A prospective, multicenter, randomized, parallel-group controlled trial to compare conservative versus surgical treatment of foot drop in peroneal nerve entrapment.

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The primary research question of the trial is to assess whether foot drop, caused by peroneal nerve entrapment in adult patients* recovers better within 9 months after decompressive surgery compared to prolonged standard conservative treatment. *...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Peripheral neuropathies
Study type	Interventional

Summary

ID

NL-OMON54026

Source
ToetsingOnline

Brief title
FOOTDROP

Condition

- Peripheral neuropathies
- Nervous system, skull and spine therapeutic procedures

Synonym
compression of the peroneal nerve, peroneal neuropathy

Research involving
Human

Sponsors and support

Primary sponsor: Universitaire ziekenhuizen Leuven
Source(s) of monetary or material Support: Federaal Kenniscentrum voor Gezondheidszorg België (KCE)

Intervention

Keyword: conservative treatment, footdrop, neurolysis, randomized controlled trial

Outcome measures

Primary outcome

The primary research question of the trial is to assess whether foot drop, caused by peroneal nerve entrapment in adult patients* recovers better within 9 months after decompressive surgery compared to prolonged standard conservative treatment.

The primary endpoint is the difference in distance covered in meters during the six-minute walk test (6MWD) between baseline and 9 months after randomization.

Secondary outcome

The secondary objectives of the foot drop trial are:

- To collect pathology-related data in peroneal nerve entrapment.

- To evaluate and compare quality of life data of patients with foot drop due to peroneal nerve entrapment and to assess the evolution of quality of life during conservative/surgical treatment

- To assess and compare follow-up electrophysiological data in patients with peroneal nerve entrapment

- To assess the evolution of gait impairment in patients with foot drop due to peroneal nerve entrapment through a broad range of questionnaires/gait

assessments.

- To assess long-term follow-up (18 months after randomization) data after cross-over is allowed (to collect prospective data on long term follow-up).

- To evaluate the cost-effectiveness of both treatment strategies.

Key secondary endpoint: time to recovery.

1. Ankle dorsiflexion strength: measured by the MRC-score and isometric dynamometry at 10 days, 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization. Ankle dorsiflexion strength will also be assessed after 10 days in the surgical arm of the trial.

2. Gait assessment at 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization with

a. Functional ambulation categories, Stanmore questionnaire

b. Gait speed during the 10-meter walk test

c. The proportion of patients in both groups who reach minimal normal age- and sex-specific reference values for 6MWD, 9 months after randomization.

d. Difference in distance covered in meters during the six-minute walk test between baseline and 6 weeks, 3 months, 6 months and 18 months after randomization

3. Complications and neurological deficits :

a. Motor changes including MRC-score for ankle eversion and hallux extension at

6 weeks, 3 months, 6 months, 9 months and 18 months after randomization. Motor function will also be assessed after 10 days in the surgical arm of the trial.

b. Sensory changes at 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization. Sensory changes will also be assessed after 10 days in the surgical arm of the trial.

c. Surgical complications at 10 days, 6 weeks and 18 months after surgery: a list of possible complications is composed to score in a uniform way in all centers.

4. Health-economic assessment:

a. Work productivity and Activity Impairment Questionnaire at 6 weeks and 6 months after randomization.

b. Return to work at 6 weeks after randomization.

5. Electrodiagnostics (EDX) at 3 months and 9 months after randomization.

6. Patient-reported outcome measures: health-related quality of life EQ5D-5L) at 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization. Patient-reported outcome measurements will also be assessed after 10 days in the surgical arm of the trial.

For all secondary endpoints, baseline measurements will be obtained if applicable

Study description

Background summary

Conservative treatment of peroneal nerve entrapment consists of physiotherapy using stretching of the calf muscles to prevent contractures, muscle

strengthening and gait rehabilitation. Physiotherapy exercises are sometimes combined with functional electrical stimulation and electrostimulation has been applied for denervated muscles after peripheral nerve lesions. Ankle foot orthoses can improve gait parameters and functional ambulation in patients with foot drop. The available literature on the conservative treatment mainly consists of retrospective series describing a very heterogeneous patient population including traumatic and iatrogenic peroneal nerve lesions. The number of patients with peroneal nerve entrapment was low varying between 14 and 33 with a follow-up ranging between three months and three years.

One multicenter prospective study of 46 patients documented follow-up data in conservatively treated patients including 13 patients who did not receive any treatment at all due to mild symptoms. After a mean follow-up of 6 months, 39% of the conservatively treated patients (n = 33) needed a foot orthosis to be able to walk and 53% had a normal gait pattern. In patients in whom no conservative treatment was initiated 25% needed a foot orthosis and 63% had a normal gait pattern. Overall, 79% of patients with peroneal nerve entrapment reported improvement of ankle dorsiflexion at 6 months (n = 34). Taking all available literature into consideration, good outcome after conservative treatment for peroneal nerve entrapment varies between 53% and 100% in the literature. When interpreting these range of outcome percentages, one should realize that outcome measures differ between the studies. If data was available, good outcome was translated to an MRC-score >= 4 for ankle dorsiflexion. If data was not available, outcome measure of the study was documented.

Sangwan et al. reported the results of conservative treatment of foot drop due to prolonged squatting in a prospective case series of 30 patients (34 limbs). Thirty-two foot drops fully recovered after 3 to 9 weeks. The other 2 patients recovered fully after 16 and 20 weeks (100%). Cruz-Martinez prospectively documented the clinical evolution of foot drop in 30 patients receiving no or conservative treatment. Twenty-six patients fully recovered after a period of 3 weeks to 3 months, three other patients reported minimal weakness (97%). The severe muscle weakness in 1 patient did not improve after 6 months (but recovered within 2 weeks after neurolysis). Although these findings are not confirmed in other case studies, these series describe possible recovery of foot drop in an early stage with conservative therapy. These findings are important regarding the timing of randomization

The surgical approach for entrapment at the fibular head aims at decompressing the peroneal nerve as it dives under the peroneus longus muscle. Similar to the literature on conservative treatment most studies on the surgical management concerned retrospective patient series. Some studies had a very heterogeneous patient population hampering extraction of required data, or did not discuss patients with peroneal nerve entrapment. Most series suffered from a low sample size (the smallest study included only 12 patients) with a great variability in timing between symptom onset and surgery ranging from weeks to years. On

average patients were operated after 4.6 months (range:1 month -27 months for the included case series) with a follow-up duration ranging from 11 months to 7 years.

We identified 2 prospective studies, one describing 14 patients with a follow-up of one year after surgery recording improvement of ankle dorsiflexion in 13 of 14 patients (93%), with half of the patients having normal ankle dorsiflexion at one year. The prospective series of Nirenberg (56) described the outcome of 17 patients with peroneal neuropathy (of unknown etiology) and a follow-up of minimum 4 months. Seven of 17 patients (41%) reported an MRC grade >= 4 for hallux dorsiflexion. All patients reported improvement of ankle dorsiflexion and sensory changes within one week after surgery.

Broekx et al. described a large retrospective series of neurolysis after excessive weight loss. In total, 200 patients were included and on average patients were operated 4 months after symptom onset. Of all included patients, 85% had a good outcome, defined as an MRC scale for muscle strength grade >= 4 for ankle dorsiflexion. Complications after peroneal nerve are unusual. In the largest retrospective patient series, 7 out of 200 patients suffered from wound problems, 1 out of 200 patients suffered from postoperative abscess formation and subsequent bacterial sepsis. Overall, good outcome after decompressive surgery for peroneal nerve entrapment varies between 43% and 100% in the literature. When interpreting these range of percentages, one should realize that outcome measures differ between the studies. If data was available, good outcome was translated to an MRC-score >= 4 for ankle dorsiflexion. If data was not available, outcome measure of the study was documented.

There is indeed insufficient data in the available literature to make any recommendations. No studies have compared surgical versus conservative treatment in a prospective manner and currently no guidelines are available. Even data on the prevalence and the spontaneous evolution of peroneal neuropathy are virtually non-existent.
The lack of prospective studies on this topic is remarkable since most patient series on both the conservative and surgical treatment are retrospective in nature. Most patient series are very heterogeneous given the fact that patients with peroneal nerve damage due to different causes were included, which makes it difficult to draw conclusions on the clinical management. Data concerning the spontaneous evolution of peroneal nerve entrapment (without any intervention) is almost absent, except for 15 patients. Furthermore, studies discussing prevalence, report contrasting percentages.

After reviewing the current literature, we identified several methodological issues when comparing the various studies. Good outcome was not uniformly defined and duration of follow-up differed not only between, but even within studies (where follow-up could range from 5 months to 3 years). Additionally, the number of patients was low to very low in most studies.
Most studies on decompressive surgery for the treatment of peroneal entrapment

were retrospective in nature and for most studies the sample size was small. Similar to the studies on the conservative treatment, they involved a heterogeneous patient population and variable follow-up durations.

Since peroneal nerve entrapment represents one of the most common entrapments, and no practice guidelines exist on its preferred treatment, this prospective study will provide important outcome data after conservative treatment (current data very limited), as well as surgical treatment (current data very biased, retrospective in nature and uncontrolled). The impact on quality of life will be assessed and the complications (surgical, chronic pain, sensory changes, *) of both treatments will be recorded. These data will define future treatment guidelines for this mononeuropathy and is thus relevant for all physicians treating entrapment neuropathies (neurology, neurosurgery, physical medicine, orthopaedic surgery, *).

1. Aprile I, Tonali P, Caliandro P, Pazzaglia C, Foschini M, Di Stasio E, et al. Italian multicentre study of peroneal mononeuropathy: multiperspective follow-up. Neurol Sci. 2009;30(1):37-44.
2. Eberstein A, Eberstein S. Electrical stimulation of denervated muscle: is it worthwhile? Med Sci Sports Exerc. 1996;28(12):1463-9.
3. Salmons S, Ashley Z, Sutherland H, Russold MF, Li F, Jarvis JC. Functional electrical stim

Study objective

The primary research question of the trial is to assess whether foot drop, caused by peroneal nerve entrapment in adult patients* recovers better within 9 months after decompressive surgery compared to prolonged standard conservative treatment.

* Exclusion of iatrogenic or traumatic peroneal nerve palsies. Exclusion of peroneal nerve compression caused by cysts or tumours. Exclusion of patients with polyneuropathy. Exclusion of other surgical techniques than neurolysis.

Intervention A: Decompressive release of the peroneal nerve at the level of the fibular head in patients with foot drop due to peroneal nerve entrapment.
Intervention B: Prolonged conservative treatment of foot drop due to peroneal nerve entrapment.
Null hypothesis: There is no difference in recovery of foot drop due to peroneal nerve entrapment after intervention A or intervention B.
Alternative hypothesis: Recovery of foot drop due to peroneal nerve entrapment is superior after intervention A compared to intervention B.

Study design

The overall objective of the foot drop trial is to test the superiority of surgical release of the peroneal nerve at 10 +/- 4 weeks after symptom onset to maximal conservative treatment. The foot drop trial is designed as a prospective, multicenter, randomized, parallel-design study. A double-blind design is not possible, given the fact that both the treating physician and the patient will always know the allocated treatment strategy. The clinical researcher (= outcome assessor) will be blinded for treatment.
Subjects will be randomized 1:1 to surgery or conservative treatment (simple randomization based solely on a single, constant 1:1 allocation ratio). If a patient, that signed the informed consent form (ICF), cannot be randomised because the foot drop has recovered, this will be documented in the eCRF. After randomization, the patients allocated to conservative treatment will enter a treatment period of approximately 9 months (individualised physiotherapy program). Patients allocated to the surgical arm will undergo surgery as soon as feasible after randomization (maximum within 1 week, preferably within 2 days). For all participating patients that signed the informed consent at the screening visit, an operation day will be scheduled, maximum one week after the randomization visit (due to practical scheduling reasons). At the moment of scheduling, the patient will be unaware of this date to prevent bias (and orientation of the mindset of patients toward surgery). If a patient is allocated to the conservative arm of the trial, the scheduled operation date will be cancelled, without knowledge of the patient. Patients in the surgical arm of the trial, are allowed to follow physiotherapy after surgery. The frequency and intensity are to be determined by the treating physician. All participants are allowed to use an ankle-foot orthosis. The use of electrostimulation is not advised, although not forbidden.
The endpoints will be evaluated at fixed time-points: 6 weeks, 3 months, 6 months and 9 months after randomization. Extended follow-up is scheduled 9 months after the primary endpoint is reached i.e. 18 months after randomization. Most trial assessments will be performed by the site-specific blinded researcher, ideally an independent physiotherapist. Patients allocated to the surgical arm of the trial will be evaluated 10 days after neurolysis. A postoperative control is considered standard of care. Sensorimotor function, quality of life and complications will be assessed during this postoperative control. Assessment of MRC-scores for ankle dorsiflexion and ankle eversion, as well as ankle range of motion is considered standard of care and shall be performed by the treating physician. The treating physician can also assess ankle dorsiflexion strength measured by isometric dynamometry. This cannot be done by the outcome assessor because this would lead to unblinding.
A list of standard assessments (clinical records, considered daily practice = SOC; including motor and sensory function,, ability to walk (barefoot), need for orthosis, treatment) will be composed for uniformity across centers. Standard assessments will be conducted at each study visit.

Cross-over is not allowed until the primary endpoint at 9 months is assessed. After the primary endpoint is assessed, cross-over from the conservative arm to surgery is allowed and patients will be treated according to standard of care

(decision between treating physician and patient). Extended follow-up for all patients will be organised, 18 months after randomization. All primary and secondary endpoints, with the exception of electrodiagnostics, WPAI and return to work, will be assessed at 18 months. The End-of-Study (EOS) visit will take place at 18 months post-randomization.

A pilot study will be conducted in 6 centers to assess feasibility of the foot drop trial, since studies of surgery compared to no or delayed surgery are challenging. These 6 centers include:
1. University hospitals of Leuven (UZL, prof. dr. Tom Theys)
2. CHU de Liège (ULG, prof. dr. Annie Dubuisson)
3. Ziekenhuis Oost-Limburg (ZOL, prof. dr. Frank Weyns)
4. Leids Universitair Medisch centrum (LUMC, dr. Justus Groen)
5. AZ Groeninge Kortrijk (dr. Jeroen Ceuppens)
6. ULB Erasme Brussel (dr. Sophie Schuind)
The pilot centers will include patients over a period of six months. Inclusion criteria and exclusion criteria are the same as in the full-scale trial.

The assessments conducted in the pilot study will be the same as in the full-scale study. The go/no go criterion to embark on a full-scale trial is a recruitment rate of at least 14 patients in the 6 including centers at 6 months.

Intervention

Surgical decompression of the peroneal nerve can be performed under local, locoregional or general anaesthesia. Pneumatic compression to restrict blood flow in the operation area during surgery can be used (and will be recorded in the surgery report).
The surgical approach for entrapment at the fibular head is usually through a curvilinear incision just distal to the fibular head. The length of the incision can vary between 3 and 10 centimeters. The subcutaneous tissue is bluntly dissected, and the common peroneal nerve is identified proximal to the peroneus longus muscle. The peroneal nerve is then released from the surrounding fibrous tissue and fascia. The anterior intermuscular septum is usually not cut, but this can be done if deemed necessary. The nerve is decompressed distally as it dives under the peroneus longus muscle. The decompression at this site is essential. Certain authors state that an adequate decompression should extend beyond the bifurcation in the deep and superficial peroneal nerve and should involve cutting the intermuscular septa. It is up to the surgeon to decide if decompression beyond the bifurcation is necessary, based on intraoperative findings (recorded in the surgery report).

Study burden and risks

As mentioned, both treatment arms of the trial are considered standard of care.

Risks and complications of treatment are limited.
Broekx et al. published a large retrospective case series on operative treatment of peroneal nerve entrapment and found complications of surgery in 4.5% of included patients (n = 200). These risks were mostly limited to wound problems (infections, hematoma) or residual pain at the level of the scar. One patient with severe pre-existing comorbidities (aged 87) developed a postoperative abscess and S. aureus sepsis. She died of sepsis 28 days after surgery. Globally, surgery is considered very safe.

We inform patients about the risks at screening and randomization visits and these risks are discussed in the informed consent form. Since risks are minimal and the other study group receive physiotherapy no additional measures are taken.

Contact numbers of the study team are provided. In the highly unlikely event of an emergency after surgery (which again, is standard of care), patients are advised to consult the emergency department.

The trial assessments are not invasive. During EMG patients can experience some discomfort (pain, or a limited electric shock). The EMG in follow-up will be limited since there is no need to make a diagnosis anymore.

There are no direct advantages for trial participants expect for the fact that follow-up of the foot drop will be optimal.
Patients are financial compensated for their participation (voucher of ¤175) and this can be considered an advantage.

Results of the trial can be used to council and treat future patients in the best way possible. This is important since peroneal neuropathy is the most frequent neuropathy in the lower limb and a frequent cause of foot drop.

Contacts

Public
Universitaire ziekenhuizen Leuven

Herestraat 49
Leuven 3000
BE
Scientific
Universitaire ziekenhuizen Leuven

Herestraat 49
Leuven 3000
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Written informed consent to participate in the study must be obtained from the subject or proxy / legal representative prior to initiation of any study-mandated procedure
2. EDX-documented peroneal nerve entrapment with persisting (10 ± 4 weeks) foot drop (MRC-score <= 3)
3. Imaging (ultrasound/MRI) performed to exclude a compressive mass
4. Age >= 18 years

Exclusion criteria

1. Subjects with posttraumatic or iatrogenic peroneal nerve injury
2. Subjects with peroneal neuropathy due to a compressive mass (e.g. cyst, tumour)
3. Peroneal nerve entrapment at other sites than the fibular head
4. Bilateral peroneal nerve entrapment
5. Patients with mental or physical problems that incapacitate them to participate in a physiotherapy program
6. Psychiatric illness
7. Pregnancy
8. Planned (e)migration within 1 year after randomization to another country
9. Subjects with previous foot drop
10. Permanently bedridden subjects
11. Subjects with neurological or musculoskeletal history which could impact

foot drop assessment and/or gait analysis (e.g. polyneuropathy, hereditary neuropathy with pressure palsies, critical illness polyneuropathy, previous stroke, ankle surgery, ankle sprain, *).

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-10-2021
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO

Date:	06-07-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	22-05-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT04695834
CCMO	NL76880.058.21