A comparative study of two methods of surgical treatment for painful neuroma

H. Balcin, MD, Research Fellow
P. Erba, MD, Plastic and Reconstructive Surgeon
R. Wettstein, MD, Plastic and Reconstructive Surgeon
D. J. Schaefer, MD, Plastic and Reconstructive Surgeon
G. Pierer, MD, Plastic and Reconstructive Surgeon, Departmental Director
D. F. Kalbermatten, MD, MPhil, Plastic and Reconstructive Surgeon

From University Hospital of Basel, Basel, Switzerland

Painful neuromas may follow traumatic nerve injury. We carried out a double-blind controlled trial in which patients with a painful neuroma of the lower limb (n = 20) were randomly assigned to treatment by resection of the neuroma and translocation of the proximal nerve stump into either muscle tissue or an adjacent subcutaneous vein. Translocation into a vein led to reduced intensity of pain as assessed by visual analogue scale (5.8 (SD 2.7) vs 3.8 (SD 2.4); p < 0.01), and improved sensory, affective and evaluative dimensions of pain as assessed by the McGill pain score (33 (SD 18) vs 14 (SD 12); p < 0.01). This was associated with an increased level of activity (p < 0.01) and improved function (p < 0.01).

Transposition of the nerve stump into an adjacent vein should be preferred to relocation into muscle.

Regeneration of axons following nerve injury may lead to the formation of a bulb-shaped thickening termed neuroma.1 An ingrowth of connective tissue2,3 and the diffusion of neurotrophic factors from the distal nerve stump in several directions4 seem to be involved in the chaotic orientation of the regenerating axons. If the neuroma lies adjacent to a joint, or the site of tendon excursion, or is superficially located these axons are vulnerable to stimulation. Spontaneous pain signals have also been identified.5 The pain associated with a neuroma is difficult to treat and may become chronic, producing a physically and psychologically disabling fixed central pain.6 Relief of pain may be achieved through desensitisation therapies or massage that may re-orientate the scar tissue about the nerve stump. Surgical treatment by resection of the neuroma and reinnervation of the distal target, or translocation from the distal end organ to a site with minimal potential for further stimulation is the usual treatment. Translocation of the nerve stump into muscle tissue is probably the most commonly used technique at present, and pain relief is achieved in between 35% to 100%.7-9 More recently, the principle of transposition of the nerve stump into an adjacent vein has been proposed and promising results have been obtained.3,10-14 The hypothesis of this study was that the environment provided by intravenous transposition of the nerve stump improves the outcome of neuroma treatment by reducing the ingrowth of surrounding connective scar tissue, and by a more physiological distribution of neurotrophic factors released from the distal stump within the closed, tube-like structure provided by the vein.3,5,11,12,14

The analysis of outcome and inclusion criteria of previous studies have often been inconsistent, so that objective comparison of the available data is impossible. The quality of assessment of pain relief is highly subjective and its perception is easily influenced by external conditions, such as the quality of relationships, financial status, employment and other factors.15-17 No single assessment of outcome is able to adequately describe the effect of a treatment on pain, and a differentiated approach is needed, including assessment of the character and intensity of the pain, as well as its physical parameters.

A prospective randomised double-blind study was designed to compare translocation of the nerve stump into either muscle tissue or a subcutaneous vein. The reduction in pain and its impact on general well-being was assessed with the McGill pain questionnaire,18 a visual analogue scale (VAS) questionnaire, and by physical examination.

Patients and Methods

Patients presenting with a painful neuroma following orthopaedic surgery to the lower limb were enrolled in this prospective double-blind clinical study, which was approved by the local
ethical committee and used informed consent. A neuroma was diagnosed by dysaesthesia or hyperalgesia in the proximity of the scar, a positive Tinel’s sign and temporary relief of pain following a diagnostic nerve block with infiltration of 1% lidocaine. Patients who had undergone a previous attempt at operative revision of the neuroma or had comorbidities that might affect peripheral nerve function, such as diabetes, autoimmune diseases, herpes zoster infection, HIV, nutritional deficiencies, cancer, and peripheral artery occlusive disease Fontaine stage II or greater, were excluded from the study.

Between May 2005 and June 2007, 32 patients with a painful neuroma of the lower limb were seen in our department. Of these, ten were excluded from the study because of a prior attempt at surgical revision and two because of diabetes mellitus. There were six men and 14 women with a mean age of 46 years (19 to 74) eligible for inclusion in the study. Each study group comprised ten patients and all completed the 12 months of follow-up. The non-dominant left leg was involved in 15 patients and the dominant right leg in five. In ten patients the neuroma involved the sural nerve, in five the dorsal cutaneous nerves of the foot, in three the superficial branch of the peroneal nerve, and in two the saphenous nerve. Intra-operative examination revealed one neuroma to be in continuity. Patients in the nerve-into-muscle group had pain for 48 months (SD 40, median 32) and in the nerve-into-vein group 40 months (SD 29, median 33). The patient characteristics, the duration and location of the neuroma and the assessment of pain prior to surgery were comparable in the two groups.

**Surgical technique.** Patients were assigned to the nerve-into-muscle group or to the nerve-into-vein group by a computerised random-number generator. Based on 0.9 power to detect a significant difference in the McGill score (p = 0.05, two-sided), ten patients were required for each group. Patients were blinded as to the treatment performed. A rough estimation of the localisation of the neuroma was made pre-operatively by the Tinel sign. All patients received 1 g cefazolin intravenous (IV) (Kefzol, Teva Pharma, Israel) 30 minutes before operation. No attempt was made to reinnervate the distal target and all neuromas were resected. The proximal part of the nerve was mobilised from the scar tissue to allow transposition of at least 5 mm of the nerve into an adjacent muscle or subcutaneous vein. Particular attention was paid to achieve tension-free positioning as far from the overlying denervated skin and adjacent joints as possible, in order to avoid mechanical stress. Transposition was performed under loupe magnification with microsurgical instruments. In the nerve-into-vein group a subcutaneous vein was dissected out and the proximal nerve ending introduced end-to-side or end-to-end. One to two stitches (transmural and epineurial) with 8/0 nylon filament were used to secure the nerve ending to the vein (Fig. 1). In the nerve-into-muscle group no fixation stitches were applied. In both groups, fibrin glue (Tissel, 400IU thrombine/ml, Baxter Inc., Deerfield, Illinois) was used in addition to seal the transposed nerves. Low molecular weight heparin was administered during the entire in-patient stay.

**Parameters analysed.** One independent investigator (HB) who was blinded to the operative technique performed was responsible for patient assessment one day before surgery and three and 12 months after.

**Surgical complications.** During the hospital stay and in the outpatient clinic, wounds were monitored by the surgeon for complications such as infection, breakdown, and haematoma. Wound infection was diagnosed by redness, swelling and tenderness, and/or the presence of pus, an elevated white blood cell count or the level of CRP and required treatment with antibiotics.
Pain. This was assessed by means of the McGill pain questionnaire,\(^\text{18}\) which evaluates sensory, affective and evaluative dimensions of pain. Specific points are assigned to each pain character and the sum of the scores gives the McGill score (maximum = 78 points). Pain was also assessed by a VAS ranging from 0 to 10 (maximal pain). Values are indicated as mean (sd).

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<tr>
<th></th>
<th>McGill score</th>
<th>Visual analogue scale</th>
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<tr>
<td></td>
<td>Pre-operative</td>
<td>3 months</td>
</tr>
<tr>
<td>Nerve-into-muscle group (sd)</td>
<td>39 (13)</td>
<td>31 (13)</td>
</tr>
<tr>
<td>Nerve-into-vein group (sd)</td>
<td>32 (12)</td>
<td>17 (13)*(\dagger)</td>
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<tr>
<td>Difference (95% CI)</td>
<td>1.4 (0.8 to 2.7)</td>
<td>2.4 (1.2 to 4.8)</td>
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</table>

Pain character was assessed by the McGill score (maximum pain = 78 points). Pain intensity was assessed by a visual analogue scale (VAS; ranging from 0 to 10, 10 = maximal pain). Values are indicated as mean (sd).

\* \(p < 0.05\) vs pre-operative

\(\dagger\) \(p < 0.05\) vs muscle group

\(\dagger\) \(p < 0.01\) vs pre-operative

Social parameters and patient satisfaction. Social parameters were addressed by a questionnaire defining the level of activity in everyday life, mood, mobility, working ability, relationships, quality of sleep, independence, and optimism on a VAS, with maximal impairment graded at 10. Patient satisfaction was assessed on a VAS ranging from 0 to 10 for maximal satisfaction.

Statistical analysis. Statistical analyses were performed using one-way analysis of variance with Tukey-Kramer correction for multiple comparisons. A \(p\)-value of < 0.05 was taken as significant.

Results

Post-operative complications. In the early post-operative period two patients from the muscle group developed signs of a wound infection, with swelling and redness over the suture but without purulent drainage. Both were treated with amoxicillin for seven days and did not require further surgery.

Pain. Both the McGill and the VAS scores showed a significant improvement in pain in the vein group, compared to their pre-operative levels and to that seen in the muscle group three and 12 months after surgery (Table I). No correlation was found between the duration of the neuroma and the outcome of treatment. Although the brief, momentary or transient, and the rhythmic, periodic and intermittent characters of the pain remained unchanged after surgery, a decrease in the continuous, steady and constant patterns was found in both groups (Fig. 2). Spontaneous pain was present in eight patients in the muscle and five in the vein group before surgery, and in four in the former and three in the latter, 12 months afterwards. Pain was triggered by temperature changes in eight patients in the muscle group and five in the vein group before operation, and in
improved to a significant degree ($p < 0.05$). Patients had a similar, albeit not significant, improvement in most social parameters assessed by the VAS questionnaire. Only mood relief of pain found in the vein group was associated with a significant reduction in intake of analgesics and the number of patients needing analgesics. * $p < 0.01$ vs pre-operative value. † $p < 0.05$ vein vs muscle group.

Graph showing intake of analgesics and the number of patients needing analgesics. * $p < 0.01$ vs pre-operative value. † $p < 0.05$ vein vs muscle group.

four in the former and three in the latter 12 months later. Movement triggered pain in all patients before surgery, and in nine in the muscle group and seven in the vein group 12 months later. A significant reduction in intake of analgesics was observed in the vein group (Fig. 3).

**Clinical examination.** Nearly all features assessed by clinical examination improved after surgery in both groups, with the vein group achieving better results than the muscle group. Comparison of the walking ability between the groups, calculated as the sum of the five different features of walking described, showed a significant improvement in function in the vein group (Table II).

**Social parameters and patient satisfaction.** The significant relief of pain found in the vein group was associated with a similar, albeit not significant, improvement in most social parameters assessed by the VAS questionnaire. Only mood improved to a significant degree ($p < 0.05$). Patients had a significantly higher activity level in the vein group (Fig. 4), and the mean increase in working ability over the period of follow up was 8% in the muscle and 27% in the vein group. Patient satisfaction was significantly higher in the latter than in the former (Fig. 5) ($p < 0.01$ at three months and $p = 0.03$ at 12 months after operation).

**Discussion**

The options for treatment for a painful neuroma include simple ligation,19,20 sealing or capping of the nerve stump,21-24 translocation into nerve tissue through an end-to-side or a centro-central coaptation,25-27 and implantation into other tissues such as bone,28-33 fat,28,34 muscle,7-9 vein10,13,14 and vascularised flaps.8,35-38 Implantation of the nerve stump into well-vascularised muscle seems to be the most commonly used procedure in clinical practice. The reasons for pain relief following relocation into muscle tissue appear to rely on reduced mechanical irritation, reduced scarring of the proximal nerve stump and an increase in the distance from tissues producing high concentrations of free neurotrophic factors, such as the overlying denervated skin and the distal nerve stump.39-41

We observed a significant reduction of the intensity of pain as assessed by the VAS questionnaire in the group having the transposition of the nerve stump into a vein, but not in the group with the nerve placed into muscle tissue. Transposition into both muscle and vein led to a reduction in continuous, steady and constant pain. This can be explained by the resection removing the majority of axons vulnerable to stimulation and capable of producing spontaneous pain signals.5 The improvement in pain and function of the affected leg following the reduction in this type of pain suggests that it is the most debilitating feature for the patients, and confirms the importance of surgical resection of the neuroma in order to help alleviate this. Brief and transitory pain, as encountered by movement or in the presence of external pressures such as in the Tinel examination, did not change after surgery, probably related to the development of a fixed central pain.

The implantation of the nerve stump into a vein was first described by Herbert and Filan in 1998.10 Animal studies demonstrated that the nerve stump grew into the lumen of the vein or into its wall, without forming a neuroma.3,11,12 The walls of the vein remain covered by endothelium and no narrowing or formation of thrombus was observed. The diameters of the nerve stumps were smaller, the nerve fascicles less chaotically arranged, and the production of scar and connective tissue in the developing neuroma was reduced.3,11,12,14 It has been suggested that the endothelium may play an inhibiting role on the formation of neuroma, and that the blood flow may remove neurotrophic factors released by the nerve stump.3,11,12,42 In contrast to previous studies, where the coaptation was always performed end-to-side,3,10-13 we transected the vein and performed an end-to-end anastomosis if an end-to-side arrangement would have required excessive mobilisation. No difference was found with regard to post-operative pain, function, neurological status, social aspects and patient satisfaction between patients who had end-to-end and those who had an end-to-side coaptation. In spite of the small number of patients, this study shows the importance of blood flow for the inhibition of neuroma formation and provides further evidence that veins present a suitable natural conduit which protects sprouting axons from the invasion of scar tissue from the surrounding tissues and allows their undisturbed growth, which minimises the formation of neuromas.

Potential biases in the study are the subjective experience and evaluation of pain, and the physical examination, which can be easily influenced by patient motivation and...
other issues such as workers compensation or insurance. However, the effort made to assess pain correctly and to give enough consideration to the multiple factors that influence its perception, increased the complexity of the design and method of the study.

In the vein group all pain assessment scores revealed an improvement from the third month after operation, whereas in the muscle group a delayed, less marked, and not significant improvement of pain was found. This was confirmed by the reduction in need for medication for pain, improvement in function, the increased level of activity and the increase in patient satisfaction in the vein group. Employment status and the analysed social parameters also showed a tendency towards a more marked improvement in the vein group. The only disadvantage of transposition of the nerve stump into an adjacent vein was the need for surgeons with microsurgical skills, although access to the veins is easier. Excessive mobilisation of the nerve stump or even fasciotomy are occasionally required for relocation into muscle.9 Although we did not measure the degree of mobilisation required, the wide exposure usually needed to transpose the nerve stump into muscle tissue might have been responsible for the two wound infections in this group.

Transposition into an adjacent vein represents a valid alternative technique, especially in the lower third of the leg and on the dorsum of the foot, where muscle bellies are thinner. The modest improvement in the social parameters and the non-significant reduction in unemployment found in our study may be attributable to the late diagnosis and treatment at a mean of 44 months (SD 34, median 33) after

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<tr>
<th></th>
<th>Nerve-into-muscle group</th>
<th>Nerve-into-vein group</th>
<th>Difference % (95% confidence interval)</th>
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<tr>
<td></td>
<td>Pre-operative 12 months</td>
<td>Pre-operative 12 months</td>
<td>12 months</td>
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<tr>
<td>Pain as palpation (sd)</td>
<td>8 (2)</td>
<td>5 (2.8)*</td>
<td>2.3 (0.4 to 14.6)</td>
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<tr>
<td>Tinel’s test (sd)</td>
<td>9.8 (0.8)</td>
<td>5 (2.8)*</td>
<td>1.3 (0.2 to 7.7)</td>
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<tr>
<td>Paraesthesiae (sd)</td>
<td>8.3 (1.8)</td>
<td>6.0 (3.0)*</td>
<td>2.8 (0.5 to 17.1)</td>
</tr>
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<td>Leg function (sd)</td>
<td>4.5 (2.3)</td>
<td>3.3 (2.3)</td>
<td>3.3 (0.3 to 31.8)</td>
</tr>
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* p < 0.01 vs pre-operative
† p < 0.05 vs muscle group
‡ p < 0.05 vs pre-operative
the initial trauma, and the well-developed social system. Pain which has lasted for over 90 days is a negative prognostic factor leading to delayed recovery.43,44 Probably because of this delay in treatment, a correlation between the duration of symptoms and the degree of improvement in the post-operative pain could not be established in our patients. It has been suggested that prompt diagnosis followed by rapid appropriate pharmacological therapy and surgical treatment within six months of the initial trauma is mandatory to achieve complete remission of pain without sequelae as a result of somatosensory cortical reorganisation that might affect social interactions and return to work.45 Nevertheless, the positive results of this study are similar to those of previous accounts dealing with transposition of a nerve stump into a vein, and show the superiority of this technique over transposition into muscle. It also shows that a painful neuroma can be successfully addressed after a lengthy delay, and that a significant reduction in pain can be obtained. However, in order to achieve relief of pain and avoid the development of disabling sequelae associated with progression to a complex pain syndrome, priority should be given to a prompt diagnosis and aggressive multidisciplinary approach.

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References