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Clinical Outcome for Surgical Treatment of Traumatic Neuroma With a Processed Nerve Allograft: Results of a Small Prospective Case Series

Anne Bolleboom, MD[1], Karin Boer, BSc[2], Godard C.W. de Ruiter, MD, PhD[3]

[1] *Student, Department of Neurosurgery, Haaglanden Medical Center, The Hague, The Netherlands*
[2] *Hand Therapist, Hand and Wrist Center The Hague, The Hague, The Netherlands*
[3] *Neurosurgeon, Department of Neurosurgery, Haaglanden Medical Center, The Hague, The Netherlands*

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ABSTRACT

Processed nerve allografts are used increasingly in the treatment of traumatic neuroma in small sensory nerves. The goal of the present study was to investigate the use of an allograft after different intervals between injury and repair and to analyze results, not only for the success of pain relief, but also for potential recovery of sensation in time. Four patients with painful neuroma in small sensory nerves in the lower extremity were surgically treated with a decellularized allograft. Patients were followed prospectively for at least 1 y. Clinical outcome was assessed using the Likert scale. Recovery of sensation was tested using Semmes-Weinstein monofilaments. In all 4 cases an allograft of 3-cm was used to reconstruct a defect in the superficial peroneal (3) or sural nerve (1) after excision of the neuroma. Complete relief of pain symptoms was achieved in 2 patients: 1 case concerned the reconstruction of a neuroma with an interval of less than 1 y between injury and repair and 1 case a neuroma-in-continuity. Sensation recovered completely in these 2 cases. In the other 2 cases, that had an interval between injury and reconstruction of more than 1 y, there was neither successful pain relief nor recovery of sensation. This prospective study shows that processed nerve allografts can be successful for the reconstruction of small sensory nerves after excision of the traumatic neuroma both for recovery of pain and sensation, but in this small case series only if the interval between injury and reconstruction was <1 y.

Painful neuromas can develop after all different types of injury (1). Sharp injury frequently results in a terminal neuroma. Blunt injury can lead to the development of a neuroma-in-continuity. Currently, there is no consensus on what type of treatment can best be performed in case of a traumatic neuroma. Several surgical interventions have been shown to result in pain relief, including neurectomy, excision of the neuroma and insertion of the proximal nerve stump into an adjacent anatomical structure or covering the nerve stump with artificial material or epineurium (2-8). However, the effect of these treatments is often temporarily, due to recurrence of the neuroma, requiring additional surgical interventions with reported reoperation rates as high as 65% (9-11).

The best option is, if possible, to restore the nerve function by reconstruction of the continuity of the nerve (12,13). In the repair of large motor nerves where direct repair is not possible, the autologous nerve graft (the sural nerve is most commonly used and taken from the patients' leg) still is the gold standard for reconstruction. In the repair of small sensory nerves, however, this would mean that 1 sensory nerve has to be sacrificed to reconstruct the other. In these cases, an allograft represents a good alternative since it lacks additional donor-site morbidity. Recently, Souza et al already demonstrated in a retrospective case series of 22 patients with ankle and foot neuroma, that the application of allografts results in a significant pain reduction with only 1 case of recurrent neuroma (14). Unfortunately, the interval between nerve trauma and reconstruction in that study was not reported. Furthermore, recovery of sensation in the foot postoperatively was not investigated. The goal of the present study was to prospectively evaluate pain and sensation after surgical reconstruction using an allograft for the treatment of painful traumatic neuroma in the lower extremity.

Case Series

Patients

Four patients (3 males, 1 female) who underwent surgical repair of a symptomatic ankle neuroma with a processed nerve allograft (Avance®, AxoGen, Inc., Alachua, FL) between September 2014 and November 2016 in the Haaglanden Medical Center were prospectively followed. The mean age of the patients at presentation was 33 (range 19-50)

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Address correspondence to: Godard de Ruiter, MD, PhD, Department of Neurosurgery, Haaglanden Medical Center, Lijnbaan 32 2501CK The Hague, The Netherlands.
E-mail address: g.de.ruiter@haaglandenmc.nl (G.C.W. de Ruiter).

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Table 1
Patient characteristics

Pt. No.	Age (y)	Gender	Mechanism of Injury	Preoperative US	Tinel Sign	Affected Nerve	Preoperative Interval (Days)
1	19	Male	Neurotmesis injury due to autograft harvest	+	+	Sural nerve	393
2	21	Male	Neurotmesis injury due to scooter accident	+	+	Superficial peroneal nerve	425
3	42	Female	Unknown	+	+	Superficial peroneal nerve	0
4	50	Male	Neurotmesis injury due to plate osteosynthesis	+	+	Superficial peroneal nerve	191

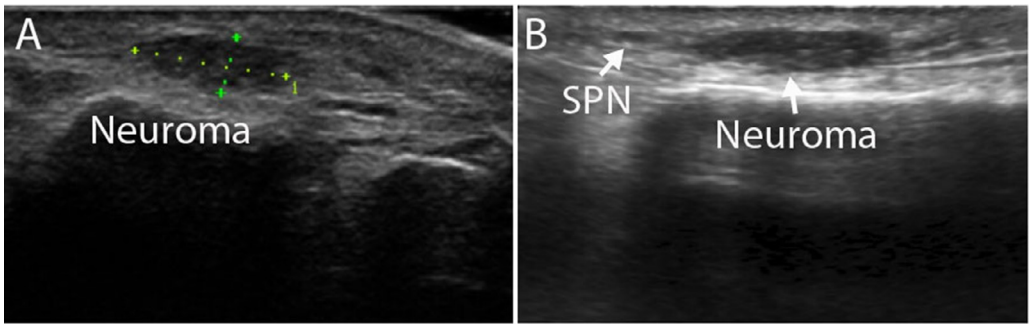

Fig. 1. Transverse (*A*) and longitudinal (*B*) ultrasound images showing the neuroma originating from the superficial peroneal nerve (SPN) located in the subcutis.

Table 2
Individual patient data

Pt. No.	Neuroma Type	Allograft Diameter (mm)	Allograft Length (mm)	Follow-up (Months)	Postoperative Likert	Postoperative Tinel Sign	Semmes-Weinstein Monofilament Test
1	End	3	30	12	4	+	5.18
2	End	3	30	18	3	+	4.56
3	NIC	3	30	12	1	-	3.61
4	End	3	35	12	1	-	3.61

Abbreviation: NIC, neuroma-in-continuity.

years. Characteristics of the patients are presented in Table 1. All nerves that were repaired concerned small sensory nerves: the superficial peroneal nerve in 3 cases and the sural nerve in 1 case. Mechanism of nerve injury was traumatic in 1 case and iatrogenic in 2 cases (Table 1). One case presented with a painful neuroma without evidence of any previous trauma or surgery at the neuroma site (Case 3). There was no significant medical history that may have had an effect on the recovery of nerve function. Typically, patients presented with pain or paresthesia in the original surgical site or localized at the site of the scar tissue. Physical examination in all patients showed a discrete area of tenderness with a positive Tinel's sign and hypoesthesia in the territory of the affected nerve. Ultrasound imaging was performed in all patients preoperatively (Fig. 1), to measure the size of the neuroma, the diameter of the affected nerve and the distance between the nerve ends in order to determine the required dimensions of the allograft prior to surgery. All neuromas that were resected during surgery were sent for histopathologic analysis. The follow-up time was 12 months in 3 cases and 18 months in 1 case (Table 2).

Surgical Technique

The area of greatest tenderness was preoperatively marked. The affected nerves and neuromas were exposed with the patients in supine position under general anesthesia using the operating microscope. The neuromas were excised until healthy nerve tissue was visualized with a normal architecture of the fascicles. The neuroma was sent for histopathologic analysis. Subsequently, the gap between the nerve ends was measured and the allograft of a suitable caliber was adjusted to the appropriate length to ensure a tension-free nerve repair. The allograft was then placed as an interposition graft between the 2 nerve ends to bridge the resulting gap using four 10-0 nonabsorbable epineural sutures at each coaptation site (Fig. 2). No additional ensheathment or wrapping was used in any of the 4 cases. Each patient then underwent primary skin closure. An ankle brace was used for 2 weeks to prevent mobilization and tension at the coaptation sites.

Follow-up

Patients were postoperatively followed for a period of at least 12 months. After the 2 weeks of immobilization, range of motion exercises for the ankle was employed as physical therapy, which was continued for 6 weeks. Patients were allowed during this period to slowly resume daily activities. Postoperative evaluation was performed in the outpatient clinic and graded using a 7-point Likert scale: complete recovery of symptoms = 1, almost complete recovery of symptoms = 2, partial recovery of symptoms = 3, symptoms unchanged = 4, small increase of symptoms = 5, severe increase of symptoms = 6, worst symptoms ever = 7. Likert grade 1 or 2 was regarded as good outcome. Evaluation of sensibility was performed in all patients by a certified clinical therapist using Semmes-Weinstein monofilaments (North Coast Medical Inc., Morgan Hill, CA) (15) at 3, 6, 9, and 12 months after surgical reconstruction. The area corresponding to the innervation area of the affected nerve was measured and the pressure threshold was reported in grams per square millimeter. Patients who were able to sense the 3.61 size of the filaments were considered to have normal sensation and 4.31 diminished light touch (15,16). Furthermore, implantation sites were monitored for any signs of infection, graft rejection and signs of pain.

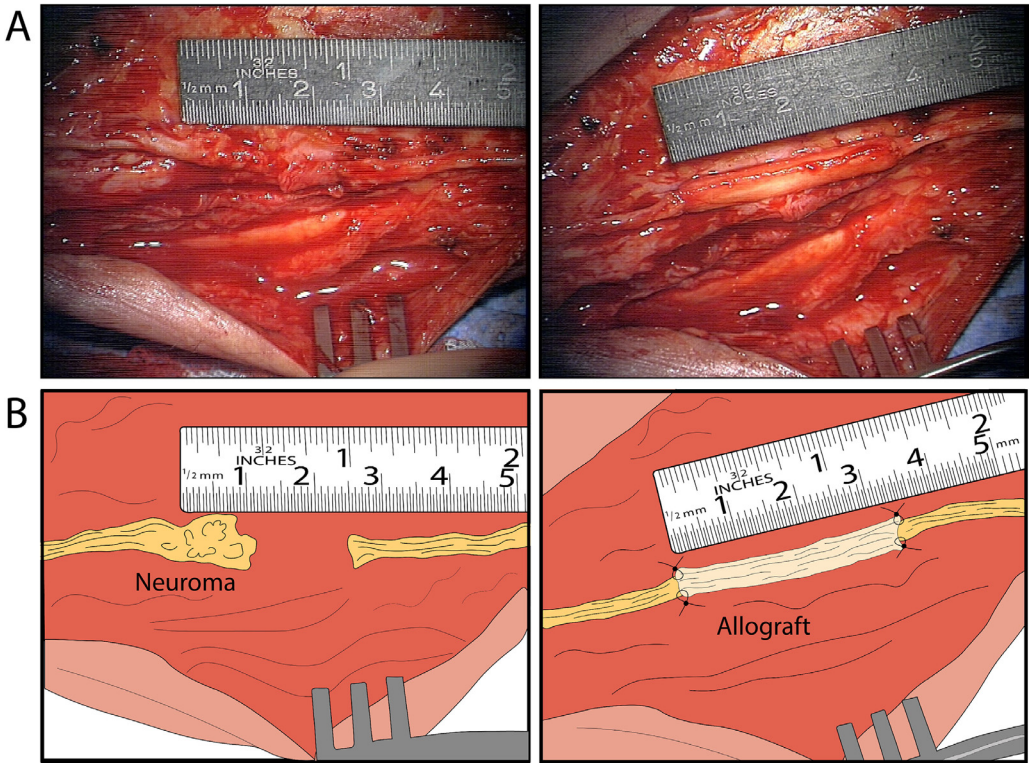

Fig. 2. Surgical procedure. (*A*) Intraoperative images of the procedure where the Axogen nerve graft is being used to repair 2 nerve ends after resection of a terminal neuroma. The neuroma is exposed (left), an allograft of suitable caliber is adjusted to an appropriate length to fill the gap and the neuroma is resected till healthy nerve tissue is visualized and the allograft is tension-free sutured between the proximal and distal nerve ends (right). (*B*) Schematic presentation of images presented in *A*.

Intraoperative Data

Surgery was performed in all patients by the senior author (GdR). In all subjects the neuroma was intraoperatively identified by the presence of a thickening originating from the corresponding nerve. One case concerned a neuroma-in-continuity and 3 cases a terminal neuroma. The diagnosis was confirmed in all cases by histologic analysis of the resected nerve tissue (Fig. 3). Nerve defects were reconstructed with a 3 mm diameter allograft in all cases. The allograft length ranged from 30 mm ($n = 3$) to 35 mm ($n = 1$) corresponding to the gap length (Table 2). The mean duration of surgery was 91 minutes. Prior to surgery, the subjects had a mean preoperative interval of 252 (range 0-425) days from the date of injury.

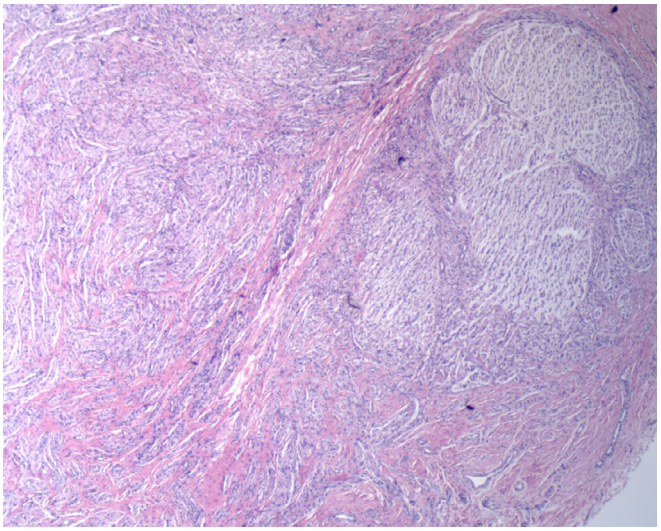

Fig. 3. Microscopic image of resected nerve tissue in transversal orientation stained with hematoxylin-eosin showing a haphazard orientation of axons with intraneural connective tissue consistent with a neuroma. Original magnification 40×.

Postoperative Data

There were no implant complications, tissue rejections, or adverse effects related to the use of the processed nerve allografts. All patients were followed for at least 1 y postoperatively for sensory recovery and pain relief. Good outcome (Likert 1) was achieved in 2 patients, already at the first follow-up moment (6 weeks after the surgery), which persisted for at least 1 y (Case 3 and 4 in Table 2). Persistence was reported by the other 2 cases: 1 (Case 1) had persistence of pain symptoms in the area of numbness with a positive Tinel sign (Likert 4), the other case (Case 2) had relatively mild symptoms consisting of an area of tenderness at the injury site with a positive Tinel sign (Likert 3). Re-exploration to excise the graft and potentially recurrence of neuroma was offered to them, but both patients did not want to undergo another operative procedure.

Using the Semmes Weinstein monofilament tests for assessing recovery of sensation, sensory improvement was observed in 3 patients at 6 months follow-up. At 9 months follow-up, substantial improvement in sensation was found in 2 patients, both patients recognized the 3.61 monofilament applied, corresponding to normal sensation at 9 months follow-up (Table 2). Of the subjects with both pain relief and recovered sensation (Case 3 and 4, Table 2), the preoperative interval between injury and reconstruction was less than 1 y (direct reconstruction and 191 days respectively). Surgical reconstruction of the neuromas with a preoperative interval of more than 1 y after injury demonstrated no substantial recovery of sensation.

Discussion

The results of this prospective study show that processed nerve allografts can be successfully used for the reconstruction of small sensory nerves after excision of a neuroma, but in our small case series, only if the interval between injury and reconstruction was less than 1 y. Complete relief of pain was observed in the 2 successful cases, along with substantial improvement in sensation. In contrast, the 2 patients in our study with an interval of more than 1 y between injury and reconstruction showed no substantial improvement of sensation and continued to have pain.

In recent years processed nerve allografts have become an alternative to the autologous nerve graft that is increasingly used in the reconstruction of nerve defects in peripheral nerve injury. In general, most peripheral nerve surgeons still prefer to use an autologous nerve graft, because these grafts not only provide the internal structure for regeneration, but also provide neurochemical cues secreted by Schwann cells that stimulate regeneration (17,18). Obviously, the use of an autograft also has several disadvantages, such as the limited availability, potential >mismatch between the severed nerve and the graft, increased operating time and donor site morbidity, consisting of sensory loss within the area of harvest, scarring and the potential for neuroma formation (17,19,20). Nerve allografts, on the other hand, are readily available in different sizes and lengths. In 2012 Brooks et al demonstrated in the RANGER study that processed nerve allograft are a safe and effective alternative for nerve reconstructions with meaningful recovery in 87.3% of the cases (21). In the same study, they found functional recovery after repair of sensory, mixed and motor nerves with gaps up to 50 mm. It is still difficult however, to compare these results to these for autograft repair, because of the heterogeneity of the group (e.g., differences in reconstructed nerves, gap lengths and age of the patients). Because of this probably, most peripheral nerve surgeons still use the autograft for the repair of large motor/mixed nerves. As illustrated in this study, however, for sensory nerve repair, the allograft is a good alternative, because it prevents the sacrifice of 1 sensory nerve to repair the other.

Others have previously reported successful results for the surgical strategy as presented in this study. Souza et al for example in 2016, demonstrated significant improvement in pain symptoms in 22 patients with neuroma (both neuroma-in-continuity and terminal end-neuroma in the foot and ankle) after excision of the neuroma and reconstruction of the nerve gap with a processed allograft (14). Unfortunately, sensory outcomes and interval between injury and reconstruction in that study were not reported. Our study shows that reconstruction of a neuroma with an allograft can lead to return of normal sensation. Recently 2 case reports have been published that have shown similar results. Bi et al used an allograft to treat a neuroma-in-continuity of an intercostal nerve in the abdominal wall 2 months after injury, which resulted in pain relief 5 weeks postsurgery and a subjective gradual return of normal sensation (22). Habre et al used an allograft to reconstruct the supraorbital nerve after excision of a neuroma, which resulted in complete pain relief and restoration of sensation of the forehead 1 y after injury (23). In our study, similar results were found in 2 cases. However, we also had 2 cases, in which sensation did not recover. Interestingly, the interval between injury and reconstruction was longer (>1 y) than in the other 2 cases. The explanation that reconstruction with an allograft in these cases did not lead to functional recovery might be explained by the fact that regeneration capacity decreases over time (24-26), which may be due to a diminished ingrowth of Schwann cells into the graft (27). Of course, this is merely a theoretical explanation that needs to be further investigated, preferably in animal models. In our opinion however, the finding of this study that reconstruction with an allograft more than 1 y after the injury does not results in recovery of sensation in our opinion does not justify the use of these relatively expensive grafts to repair small sensory nerves after excision of traumatic neuroma.

We acknowledge that this study has several limitations, most important the small sample size. The reason for this is that we first wanted to test this alternative surgical strategy in a relatively small group of patients, not only because of the uncertain effect, but also because of the relatively high costs of this intervention with a commercially available allograft. As our study shows the chance for successful pain relief and sensory recovery is substantially reduced if the interval between trauma and reconstruction is longer than 1 y. Question is whether another surgical technique, as for example excision of the neuroma and coverage of the proximal stump with fat tissue, in these patients would have led to sufficient pain relief. Our patients did not want further surgical treatment. Apart from the effect however, our disappointing results in these 2 patients led us to conclude that this surgical strategy in patients with an interval of more than 1 y do not justify the costs for this surgical treatment. On the other hand, the good outcome for pain relief and recovery of sensation in the other 2 cases do encourage the use of allografts in patients with a neuroma-in-continuity or an interval less than 1 y, because this reconstruction not only results in pain relief, but also in recovery of sensation.

The results of study demonstrate that processed nerve allograft can be an effective surgical treatment for the reconstruction of small sensory nerves after excision of a neuroma, both in terms of pain relief and recovery of sensation. Successful results in our study however were only found if the interval between injury and reconstruction was less than 1 y.

Compliance With Ethical Standards

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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