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Treatment of painful peripheral neuromas by vein implantation

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Abstract Firstly, we designed a vein-implantation model using the rat femoral nerve and vein to study the morphometric changes in nerve endings inserted into venous lumina. By 4 weeks, nerve fibers had extended from the nerve stump into the lumen of the vein and along the endothelium of the vein. After 8 weeks, the lengths and number of nerve fibres extending into the vein lumen began to decrease. At 12 weeks, the nerve ending had developed a hemispherical shape. In none of the experiments was a neuroma formed. Secondly, we treated ten neuromas in ten patients by the vein-implantation method. We obtained excellent results in seven patients.

Résumé Dans un premier temps nous avons conçu un modèle d'implantation qui utilise le nerf et la veine fémorale du rat pour étudier les changements morphométriques des terminaisons nerveuses insérées dans la lumière veineuse. A 4 semaines, les fibres du nerf s'étaient étendues à partir de l'extrémité nerveuse le long de l'endothélium de la veine. Après 8 semaines, les longueurs et le nombre de fibres nerveuses développées dans la veine ont commencé à diminuer. À 12 semaines, la terminaison nerveuse avait développé une forme hémisphérique. Dans aucun des cas un névrome ne s'est formé. Dans un deuxième temps nous avons traité 10 névromes chez 10 malades par la méthode de la veine – implantation. Nous avons obtenu d'excellents résultats pour 7 malades.

Introduction

In clinical practice, we often find it difficult to treat painful neuromas. Several authors have reported various treatments, including simple resection [7]; simple resec-

tion and wrapping of the nerve stump in its epineurium [13]; translocation of the transected nerve stump into a bone cavity [1], a muscle belly [3, 5] or subcutaneous fat tissue [1]; coagulation or freezing [9]; use of chemical agents to inhibit axonal regeneration [10]; and use of silicone to cap the nerve ending [12]. However, none is uniformly successful for treating painful cutaneous neuromas. Lundborg [8] reported that a peripheral nerve stump joined to one end of a silicone tube, with the other end left free, terminated without forming a neuroma, suggesting the possibility of treating neuromas by using silicone tubes. This concept was modified and developed by Herbert and Filan [6]. They treated painful neuromas by inserting the proximal nerve stump into the lumen of a pedicled subcutaneous vein instead of a silicone tube, and reported good or excellent results in ten of 13 patients. Despite these reports of successful clinical outcomes, the fate of the nerve stump after vein implantation has remained unclear.

Materials and methods

Experimental study

Eighteen Sprague-Dawley rats were used. The left femoral nerve was exposed and ligated with 5–0 nylon suture to form a neuroma (Fig. 1). The nerve was exposed again 3 weeks after ligation, and the neuroma that had formed just proximal to the ligation site was resected.

The femoral vein was incised and the proximal nerve stump remaining after resection of the neuroma was inserted about 2–3 mm into the lumen of the proximal stump of the vein. The epineurium was sutured to the vein stump with a 10–0 nylon suture to prevent the tip of the nerve stump from deviating from inside the vein lumen (Fig. 1C). The distal nerve stump was ligated with a 5–0 nylon suture, turned around distally, and placed in the thigh muscle. Three rats were killed with an intraperitoneal overdose of pentobarbital at 2, 4, 6, or 8 weeks after vein implantation, and six rats were killed at 12 weeks. The junction of the inserted nerve stump and the vein stump was harvested from each rat. Three specimens obtained from the rats sacrificed at each time point were fixed with 10% (v/v) formaldehyde and embedded in paraffin. Two 5- μ m-thick sections sliced parallel to the direction of the inserted nerve and overlapping vein were obtained from the center of each speci-

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Fig. 1 Schematic diagrams of the surgical procedures of vein implantation described by Herbert and Filan. **A** The femoral nerve was ligated. **B** By 3 weeks, a neuroma had formed just proximal to the ligation. **C** The nerve stump after resection of the neuroma was inserted into the proximal stump of the femoral vein

men. One section was stained with hematoxylin and eosin and the other with reticulin silver stain, and the stained sections were observed by light microscopy. The three remaining specimens from the rats sacrificed at 12 weeks were fixed with 2.5% (v/v) glutaraldehyde, post-fixed with 2% (v/v) osmic acid and then embedded in epoxy resin. A longitudinal section 1–2 μm thick was obtained from the center of the neurovascular junction of each vein-implantation site and stained with toluidine blue. After light microscopic observation, an ultrathin section was made and examined under an electron microscope (HITACHI 7000, Hitachi, Tokyo, Japan). The resected neuromas were also fixed in formaldehyde or glutaraldehyde and embedded in paraffin or epoxy resin. Sections taken from the center of each neuroma were prepared in the same way described above and observed under light and electron microscopy.

Clinical study

Ten patients ranging in age from 19 to 74 years who had painful cutaneous neuromas were treated by an author (RK) using the vein-implantation method described by Herbert and Filan [6] and followed up for an average of 23 (12–42) months. The patient data and the results of the surgery are summarized in Table 1. Six neuromas had resulted from traumatic injuries, two from surgery, another from needle injury during medical treatment (patient 7), and the remaining one from an attempted suicide (patient 10). The mean interval between injury and surgery was 9 (3–41) months. Two patients (patients 6 and 10) showed some restriction of finger motion, and preoperative X-ray examination revealed mild bone resorption in the hands of these patients. They were diagnosed as having mild refractory sympathetic dystrophy (RSD), but were not treated for RSD preoperatively.

Results

Experimental study

Bending or meandering of the nerve fibers was observed at the distal tip of the neuroma on light microscopy. Many terminal axons and end bulbs were visible at the tips of the distal axons in the neuroma on electron microscopy.

At 2 weeks after vein implantation, the nerve fibers were seen to extend from the proximal nerve stump into the vein lumen along the vein wall (A and a in Fig. 2). At 4 weeks, more nerve fibers extended further than at 2 weeks (B and b in Fig. 2). At 6 weeks, the length and number of the nerve fibers extending into the vein lumen continued to increase. However, at 8 weeks, the proximal nerve stump had become rounded, and the nerve fibers extending from the nerve terminal were shorter than those seen at 6 weeks (C and c in Fig. 2). At 12 weeks, the proximal nerve stump was hemispherical, and the nerve fibers that had extended into the venous lumen had disappeared. None of the nerve stumps had formed neuromas in the vein lumina (A and a in

Table 1 Patients and surgical results

Patients	Gender	Age	Injured nerves	Interval between injury and surgery (months)	Follow-up period (months)	Results
1	M	47	R-saphenous	4	18	Excellent
2	M	23	R-ulnar (Dorsal br.)	3	13	Excellent
3	F	74	L-saphenous	41	42	Poor
4	M	56	L-radial (Superficial br.)	6	39	Fair
5	M	33	R-saphenous	2	36	Excellent
6	M	19	R-median (Palmar br.)	3	13	Excellent
7	F	55	L-radial (Superficial br.)	5	24	Good
8	M	65	R-ulnar (Dorsal br.)	8	17	Excellent
9	M	33	R-superficial peroneal	12	15	Excellent
10	F	25	L-median	5	12	Excellent

(Palmar br.)

Fig. 2 Longitudinal section of the nerve–vessel junction observed under a light microscope at 2 weeks (**A**, *a*), 4 weeks (**B**, *b*), and 8 weeks (**C**, *c*). Bar = 200 μ m in **A**, **B**, and **C**. Bar = 60 μ m in *a*, *b* and *c*. Each square area in **A**, **B**, and **C** was magnified into *a*, *b*, and *c*, respectively. Nerve fibers extended from the nerve stump into the venous lumen along the inner surface of the vein, but by 8 weeks they had become shortened. * = vein lumen

Fig. 3). Under the electron microscope, no axons were found just under the tip of the hemispherical nerve stump. A layer of endothelial cells, which contained numerous vesicles in the cytoplasm, covered the proximal nerve stump within the venous lumen. Under the layer of endothelial cells there were several layers of Schwann cells. Proximal to the layers of Schwann cells, a few small nonmyelinated axons were found. Proximal-

ly, myelinated axons with diameters of 2–3 μ m were observed. The diameter and number of myelinated axons were greater in the more proximal part of the nerve stump. No end bulbs were found at the tip of the nerve terminal (B and b in Fig. 3).

Fig. 3 Longitudinal section of a nerve stump inserted into the vein 12 weeks after vein implantation, observed under light (**A, a**) and electron (**B, b**) microscopy. Square areas in **A** and **B** were magnified into **a** and **b**, respectively. **A, a**: The nerve stump inserted into the vein developed a hemispherical shape. No neuroma formed at the distal tip of the nerve stump. Bar = 100 μ m in **A** and 60 μ m in **a**. **B, b**: A layer of endothelial cells, which contained numerous vesicles, covered the distal surface of the nerve terminal. End bulbs or terminal axons were not found at the tip of the nerve terminal. Bar = 10 μ m in **B** and 1 μ m in **b**. * = vein lumen

Clinical study

We evaluated the postoperative results of vein-implantation surgery by patient reports of pain, local tenderness, and numbness on examination. Results were expressed by the following four grades:

1. Excellent: symptom free. Patients were relieved of the pain, tenderness, or numbness they had felt before surgery.
2. Good: patients felt some numbness, radiating pain, or tenderness when the site of vein implantation was stimulated strongly, but this disappeared in a few seconds.
3. Fair: patients sometimes felt moderate numbness, tingling pain, or tenderness on touching the site of vein implantation, but this did not disturb their daily lives.
4. Poor: patients always felt severe pain or numbness on lightly touching the site of vein implantation, even after surgery, and this disturbed their daily lives.

Seven patients were assessed as being in the excellent group, one patient was good, another was fair, and the other was poor. The last patient experienced recurrence of the symptoms and underwent another trial of vein-implantation surgery, and subsequently she was assessed as being in the excellent group. The preoperative RSD symptoms in patients numbers 6 and 10 disappeared after surgery.

Case presentation

Four months before the vein implantation, a 47-year-old man (patient 1) sustained a crush injury to the medial side of the right lower leg in a traffic accident and underwent surgery for debridement

Fig. 4 **A** The patient had had a crush injury to the right lower extremity 4 months earlier and felt tingling pain when the wound on the medial aspect of the lower extremity (black arrow) was tapped. **B** After removal of a neuroma formed in the saphenous nerve, the proximal nerve stump was inserted into the distal stump of the great saphenous vein (white arrow), because the proximal stump of the vein had been injured and was occluded

and suturing. The wound healed with a small area of scar formation. Three weeks after the injury, the patient began to feel tingling pain when the scar was tapped lightly (Fig. 4A). He also felt numbness on the medial aspect of the right foot and hallux. Subcutaneous lidocaine injection into the scar relieved the pain temporarily. The patient then underwent vein implantation for a neuroma that had formed in the saphenous nerve. The scar tissue and the neuroma were resected and the right great saphenous vein was exposed. Because the proximal vein stump was injured and occluded, the proximal nerve stump was inserted into the distal stump of the vein, and the epineurium was sutured to the vein lumen with 9-0 nylon suture (Fig. 4B). One and a half years after

vein implantation, Tinel's sign had disappeared and the patient was completely free of pain and numbness.

Discussion

Lundborg [8] found that nerves terminated in a silicone tube, with the nerve stump at one end and free at the other end, did not form a neuroma, and thus suggested the possibility of treating neuromas by using silicone tubes. When a tube is used to prevent neuroma formation, it must be longer than the maximum distance over which axons can regenerate. Otherwise, regenerated axons may pass through the silicone tube and form a neuroma again just distal to the tube. Autogenous vein grafts have been used as nerve conduits in clinical and experimental studies of peripheral nerve regeneration. These studies have demonstrated that the maximum distance over which nerves regenerate in a vein conduit is about 3 cm in humans [2, 11]. The biggest problem in using a vein as a nerve conduit is that the venous lumen can easily be collapsed. Because a vein segment is more easily collapsed than a pedicled vein, a pedicled vein is better for vein-implantation operations. Moreover, since the lumen of a pedicled vein is continuous and endless, regenerated axons would not be prevented from extending into a vein lumen. It can be presumed that nerves terminate without forming neuromas in a pedicled vein to which a transected nerve stump has been joined. However, the morphometric changes in the nerve terminal in the vein over time were unknown.

Our experimental study of rat femoral nerves revealed that insertion of the proximal nerve stump into the lumen of a vein did not generate a neuroma but formed a terminal covered by a layer of endothelial cells within the vein lumen. No axons were found just under the nerve terminals. Nonmyelinated axons were evident proximally, but they did not form terminal axons or end bulbs. Myelinated axons were present in the more proximal portion of the proximal nerve stump. Axon bending or meandering, which is usually seen at the tip of a neuroma, was not found at the proximal nerve terminals that were inserted into the veins.

Devor et al. [4] has reported that, at the tip of a neuroma, axons form end bulbs, and sodium channels accumulate. Even slight stimulation of a neuroma easily depolarizes the accumulated sodium channels, and this is recognized as a cause of neuralgia. The nerve terminal did not form an end bulb or a terminal axon when the vein-implantation method was used. Therefore, it is possible that sodium channels did not accumulate in the nerve terminals and that depolarization at the nerve terminal did not

occur easily in response to stimulation at the site of vein implantation.

Herbert and Filan [6] reported that the unsuccessful results in two of their cases treated by vein implantation were due to separation of the proximal nerve stump from the vein lumen. In our one case that had a poor result, a new neuroma had formed just proximal to the nerve-vein junction of the previous vein implantation. Because scar tissue had formed around the nerve-vessel junction, we could not determine whether the proximal nerve stump had been separated from the vein. Cases of unsuccessful vein implantation both by us and by Herbert and Filan [6] were relieved by additional vein implantation. These experimental and clinical results demonstrate that vein implantation is an excellent procedure for the treatment of painful neuromas.

References

1. Burchiel KJ, Johans TJ, Ochoa J (1993) The surgical treatment of painful traumatic neuromas. *J Neurosurg* 78: 714–719
2. Chiu DTW, Strauch B (1990) 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* 86: 928–934
3. Dellon AL, Mackinnon SE (1986) Treatment of the painful neuroma by neuroma resection and muscle implantation. *Plast Reconstr Surg* 77:427–436
4. Devor M, Govrin-Lippman R, Angelides K (1993) Na⁺ channel immunolocalization in peripheral mammalian axons and changes following nerve injury and neuroma formation. *J Neuro Sci* 13: 1976–1982
5. Evans GRD, Dellon AL (1994) Implantation of palmar cutaneous branch of the median nerve into the pronator quadratus for treatment of painful neuroma. *J Hand Surg [Am]* 19: 203–206
6. Herbert TJ, Filan SL (1997) Vein implantation for treatment of painful cutaneous neuromas. *J Hand Surg [Br]* 23: 220–224
7. Laborde KJ, Kalisman M, Tsai TM (1982) Results of surgical treatment of painful neuromas of the hand. *J Hand Surg* 7: 190–193
8. Lundborg G (1997) Tubular repair of nerves. In: Saffar P, Amadio PC, Foucher G (eds) *Current practice in hand surgery*. Martin Dunitz, London, pp161–169
9. Petropoulos PC, Stefanko S (1961) Experimental observations on the prevention of neuroma formation. *J Surg Res* 1: 241–248
10. Smith JR, Gomez NH (1970) Local injection therapy of neuromata of the hand with triamcinolone acetonide. A preliminary study of twenty-two patients. *J Bone Joint Surg [Am]* 52: 71–83
11. Suematsu N, Atsuta Y, Hirayama T (1988) Vein graft for repair of peripheral nerve gap. *J Reconstr Microsurg* 4: 313–318
12. Swanson AB, Boever NR, Lumsden RM (1977) The prevention and treatment of amputation neuromata by silicone capping. *J Hand Surg* 2: 70–78
13. Tupper JW, Booth DM (1976) Treatment of painful neuromas of sensory nerves in the hand: A comparison of traditional and newer methods. *J Hand Surg* 1: 144–151