby the blind-ending nerve stumps are placed on a motor nerve branch leading to a muscle that is still intact (targeted muscle reinnervation). This enables highly selective reinnervation of individual areas of the muscle and increases the number of signals that can be individually controlled and captured for prosthetic fitting. Lower neuroma rates and a reduction in phantom pain have been observed as a secondary effect (*eSupplement*).

Postoperative follow-up care

Pharmacological treatment to improve nerve regeneration cannot be recommended (grade 0 recommendation). Electrotherapy and (laser-)photostimulation can be used as a complementary treatment option for nerve lesions with axonal damage (axonotmesis or neurotmesis) (grade 0 recommendation). For neuropathic pain, guideline-compliant pain medicine treatment shall be given (grade A recommendation). Pain-relieving components of occupational therapy and physiotherapy should be used (mirror therapy, transcutaneous electrical nerve stimulation [TENS]; grade B recommendation).

In the case of nerve injuries and following nerve reconstruction, concomitant occupational therapy and physiotherapy shall be provided as soon as possible after trauma or surgical reconstruction (recommendation grade A).

This includes targeted sensory re-education (mirror therapy, graded motor imagery program, sensitivity training; grade B recommendation) and interventions to improve motor functions (mirror therapy, electrical muscle stimulation, motor function training; grade B recommendation).

Discussion

The frequently problematic or incomplete healing of peripheral nerve injuries can only be reduced by a guideline-compliant combination of early diagnosis and correct treatment measures. An interdisciplinary collaboration between all specialist areas is of paramount importance for the best possible restoration of function. This literature analysis shows that the need for research remains high.

Acknowledgments

The authors would like to thank all participating specialist societies and, in particular, the authors that participated on the guideline (*eBox 1*): Susanne Rein, Elisabeth Haas-Lützenberger, Frank Siemers, Johannes Frank, Clemens Dumont, Jonas Kolbenschlag, Johannes Heinzel, Michael Schädel-Höpfner, Maria T. Pedro, Peter Pöschl, Rezvan Ahmadi, Sascha Tafelski, Hannelore Wendt, Natalie Winter, Ingela Henningsen, Thomas Kretschmer, Christian Heinen, Christian Bischoff, Alexander Grimm, Wilhelm Schulte-Mattler, Katrin Hahn, Daniel Schwarz, Martin Bendszus, Holm Thieme, Reinhard Meier as well as Ms. Lena-Marie Marter and Ms. Diana Schoppe from the Guidelines Office of the German Society for Orthopaedics and Trauma Surgery (*Deutsche Gesellschaft für Orthopädie und Unfallchirurgie*, DGOU) for the constructive collaboration.

Conflict of interest statement

The authors declare that no conflict of interest exists.

Manuscript received on 29 January 2024, revised version accepted on 9 April 2024.

Clinical guidelines in the *Deutsche Ärzteblatt*, as in numerous other specialist journals, are not subject to a peer review procedure, since S3 guidelines represent texts that have already been evaluated, discussed, and broadly agreed upon multiple times by experts (peers).

Translated from the original German by Christine Rye.

References

1. Aman M, Zimmermann KS, Thielen M, et al.: An epidemiological and etiological analysis of 5026 peripheral nerve lesions from a European level I trauma center. *J Pers Med* 2022; 12: 1673.
2. Bergmeister KD, Große-Hartlage L, Daeschler SC, et al.: Acute and long-term costs of 268 peripheral nerve injuries in the upper extremity. *PLoS One* 2020; 15: e0229530.
3. Leitlinien-Report Versorgung peripherer Nervenverletzungen, AWMF-Register Nr. 005/010 Klasse: S3 Update (revidierte Fassung V 2.0) 2023. register.awmf.org/assets/guidelines/005-010m_S3_Versorgung-peripherer-Nervenverletzungen_2023-12.pdf (last accessed on 31 March 2024).
4. Leitlinie Versorgung peripherer Nervenverletzungen, AWMF-Register Nr. 005/010 Klasse: S3 (Fassung V 12.0) 2013. www.awmf.org/service/awmf-aktuell/versorgung-peripherer-nervenverletzungen (last accessed on 31 March 2024).
5. Kato N, Birch R: Peripheral nerve palsies associated with closed fractures and dislocations. *Injury* 2006; 37: 507–12.
6. Kretschmer T, Antoniadis G, Braun V, Rath S, Richter H: Evaluation of iatrogenic lesions in 722 surgically treated cases of peripheral nerve trauma. *J Neurosurg* 2001; 94: 905–12.
7. Antoniadis G, Kretschmer T, Pedro MT, König RW, Heinen CP, Richter HP: Iatrogenic nerve injuries: prevalence, diagnosis and treatment. *Dtsch Arztebl Int* 2014; 111: 273–9.
8. Alon M, Rochkind S: Pre-, intra-, and postoperative electrophysiologic analysis of the recovery of old injuries of the peripheral nerve and brachial plexus after microsurgical management. *J Reconstr Microsurg* 2002; 18: 77–82.

9. Altintas AA, Altintas MA, Gazyakan E, Gohla T, Germann G, Sauerbier M: Long-term results and the disabilities of the arm, shoulder, and hand score analysis after modified Brooks and D'Aubigne tendon transfer for radial nerve palsy. *J Hand Surg Am* 2009; 34: 474–8.
10. Amillo S, Barrios RH, Martinez-Peric R, Losada JL: Surgical treatment of the radial nerve lesions associated with fractures of the humerus. *J Orthop Trauma* 1993; 7: 211–5.
11. Anders JJ, Geuna S, Rochkind, S: Phototherapy promotes regeneration and functional recovery of injured peripheral nerve. *Neurol Res* 2004; 26: 233–9.
12. Antoniadis G: Traumatische Nerven- und Plexusschäden: Prä- und klinische Versorgungsalgorithmen und Behandlungsoptionen. *Notfallmedizin up2date* 2011; 6: 125–39.
13. Rasulić L, Savić A, Vitošević F, et al.: Iatrogenic peripheral nerve injuries—surgical treatment and outcome: 10 years' experience. *World Neurosurg* 2017; 103: 841–51. e6.
14. Guerra WKW, Schroeder H: Iatrogene Nervenläsionen der oberen Extremität—Häufigkeit und Ergebnisse der mikrochirurgischen Therapie. *Aktuelle Neurologie* 2008; 35: 280–4.
15. Eglseider WA: Distal humeral fractures: impact of lateral approach and fracture-specific plating on radial nerve palsies. *Tech Hand Up Extrem Surg* 2012; 16: 127–31.
16. Jawa A, McCarty P, Doornberg J, Harris M, Ring D: Extra-articular distal third diaphyseal fractures of the humerus: a comparison of functional bracing and plate fixation. *J Bone Joint Surg Am* 2006; 88: 2343–7.
17. Mahabier K, Vogels L, Punt B, Roukema G, Patka P, Van Lieshout E: Humeral shaft fractures: retrospective results of non-operative and operative treatment of 186 patients. *Injury* 2013; 44: 427–30.
18. Rommens P, Kuehle R, Bord T, Lewens T, Engelmann R, Blum J: Humeral nailing revisited. *Injury* 2008; 39: 1319–28.
19. Midha R: Mechanisms and pathology of injury. In: Kline DG, Hudson AR (eds.): *Nerve injuries: operative results for major nerve injuries, entrapments and tumors*. 2. Edition. Philadelphia: Saunders 2007.
20. Costales J, Socolovsky M, Sánchez Lázaro J, Álvarez García R: Peripheral nerve injuries in the pediatric population: a review of the literature. Part I: traumatic nerve injuries. *Childs Nerv Syst* 2019; 35: 29–35.
21. Kwok IH, Silk, ZM Quick TJ, Sinisi M, MacQuillan A, Fox M: Nerve injuries associated with supracondylar fractures of the humerus in children: our experience in a specialist peripheral nerve injury unit. *Bone Joint J* 2016; 98: 851–6.
22. Aman M, Böcker A, Kneser U, Harhaus L: Selective nerve transfers for thenar branch reconstruction. *Oper Orthop Traumatol* 2021; 33: 384–91.
23. Pfister G, De Carbonnières A, Dubourg O, Prat N, Cremades A, Mathieu L: Traumatismes balistiques des nerfs: quelles lésions microscopiques sur la partie continue des sections partielles? *Hand Surg Rehabil* 2018; 37: 384–5.
24. Pfister G, Ghabi A, de Carbonnières A, Oberlin C, Belkheyar Z, Mathieu L: Direct suturing of sciatic nerve defects in high-degree knee flexion: an experimental study. *World neurosurg* 2020; 133: e288–e92.
25. Straszewski AJ, Schultz K, Dickherber JL, Dahm JS, Wolf JM, Strelzow JA: Gunshot-related upper extremity nerve injuries at a level 1 trauma center. *J Hand Surg Am* 2022; 47: 88.e1–88.e6.
26. Pannell WC, Heckmann N, Alluri R, Sivasundaram L, Stevanovic M, Ghiassi A: Predictors of nerve injury after gunshot wounds to the upper extremity. *Hand* 2017; 12: 501–6.
27. Akhavan-Sigari R, Mielke D, Farhadi A, Rohde V: Study of radial nerve injury caused by gunshot wounds and explosive injuries among Iraqi soldiers. *Open Access Maced J Med Sci* 2018; 6: 1622.
28. Bercik MJ, Kingsbery J, Ilyas AM: Peripheral nerve injuries following gunshot fracture of the humerus. *Orthopedics* 2012; 35: e349–52.
29. Jandial R, Reichwage B, Levy M, Duenas V, Sturdivan L: Ballistics for the neurosurgeon. *Neurosurgery* 2008; 62: 472–80.
30. Oberlin C, Rantissi M: Gunshot injuries to the nerves. *Chir Main* 2011; 30: 176–82.
31. Mathieu L, Bertani A, Gaillard C, et al.: Combat-related upper extremity injuries: surgical management specificities on the theatres of operations. *Chir Main* 2014 ; 33: 174–82.
32. MacKay BJ, Cox CT, Valerio IL, et al.: Evidence-based approach to timing of nerve surgery: a review. *Ann Plast Surg* 2021; 87: e1–21.
33. Taylor KS, Anastakis DJ, Davis KD: Cutting your nerve changes your brain. *Brain* 2009; 132: 3122–33.

Corresponding author

Prof. Dr. med. Leila Harhaus
Abteilung für Handchirurgie, Periphere Nerven Chirurgie und Rehabilitation,
Klinik für Hand- und Plastische Chirurgie der Universität Heidelberg,
BG-Klinik Ludwigshafen
Ludwig-Guttmann-Straße 13, 67071 Ludwigshafen, Germany
leila.harhaus@bgu-ludwigshafen.de

Cite this as:

Harhaus L, Dengler NF, Schwerdtfeger K, Stolle A: Clinical practice guideline: The treatment of peripheral nerve injuries. *Dtsch Arztebl Int* 2024; 121: 534–8. DOI: 10.3238/arztebl.m2024.0071

Supplementary material

eReferences, eMethods, eResults, eFigure, eBoxes:
www.aerzteblatt-international.de/m2024.0071

Supplementary material to accompany the article

The Treatment of Peripheral Nerve Injuries

by Leila Harhaus*, Nora F. Dengler*, Karsten Schwerdtfeger, and Annette Stolle

Dtsch Arztebl Int 2024; 121: 534–8. DOI: 10.3238/arztebl.m2024.0071

eReferences

- e1. Thomson SE, Ng NY, Riehle MO Ki, et al.: Bioengineered nerve conduits and wraps for peripheral nerve repair of the upper limb. *Cochrane Database Syst Rev* 2022; 12: CD012574.
- e2. Ahmad I, Mir MA, Khan AH: An evaluation of different bridging techniques for short nerve gaps. *Ann Plast Surg* 2017; 79: 482–5.
- e3. Mauch JT, Bae A, Shubinets V, Lin IC: A systematic review of sensory outcomes of digital nerve gap reconstruction with autograft, allograft, and conduit. *Ann Plast Surg* 2019; 82: S247–55.
- e4. Saeki M, Tanaka K, Imatani J, et al.: Efficacy and safety of novel collagen conduits filled with collagen filaments to treat patients with peripheral nerve injury: a multicenter, controlled, open-label clinical trial. *Injury* 2018; 49: 766–74.
- e5. He BO, Zhu Q, Chai Y, et al.: Safety and efficacy evaluation of a human acellular nerve graft as a digital nerve scaffold: a prospective, multicentre controlled clinical trial. *J Tissue Eng Regen Med* 2015; 9: 286–95.
- e6. Erakat MS, Chuang SK, Shanti RM, Ziccardi VB: Interval between injury and lingual nerve repair as a prognostic factor for success using type I collagen conduit. *J Oral Maxillofac Surg* 2013; 71: 833–8.
- e7. Herman ZJ, Ilyas AM: Sensory outcomes in digital nerve repair techniques: an updated meta-analysis and systematic review. *Hand* 2020; 15: 157–64.
- e8. Böcker A, Aman M, Kneser U, Harhaus L, Siemers F, Stang F: Closing the gap: bridging peripheral sensory nerve defects with a chitosan-based conduit a randomized prospective clinical trial. *J Pers Med* 2022; 12: 900.
- e9. Chiu DT, Strauch B: A prospective clinical evaluation of autogenous vein grafts used as a nerve conduit for distal sensory nerve defects of 3 cm or less. *Plast Reconstr Surg* 1990; 86: 928–34.
- e10. Manoli T, Schulz L, Stahl S, Jaminet P, Schaller HE: Evaluation of sensory recovery after reconstruction of digital nerves of the hand using muscle in vein conduits in comparison to nerve suture or nerve autografting. *Microsurgery* 2014; 34: 608–15.
- e11. Garg R, Merrell GA, Hillstrom HJ, Wolfe, SW: Comparison of nerve transfers and nerve grafting for traumatic upper plexus palsy: a systematic review and analysis. *J Bone Joint Surg Am* 2011; 93: 819–29.
- e12. Texakalidis P, Hardcastle N, Tora MS, Boulis NM: Functional restoration of elbow flexion in nonobstetric brachial plexus injuries: a metaanalysis of nerve transfers versus grafts. *Microsurgery* 2020; 40: 261–7.
- e13. Ali ZS, Heuer GG, Faught RW, et al.: Upper brachial plexus injury in adults: comparative effectiveness of different repair techniques. *J Neurosurg* 2015; 122: 195–201.
- e14. Koshy JC, Agrawal N A, Seruya M: Nerve transfer versus interpositional nerve graft reconstruction for posttraumatic, isolated axillary nerve injuries: a systematic review. *Plast Reconstr Surg* 2017; 140, 953–60.
- e15. Bhandari PS, Deb P: Management of isolated musculocutaneous injury: comparing double fascicular nerve transfer with conventional nerve grafting. *J Hand Surg Am* 2015; 40: 2003–6.
- e16. Klifto KM, Azoury SD, Gurno CF, Card EB, Levin LS, Kovach SJ: Treatment approach to isolated common peroneal nerve palsy by mechanism of injury: systematic review and meta-analysis of individual participants' data. *J Plast Reconstr Aesthet Surg* 2022; 75: 683–702.
- e17. Dumanian GA, Potter BK, Mioton LM, Ko JH, Cheesborough JE, et al.: Targeted muscle reinnervation treats neuroma and phantom pain in major limb amputees: a randomized clinical trial. *Ann Surg* 2019; 270: 238–46.

eBox 1

Specialist societies participating in the German clinical practice (S3) guideline on “The treatment of peripheral nerve injuries”

- German Society for Orthopaedics and Trauma Surgery (*Deutsche Gesellschaft für Orthopädie und Unfallchirurgie*, DGOU)
- German Society of Hand Surgery (*Deutsche Gesellschaft für Handchirurgie*, DGH)
- German Society of Neurosurgery (*Deutsche Gesellschaft für Neurochirurgie*, DGNC)
- German Society of Plastic, Reconstructive, and Aesthetic Surgeons (*Deutsche Gesellschaft der Plastischen, Rekonstruktiven und Ästhetischen Chirurgen*, DGPRÄC)
- German Neurological Society (*Deutsche Gesellschaft für Neurologie*, DGN)

Other participating societies/associations

- German Society for Clinical Neurophysiology and Functional Imaging (*Deutsche Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung*, DGKN)
- German Working Group for Hand Therapy (*Deutsche Arbeitsgemeinschaft für Handtherapie*, DAHTH)
- German Association of Occupational Therapy (*Deutscher Verband Ergotherapie*, DVE)
- German Association for Physiotherapy—central association of physiotherapists (*Deutscher Verband für Physiotherapie*, ZVK)
- German Pain Society (*Deutsche Schmerzgesellschaft e.V.*, DGSS)

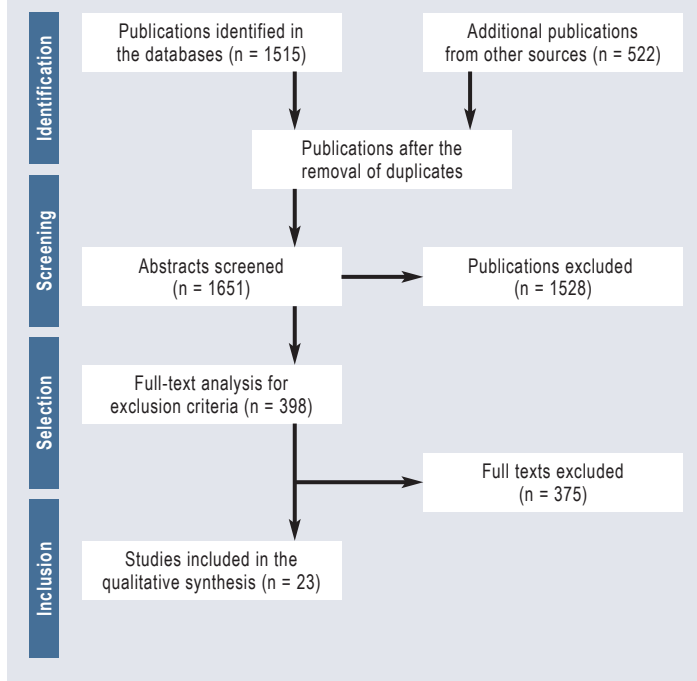
eBox 2

PICO questions for the areas with relevant developments since the publication of the previous version

- Outcomes when using vein-muscle grafts, tubes, or allografts for mixed/motor nerve injuries
- Outcomes when using vein-muscle grafts, tubes, or allografts for sensory nerve injuries
- Outcomes of distal nerve transfer compared to tendon transfer
- Outcomes of neuroma treatment following surgical ablation techniques (nerve in vein, nerve in muscle, nerve in bone, centro-central coaptation, end-to-side [ETS] coaptation)
- Outcomes of neuroma treatment following surgical reconstruction techniques (TMR, RPNI, NTT)

NTT, new target transfer; PICO, patient, intervention, control, outcome; RPNI, regenerative peripheral nerve interface; TMR, targeted muscle reinnervation

eFigure



Flowchart of the literature search for the assessment of the patient, intervention, control, outcome (PICO) questions—summarized for the six questions. Details can be found in the guideline report (3). Identification: literature screening at the title and abstract level by two independent reviewers; duplicates were discarded. Selection: screening of full texts for study design by two independent reviewers. Inclusion: final selection of included publications in collaboration with the clinical experts.

eMETHODS

Studies that met the following criteria were included:

- Publication date up to and including 31.07.2023; start date, open
- In English, French, or German
- Patients with traumatic or iatrogenic nerve lesions
- Randomized controlled studies, controlled prospective and retrospective observational studies as well as meta-analyses and systematic reviews of non-controlled observational studies
- Interventions according to the specific PICO question (PICO: patient, intervention, control, outcome)
- Any type of improvement in functional outcome as an endpoint in the treatment research questions: no restrictions regarding follow-up period.

eRESULTS

Results

Technical aspects

The management of mixed nerve injuries was evaluated in two systematic reviews and one randomized controlled study (RCT). Considerable methodological deficiencies were found in the evaluated studies, meaning that the reliability of the evidence was deemed to be very low. A Cochrane review of controlled trials (e1) showed no significant difference in mean values between autologous transplants and alternative transplants for the endpoints motor recovery (muscle strength according to the British Medical Research Council [mBMRC] grading) at 18 months, sensory recovery (according to sBMRC sensory grading) at 24 months and a functional outcome measure (Rosen model) at 5 years. However, the sample size of the studies was very small, with 11 and 28 patients, respectively. The relative risk (RR) for complications (7.15, 95% confidence interval: [1.74; 29.42]; five studies with 213 patients) and implant removal (7.61 [1.48; 39.02]; five studies with 256 patients) is increased. An older review of 33 observational studies with 311 subjects found an advantage in favor of alternative interposition grafts (RR 1.28 [1.04; 1.57]) for a combined motor and sensory outcome according to BMRC grading (dichotomized $\geq$ M4S3, follow-up period of 1–240 months). The RCT conducted by Ahmad (e2) with 18 study participants showed no significant difference in mBMRC grading at 9 months and a minimal effect in the two-point discrimination in favor of autologous interposition grafts. In summary, the trend should be towards using an autologous transplant for reconstruction.

For pure sensory nerve defects, a total of 10 studies (three systematic reviews, one RCT, six controlled studies) were included. Due to methodological deficiencies, the reliability of the evidence is once again very low here. For sensory regeneration, there was no significant difference between autologous transplants and alternative transplants in terms of the endpoint of the sensory BMRC grading $\geq$ S3+ (29 [review of eight studies, 86 patients, follow-up time of up to 12 months], e3–e6 [281 patients in total, follow-up time of 6–12 months]) or the static two-point discrimination $\leq$ 6 mm (e7 [15 studies, 152 patients, 12-month follow-up]). For chitosan-based conduits (e8 [22 study participants, 12-month follow-up]), vein conduits (e9 [19 patients, 27-month follow-up]), and muscle-in-vein conduits (e10 [31 patients, 31-month follow-up]), the data on dynamic and static two-point discrimination also show no significant difference to autologous transplants. The abovementioned Cochrane review (e1) only reports data on complication rates (five studies, 213 subjects, RR 7.15 [1.74; 29.42]) or device removal (five studies, 256 patients, RR 7.61 [1.48; 39.02]) for pure sensory nerves. Böcker et al. (e8) also describe an increased rate of transplant removal with alternative conduits: two study participants, RR 1.4 [0.06; 30.23]. However, this result is not significant due to

the small number of cases. This is in contrast to the review by Mauch et al. (e3 [eight studies, 136 subjects]), who found a lower, albeit non-significant, complication rate (RR 0.53 [0.1; 2.8]) for alternative transplants.

The role of distal nerve transfer

For the comparison of proximal nerve reconstruction using distal nerve transfer, four systematic reviews on brachial plexus injury were found, for which the level of reliability of the evidence was low due to methodological weaknesses of the studies evaluated. Garg et al. (e11 [31 studies, 356 patients]) found a trend towards better outcomes at 12 months following nerve transfer for elbow flexion (mBMRC $\geq$ 3, RR: 1.16 [1.02; 1.32]), whereas Texakalidis et al. (e12 [nine studies, 490 subjects]) saw no significant difference in elbow flexion at 24–37 months (mBMRC $\geq$ 3, RR 1.1 [0.97; 1.24]). Ali et al. (e13 [71 studies, 3187 patients]) found comparable outcomes for the elbow at 30–44 months (mBMRC $\geq$ 3, RR 0.96 [0.9; 1.01]). That study showed a slight advantage for distal nerve transfer in shoulder abduction (RR 1.17 [1.09; 1.25]) (e13), as did the study by Garg et al. (e11), particularly when two nerves were transferred (31 studies, 82 subjects, mBMRC $\geq$ 3 at 12 months, RR 1.62 [1.22; 2.22]). For axillary nerve injuries and assessment of shoulder abduction, Koshy et al. (e14 [10 studies, 66 patients]) found a trend towards a better outcome with autologous transplants at 18–24 months (mBMRC $\geq$ 3, RR 0.87 [0.78; 0.97]). However, the quality of the evidence must be deemed low due to the studies included. In the case of musculocutaneous nerve lesions, the retrospective case-control study by Bhandari et al. (e15) with 20 study participants showed no significant difference between the two groups at 24–36 months (mean difference in mBMRC grading of 0.29 [0.44; 0.0]). The systematic review by Klifto et al. (e16) of peroneal nerve lesions included a total of 144 studies with 1284 patients. It also included case series, thereby precluding a direct comparison of the various treatment forms. From the outcomes reported in the individual studies, a global function score (from 0–3) is defined, into which the results are transferred. For the comparison between proximal nerve reconstruction and distal nerve transfer, data is available for a total of 358 individuals, of which, however, only 21 belong to the nerve transfer group. The difference in effect size (median 0.54, [0.99; 0.0]) supports distal transfer, but is not significant. The quality of the evidence is greatly reduced by the quality of the included studies, the considerable variability in follow-up times (6–372 months), and the widely varying group sizes.

Salvage options

Klifto et al. (e16) also compared distal nerve transfer with tendon transfer for lesions of the peroneal nerve. They evaluated the data of 192 patients, of which only 21 belonged to the nerve-transfer group. The difference

between the two groups was not significant (mean difference in function score, 0.2 ± 0.96). Here again, the quality of the evidence is greatly reduced by the quality of the included studies, the considerable variability in follow-up times (6–372 months), and the widely varying group sizes.

Neuromas: prevention and treatment

An RCT ([e17] [30 patients, 12-month follow-up]) comparing targeted muscle reinnervation (TMR) with the standard treatment of neuroma excision and muscle burying for painful stump neuromas found a greater mean reduction in stump pain (median $\pm$ standard deviation, 2.0 ± 2.8) as well as phantom limb pain (M 3.4 ± 4.03) in the TMR group. However, the differences were non-significant. The quality of the evidence is reduced by the low case number.