STOP NEUROMA
Surgical Treatment Of symPtomatic NEUROMA:
Open non-randomized clinical investigation to evaluate the safety and effectiveness of the nerve capping device to prevent neuroma formation after traumatic nerve section

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Primary clinical investigation objectives[Safety]The primary safety objective of the clinical investigation is to provide data that demonstrates safety of the device, defined as < 8.3% serious adverse device effects, up to 6 weeks following the...

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

Summary

ID

NL-OMON43604

Source
ToetsingOnline

Brief title
STOP NEUROMA

Condition

- Peripheral neuropathies

Synonym
nerve fantom pain, symptomatic neuroma

Research involving
Human

Sponsors and support

Primary sponsor: Polyganics BV, Groningen
Source(s) of monetary or material Support: Polyganics Innovations BV

Intervention

Keyword: Nerve capping device, Symptomatic Neuroma

Outcome measures

Primary outcome

Safety:

- Rate of serious adverse device effects up to 6-week follow-up.

Note: the relatedness of a SAE to the investigational device will be determined

by an independent expert in addition to the investigators opinions.

Effectiveness:

- Pain caused by symptomatic end-neuroma: VAS score at 6-week follow-up

compared to score at baseline.

- Quick DASH11 score at 6-week follow-up compared to score at baseline.

- Quantity and class of pain medication used for the end-neuroma pain at 6-week

follow-up compared to quantity and class of pain medication at baseline.

Secondary outcome

Safety:

- Rate of serious adverse device effects up to:

o 3mo follow-up

o 6mo follow-up

o 12mo follow-up

Performance:

- Pain caused by symptomatic neuroma - VAS score at:

o 6wk follow-up compared to scores at baseline

o 3mo follow-up compared to score at baseline.

o 6mo follow-up compared to score at baseline.

o 12mo follow-up compared to score at baseline.

- Pain caused by symptomatic neuroma - DN4 score at:

o 6wk follow-up compared to scores at baseline

o 3mo follow-up compared to scores at baseline.

o 6mo follow-up compared to scores at baseline.

o 12mo follow-up compared to scores at baseline.

- Pain caused by symptomatic neuroma - Elliot score at:

o 6wk follow-up compared to scores at baseline

o 3mo follow-up compared to scores at baseline.

o 6mo follow-up compared to scores at baseline.

o 12mo follow-up compared to scores at baseline.

- Quick DASH score at:

o 6wk follow-up compared to scores at baseline

o 3mo follow-up compared to score at baseline.

o 6mo follow-up compared to score at baseline.

o 12mo follow-up compared to score at baseline.

- Rate of recurrence within 12mo following the procedure, recurrence for each subject being defined as a combination of (1) subject verbal report of daily pain, (2) amount and type of pain medication at a same or greater amount compared to baseline, (3) no improvement in Quick DASH score, and (4) pain relief following a 10min ±2min nerve block with Xylocaine (Lidocaine)

- Quantity and class of pain medication used for the neuroma pain at:

o 6wk follow-up compared to medication at baseline

o 3mo follow-up compared to medication at baseline.

o 6mo follow-up compared to medication at baseline.

o 12mo follow-up compared to medication at baseline.

User handling:

- User Device Handling Questionnaire score

Study description

Background summary

Symptomatic neuroma may develop after a nerve dissection following any trauma to a peripheral nerve, whether accidental or planned (i.e. surgery). Neuroma-induced neuropathic pain and morbidity seriously affect the patient*s daily life and socioeconomic functioning (van der Avoort, 2013). The incidence of symptomatic neuromas after peripheral nerve injury is estimated to be 3-5%, however certain surgeries (e.g. autograft procedures, amputations) may have up to a 30% incidence rate (Stokvis 2010). Autograft procedures, where the nerve is harvested from a donor site, are at risk of subsequent neuroma formation. In the US, amputation resulting from trauma (45%), and diabetes and/or vascular diseases (55%) had a prevalence of 1.6 million patients in 2005 and is projected to rise to 3.6 million patients by 2050 (Radtke 2013).

There are several surgical procedures possible to treat symptomatic end-neuromas, but none are considered gold standard for both treatment and prevention. The most common procedure is surgical removal of the neuroma and surrounding scar tissue, and subsequent capping of the nerve with a nerve graft or a nerve conduit, or placing the proximal stump into an area subjected to minimal mechanical stimulation.

Covering the nerve stump with a cap of autologous (vein, muscle, fascia, bone) or synthetic (silicone, collagen) material prevents both neuroma development and regeneration (Lewin 2006), but also has limitations. Placing the nerve stump into a vein, requires a suitable vein to be available and sacrificed and the stability of the treatment depends upon consistent venous integrity (i.e. the vein does not collapse). Muscle capping is often performed as this tissue is easily available, however the recurrence of very painful sensory neuroma has been reported (Lewin 2006). Replacing the refreshed nerve end into bone is a technically demanding option. The nerve stump must be properly placed into a drilled hole, with no kinking at the hole entrance, and requires the nerve to be fixed to prevent dislocation. A newer method for treating peripheral neuroma is coverage with a vascularized flap. The flaps can be either fascial, fasciocutaneous, muscle or adipose tissue flaps. These flaps are technically demanding and should only be considered in specific cases (Watson 2010).

Unfortunately, even following treatment, patients with symptomatic neuromas following amputation had an average of 2.8 re-operations to treat pain (van der Avoort, 2013) and the surgeries have a failure rate of 10% or more (Elliot 2011).

Covering the nerve stump in artificial material was introduced in 1976 when silicon rubber caps were used (Swanson, 1977). However, this treatment was subject to problems of dislocation of the caps and combined with current issues regarding biocompatibility with silicon, they are not present on the commercial market. Collagen nerve conduits as an adjunct to the resection of a painful neuroma were successful in treating neuromas of the foot and ankle (Gould, 2013), however these procedures require the use of materials based on animal derived tissue. More recently, silk fibroin blended with poly(L-lactid acid-co-*-caprolactone (SF/P(LLA-CL)) nanofiber conduits used in animal models show promising results regarding the nerve fiber organization (Yan, 2014).

Based on the success of the NEUROLAC® nerve guide for treatment of peripheral nerve lesions, it was considered to use this material to cap a nerve for the treatment symptomatic neuromas. A capping device can prevent dislocation of the stump by suturing the nerve end into the cap. Consequently, the end of the cap can be sutured to surrounding tissue. This allows an effective capping technique without the necessity of drilling a hole into bones, or sacrificing other tissue. This led Polyganics to design the poly-DL-lactide-caprolactone nerve capping device. By developing a conduit with a closed end (cap) it is expected that the formation of neuromas will be better controlled (compared to

the use of a nerve conduit) by preventing axonal sprouting and escape at the open end and lowering the neurotrophic effect by preventing regeneration of nerve tissue on the surrounding tissue.
The procedure will be less invasive and relatively simple in comparison with current techniques described above. The risk of dislocation is reduced as a result of the fixating techniques and the risk of biocompatibility issues is mitigated by the materials which are composed of non-animal derived products that are resorbable by the human body (Meek, 2012).

This study is conducted to clinically assess safety and performance of the Polyganics nerve capping device for the treatment of symptomatic neuroma. There is sufficient clinical experience with regard to the safety of the commercially available nerve guide, NEUROLAC®. This new nerve capping device is identical in material and manufacturing. The exception is in design, where NEUROLAC® has two open ends, the nerve capping device has one closed (sealed) end. This study will be conducted to obtain data on the clinical performance of the capping device*s ability to isolate the nerve end, resulting in a reduction of pain of experienced from the symptomatic neuroma and prevention of the reoccurrence of a symptomatic neuroma.

Study objective

Primary clinical investigation objectives
[Safety]
The primary safety objective of the clinical investigation is to provide data that demonstrates safety of the device, defined as < 8.3% serious adverse device effects, up to 6 weeks following the procedure.

[Effectiveness]
The primary effectiveness objective of the clinical investigation is to provide data that demonstrates effectiveness of the device, including:
1) Reduction of pain caused by symptomatic neuroma up to 6 weeks following the procedure, as compared to pain before the procedure.
2) Improvement of quality of life at 6 weeks follow-up, as compared to the quality of life before the procedure.
3) Reduction or stabilization of quantity/class of pain medication used to treat neuroma pain at 6 weeks, as compared to the use before the procedure.

Secondary clinical investigation objectives
The secondary objectives of the clinical investigation are to provide data that demonstrate safety, effectiveness and usability of the device, including:
1) [Safety] < 8.3% serious adverse device effects, up to 3 months, 6 months and 12 months following the procedure.
2) [Effectiveness] Reduction of pain caused by symptomatic neuroma after 3 months, 6 months and 12 months following the procedure, as compared to pain before the procedure.
3) [Effectiveness] Improvement of quality of life at 3 months, 6 months and 12

months follow-up, as compared to the quality of life before the procedure.
4) [Effectiveness] *20% recurrence of symptomatic neuroma within 12 months.
5) [Effectiveness] Reduction of pain medication used to treat neuroma pain at 3 months, 6 months and 12 months, as compared to the pain medication used for the neuroma pain before the procedure.
6) [Usability] Ease of placement of the device.

Note: All follow-up time points are post-implantation of the device i.e. post procedure (e.g. 6-week follow-up means a follow-up at 6-week post-implantation of the device).

Study design

This clinical investigation is a prospective, multicentre, open-label non-comparative clinical investigation, conducted in a minimum of 2 clinical sites in Europe.

Intervention

A nerve capping device will be placed over the nerve ending after the end-neuroma is removed. It is intended to protect the nerve end and separate the nerve from surrounding tissue to prevent the development of a symptomatic neuroma. The nerve capping device is a tubular device with one open end and one sealed end as shown below. The nerve is attached with sutures to the cap, and then the cap is attached with sutures to the surrounding tissue. This holds the nerve securely in the cap, and stabilizes the cap in the body while the nerve repairs. The cap is made of a material that will slowly and safely degrades over 16 months, therefore it doesn*t require surgical removal.

Study burden and risks

Potential Risks Associated with Surgical Procedures
These risks include post-operative complications, as well as any potential complications during the surgery which is performed under local anesthesia. The risks include but are not limited to, infection, inflammation, discomfort at the surgical site, and neurological complications resulting from the procedure. As a new device, the implantation procedure is new to the field of nerve defect repair techniques and to surgeons, however a full physician training and practical will be completed by all participating physicians before the study start.

The Potential Risk Associated with the Investigational Device
Reactions to the device itself may occur including: allergic, foreign body, or inflammatory reactions, or delayed wound healing.
Dislocation of early silicone-rubber nerve caps have been reported. NEUROLAC® (a biologically similar predicate device used as a sheet rather than a cap)

exhibited a 1/12 extrusion rate through the surgical incision site.
There is one risk that is still considered significant and needs to be analyzed for the risk-benefit. If the capping device fails to provide a sufficient barrier, it could lead to the formation of symptomatic neuroma. This clinical investigation is designed to assess this risk. However, there is still a residual risk that the barrier function of the device is not sufficient to prevent occurrence or recurrence of a symptomatic neuroma, since there is no data available to support this.
As with any novel medical device, there is always a risk of extremely rare or previously unknown side effects developing from the treatment.

Benefit Analysis
The current standard of care for treatment of neuroma-induced neuropathic pain is surgical removal, including the surrounding scar tissue and if possible repairing the nerve with either a nerve graft or a nerve conduit or placing the proximal stump into an area that is subjected to minimal mechanical stimulation. The potential benefits of this device include a less invasive, simpler procedure abandoning the need for nerve grafting, harvesting flaps or drilling holes into bones tissue. This optimized surgery time reduces the patients* stressful operative exposure, as the procedure is performed under local anesthetic. The investigational device also removes the need to sacrifice any other organic tissue from the patient.
Benefits of the investigational device may be realized from the avoidance of neuroma re-treatment (additional surgery and its inherent risks) which occur in 10% of patients under the current technique resulting from neuroma regrowth or surgical failure.
Subjects may benefit from a dramatic improvement in acute and chronic pain reduction, and subsequent improvements in quality of life and daily life activities.

Risk-benefit for subjects participating in the clinical investigation
Participation in the study requires the subject to comply with the study procedures andtravel to be available for all follow up visits over a 12-month period including travel to the investigational site at 10 days, 6 weeks, 3,6 and 12 months following the surgical procedure. It also requires the subjects to complete 4 different questionnaires at screening, discharge and at 6-weeks, 3, 6 and 12 months follow-up.
Many of the surgical procedure related risks are similar between non-study and study patients as surgery is the only current treatment for neuromas. The study subjects may be benefit from reduced surgery time, less invasive surgical techniques, and improved pain relief post-surgery. The residual risks for the subject with the investigational device is that of rare or previously unknown side effects or the inability to provide a suitable barrier to prevent reoccurrence of a painful neuroma.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subjects who are able to provide a written informed consent prior to participating in the clinical investigation.
2. Subjects who are > or <= 18 years year old.
3. Subjects with a diagnosis of symptomatic primary or secondary end-neuroma.
4. Symptomatic neuroma located on the upper limb between the metacarpophalangeal (MCP) joints to shoulder.
5. Symptomatic neuroma confirmed by pain relief following a 10min ±2min nerve block with Xylocaine (Lidocaine) - Pain relief defined as any reduction in VAS questionnaire score.
6. Subjects with history of pain in the area of the end-neuroma for at least 6-months.
7. Subjects with a positive Tinel*s sign.

Exclusion criteria

1. Inability to comply with the clinical investigation follow-up or other clinical investigation requirements.
2. Subjects who are pregnant or intend to become pregnant during the duration of the clinical investigation or subjects who are not using appropriate birth control.
3. Subjects who have had historical radiotherapy in the area of the end-neuroma.
4. Symptomatic neuroma located proximally from the shoulder or distally from MCP joints.
5. Subjects not willing to follow post-surgery protocols (e.g. avoiding pressure on the implant zone).
6. Subjects is involved in another pain study.
7. Subjects who have a known allergy to anesthetic agent or bioresorbable copolyester Poly(68/32[15/85 D/L] Lactide-*-Caprolactone) (PLCL).
8. Subjects with a symptomatic neuroma that underwent surgical treatment for pain management on two or more occasions.
9. Insufficient amount of soft tissue to cover the investigational device.
10. Immunosuppressed patients, or patients with planned immunosuppressive therapy within 12-month following the study procedure.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-02-2016
Enrollment:	20
Type:	Actual

Medical products/devices used

Generic name:	Nerve capping device

Registration:	No

Ethics review

Approved WMO Date:	15-10-2015
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	16-11-2015
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	22-12-2015
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	04-01-2016
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	26-01-2016
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	22-06-2016
Application type:	Amendment

Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

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	NCT02528266
CCMO	NL54559.099.15