Pain relief after nerve resection for post-traumatic neuralgia

Toshihiko Yamashita, Seiichi Ishii, Masamichi Usui

From Sapporo Medical University, Japan

We performed resection of part of an injured peripheral nerve in 20 patients with post-traumatic neuralgia, after conservative treatment had failed. All had burning pain, paraesthesia and dysaesthesia in the area innervated by the injured nerve. We resected the nerve in the area in which the patient felt pain, and a further 3 cm proximal to the site of injury.

In all cases, the local pain disappeared or markedly decreased. The areas of pain relief and of nerve resection coincided completely in 17 patients and partially in three. The results were assessed as excellent by five patients, good by 11, and fair by four. There were no poor results.

Histological examination of the resected nerves showed Wallerian degeneration and immunohistochemical tests indicated that substance P, a polypeptide which may contribute to nociceptive transmission, was present in the tissue around the degenerated nerves.

J Bone Joint Surg [Br] 1998;80-B:499-503.

Received 15 September 1997; Accepted after revision 29 November 1997

Peripheral nerve injury occasionally gives rise to intolerable burning pain in the area innervated by the nerve, greater than that expected from the initial trauma. This may be accompanied by dystrophic changes and is resistant to conservative treatment. Such cases of post-traumatic neuralgia are sometimes diagnosed as causalgia, reflex sympathetic dystrophy, or the shoulder-hand syndrome, but the definition and mechanism of post-traumatic neuralgia still remain controversial. There is no established treatment and it may be difficult to obtain adequate relief of the symptoms.

We have undertaken local resection of part of the injured peripheral nerve for prolonged post-traumatic neuralgia, and examined the resected nerves by histology and immunohistochemical tests to establish the presence of substance P, a polypeptide which may contribute to nociceptive transmission.

Patients and Methods

From 1979 to 1996 we carried out peripheral nerve resection on 20 patients (12 men and 8 women) for post-traumatic neuralgia. Their mean age at the time of operation was 52.2 years (30 to 63). The mean duration from the onset of symptoms to the operation was 55.7 months (7 to 276) and the mean length of follow-up was 91.2 months (24 to 216).

All patients had paraesthesia and burning pain in the area innervated by the damaged nerve, and tenderness at the site of the injury. The cutaneous dysaesthesia was so intense that the patients could not tolerate contact with clothing. In all cases, there was some swelling, vasomotor dysfunction, and dystrophic changes in the skin. Five patients had complete motor palsy and seven had incomplete paralysis in the area innervated by the injured nerves. In the other eight the nerve did not have a motor function. Conservative treatments such as medication, physiotherapy, and sympathetic ganglion block had all failed to relieve pain.

Neuralgia had developed as a consequence of open injuries affecting limbs, with obvious nerve lesions. According to the classification of Sunderland,¹ nine injuries were 3rd degree, six 4th degree and five 5th degree. The injuries were at the wrist in six, the finger in five, the palm in three, the forearm in two, and at the supraclavicular area, the elbow, the ankle and the leg in one case each. The median nerve was injured in seven cases, a digital nerve in five, the ulnar nerve and radial nerve in four each, the tibial nerve in two and the medial antebrachial cutaneous nerve, the axillary nerve and the peroneal nerve in one case each (Table I).

Operative technique. In our early cases, we resected the nerve from 3 cm proximal to 3 cm distal to the site of injury. After operation, pain disappeared in the area from which the nerve had been excised, but pain in the distal innervation of the injured nerve persisted. We therefore

T. Yamashita, MD, PhD, Assistant Professor
S. Ishii, MD, PhD, Professor and Director
M. Usui, MD, PhD, Associate Professor
Department of Orthopaedic Surgery, Sapporo Medical University, South 1,
West 16, Chuo-ku, Sapporo 060-8543, Japan.

Correspondence should be sent to Dr T. Yamashita.

©1998 British Editorial Society of Bone and Joint Surgery
0301-620X/98/38370 \$2.00

Table I. Details of the 20 patients who required nerve resection for post-traumatic neuralgia

Case	Age (yr)	Gender	Injured site	Injured nerve	Type of nerve injury* (degree)	Motor palsy	Duration from onset to operation (mth)	Number of operations	Operative result
1	30	M	Elbow	Ulnar, medial antebrachial	3rd	Incomplete	18	2	Good
2	51	F	Forearm	Radial	5th	Complete	24	2	Good
3	60	M	Wrist	Median	5th	Incomplete	36	3	Good
4	62	M	Palm	Median, ulnar	5th	†	84	6	Fair
5	62	M	Supraclavicular	Radial, axillary	3rd	Complete	276	3	Excellent
6	53	M	Forearm	Median, ulnar	4th	Complete	8	3	Good
7	58	M	Palm	Median	4th	†	40	2	Fair
8	43	F	Wrist	Median	4th	Incomplete	31	2	Excellent
9	53	F	Thumb	Digital (median)	3rd	†	12	2	Good
10	60	M	Wrist	Median	5th	Complete	17	2	Good
11	56	F	II finger	Digital (median)	3rd	†	120	1	Excellent
12	63	F	Wrist	Radial	3rd	Incomplete	12	1	Excellent
13	60	M	III, IV, V fingers	Digital (median, ulnar)	4th	†	43	1	Good
14	62	F	Wrist	Ulnar	3rd	Incomplete	74	1	Good
15	54	F	Wrist	Radial	5th	Complete	7	1	Good
16	39	F	Ankle	Tibial	3rd	Incomplete	168	1	Good
17	57	M	Palm	Median	3rd	†	46	1	Fair
18	43	M	Thumb	Digital (median, radial)	4th	†	7	1	Fair
19	31	M	III, IV fingers	Digital (median)	4th	†	19	1	Good
20	46	M	Leg	Tibial, peroneal	3rd	Incomplete	72	1	Excellent

* Sunderland¹

† the injured nerve was not related to motor function

extended the area of nerve resection step by step in subsequent operations and found that disappearance of the pain corresponded to the region of the portion of the nerve excised.

We then began to resect just the peripheral nerve within the area in which the patient felt pain, and also the normal portion for 3 cm proximal to the site of injury. Motor branches were resected if they were involved, with sensory branches to the area peripheral to the injured site.

Clinical evaluation. The results were evaluated as: 1) excellent, with complete disappearance of burning pain; 2) good, no limitation of ability in daily life in spite of slight residual pain; 3) fair, limitation of ability in daily life with residual but decreased pain; 4) poor, no change. Operations were considered successful if the results were excellent or good.

Histology. Resected nerves were fixed with 10% formalin, embedded in paraffin, sectioned and stained with haematoxylin and eosin and by the Bodian method. The stained preparations were examined under plain and polarised light microscopy.

Immunohistochemistry. The streptavidin-biotin method was used to identify substance P in resected nerves and the adjacent tissues. After the preparations had been extracted from paraffin, endogenous peroxidase activity was blocked with a 1% hydrogen peroxide methanol solution for 20 minutes. After incubation in 10% normal goat serum for 15 minutes, sections were incubated for one hour with the primary polyclonal antibody to substance P raised in rabbits (Nichirei, Tokyo, Japan). After several rinses in phosphate-buffered saline (PBS), a secondary antibody (biotinylated anti-rabbit IgG; Nichirei, Tokyo, Japan) was applied to the sections for 20 minutes. The sections were rinsed several

times in PBS, and streptavidin-peroxidase conjugate (Nichirei, Tokyo, Japan) was applied for 20 minutes. The sections were then exposed to 3,3'-diaminobenzidine (Nichirei, Tokyo, Japan) as the peroxidase-reactive chromagen, counterstained with haematoxylin, mounted and examined by plain and polarised light microscopy.

Results

Operative results. In all patients, the burning pain disappeared or decreased remarkably in the local area from which the nerves had been resected. The areas of pain relief and nerve resection coincided completely in 17 cases and partially in three. In the early cases, nerve excision was performed in stages by several operations, with six procedures in one patient, three in three, and two in six patients. The ten most recent patients had local nerve resection in one operation.

Transient recurrence of symptoms was observed in two patients during follow-up, but both had relief from conservative treatment such as medication and physiotherapy. The results were excellent in five patients, good in 11, and fair in four, giving a success rate of 80% (Table I).

Illustrative case reports

Case 2. A 51-year-old woman injured her right forearm in an industrial accident in 1976, and developed burning pain and paraesthesia in the distribution of the radial nerve in the forearm and hand. Because of increasingly severe burning pain, she enquired about the possibility of amputation in 1979.

We initially resected 5 cm of the nerve on the injured site, followed by a nerve graft for this portion, but this produced no change in her symptoms (Fig. 1a). At a second

Fig. 1a

Fig. 1b

Fig. 1c

Case 2. Injury of the superficial branch of the radial nerve. Before operation (a), after the first operation (b) and after the second operation (c). The injury site is shown by an asterisk. The areas of burning pain are shaded. Dotted lines indicate the resected portions of the nerve.

operation in 1982, the superficial branch of the radial nerve, including the graft, was resected to the wrist. After this, the local burning pain ceased in the area of the nerve resected, but pain remained in the periphery of the nerve distribution (Fig. 1b). An extended resection of residual nerve was performed two months later, and the burning pain disappeared (Fig. 1c). At 14 years after the second operation,

the patient had no limitation in activities of daily life, but slight paraesthesia in her thumb.

Case 10. A 60-year-old man injured the median nerve at his left wrist in 1990. After immediate suture by an orthopaedic surgeon, burning pain developed in the area innervated by the nerve. In 1991, a neuroma was resected from the injured site, but this had no effect on his severe pain (Fig. 2a).

In 1992, he was referred to us, and the median nerve was resected from the injury site to the proximal parts of the digital nerves. Pain disappeared in the area of nerve resection but persisted distally where the digital nerves remained (Fig. 2b). These were excised in a second operation after another eight months and his pain disappeared completely (Fig. 2c). There was no recurrence of symptoms at four years.

Histology of resected nerves. Seven resected nerves from five cases (cases 5, 6, 8, 16 and 17) were examined histologically and all showed Wallerian degeneration. In case 8, vacuoles of phagocytosed myelin remnants were seen among completely degenerated axons (Fig. 3).

Immunohistochemistry of resected nerves. Immunohistochemical investigation for substance P was performed on specimens resected from cases 16, 17 and 18. Substance P was found in all, especially in case 17. This stained as brownish spots in the fibrocytes among degenerated nerve fibres (Fig. 4).

Discussion

Mitchell² coined the term "causalgia" to describe the burning pain after damage to nerves from gunshot wounds sustained by soldiers in the American Civil War. According to Bonica's classification,³ "reflex sympathetic dystrophy" was used as a general term for chronic neuralgic entities, and causalgia was included in a category of major reflex dystrophies. Lankford and Thompson⁴ referred to a subgroup of reflex sympathetic dystrophy with nerve injury as

Fig. 2a

Fig. 2b

Fig. 2c

Case 10. Injury to the median nerve, before the first operation (a), after the first operation (b) and after the second operation (c). The injury site is shown by an asterisk. The areas of burning pain are shaded. Dotted lines indicate the resected portions of the nerve.

Fig. 3

Photomicrograph of a section from the median nerve resected from case 8. Vacuoles of phagocytosed myelin remnants are seen among completely degenerated axons (Bodian staining $\times 90$).

Fig. 4

Photomicrograph of a section from the median nerve resected from case 17. Substance P was stained as spots in fibrocytes among degenerated nerve fibres (substance P immunostaining, haematoxylin counterstain, $\times 90$).

causalgia, but Shumacker⁵ and Hodges and McGuire⁶ proposed that causalgia and reflex sympathetic dystrophy should be considered as separate entities. They defined chronic pain syndromes with nerve injury as causalgia, and those without obvious nerve injury as reflex sympathetic dystrophy. In 1986, the International Association for the Study of Pain⁷ defined causalgia as "burning pain, allodynia and hyperpathia, usually in the hand or foot, after partial injury of a nerve or one of its major branches", while reflex sympathetic dystrophy was described as "continuous pain in a portion of an extremity after trauma which may include fracture but does not involve a major nerve, associated with sympathetic hyperactivity". All patients in our study had persistent burning pain after direct injury to the trunks or branches of peripheral nerves and can therefore be classified as having causalgia. We prefer, however, to refer to these cases as 'post-traumatic neuralgia' because there is still confusion between 'causalgia' and 'reflex sympathetic dystrophy' as terms in the diagnosis of chronic pain syndromes.

Conservative treatment, such as medication and physiotherapy, should be tried first for post-traumatic neuralgia; sympathetic ganglion block may be effective in some cases. We have performed peripheral nerve resection only for post-traumatic neuralgia in which conservative treatment had failed to improve the symptoms. Palliative operations such as neurolysis or neurectomy of only the site of injury are usually not effective and may even make matters worse, as was observed by Seddon.⁸ He suggested that extensive neurectomy should be undertaken for causalgia and reported that 75% of his cases were improved by this procedure.

Coupling between sympathetic postganglionic neurones and afferent sensory neurones at the site of injury to the nerve, which results in abnormal afferent impulses to the spinal cord, has been thought to be a key to the mechanism of post-traumatic pain syndromes.^{9,10} In our cases, how-

ever, burning pain persisted in the periphery even after resection of the injured part of the nerve, and coupling between sympathetic and afferent neurones could not occur. Moreover, burning pain was relieved in the areas from which degenerated nerves had been resected. These phenomena cannot be explained by previous theories.

We speculate that degenerated nerves in the periphery may stimulate the nociceptive endings of adjacent intact nerves, probably by releasing some endogenous algogenic substances such as potassium ions and ATP.¹¹ Activation of nociceptive endings generates pain sensation and may also result in the antidromic invasion of action potentials into adjacent branches of the nociceptor which, in turn, causes the release of neuropeptides from its terminals.¹²

Substance P is one of the representative neuropeptides which is thought to play a role in the transmission of pain sensation in the peripheral and central nervous systems, acting perhaps as a neurotransmitter or neuromodulator.¹³⁻¹⁵ We have previously shown that substance P has excitatory and sensitising effects on nociceptive afferent units.¹⁶ It also acts as a mediator of neurogenic inflammation in peripheral tissues by vasodilatation, extravasation of plasma and chemotaxis of neutrophils,¹⁷ which may extend along capillary vessels and stimulate adjacent nociceptive nerve endings. These noxious stimuli may induce further release of substance P from other nociceptors.¹⁸ Thus, a positive feedback system of nociceptive signals due to axon reflexes may be formed in the peripheral nervous system and play an important role in the persistence of burning pain (Fig. 5).

Substance P was found in the tissues around the degenerated peripheral nerves. We have observed previously that burning pain in the area innervated by an injured nerve was relieved by blocking adjacent intact nerves with local anaesthetic.¹⁹ These findings corroborate our hypothesis concerning the causal mechanism of post-traumatic neur-

Fig. 5

A diagram of a possible causal mechanism for post-traumatic neuralgia. Endogenous algogenic substances (EAS) released from degenerated peripheral nerves may stimulate nociceptive endings of adjacent intact nerves. Afferent nociceptive signals generate pain sensation and also induce the release of substance P (SP) from other nociceptors by axonal reflex.

algia. Further investigation is needed to identify endogenous algogenic substances in the degenerated nerves, and the presence of substance P around the adjacent intact nerves.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

1. **Sunderland S.** *Nerve and nerve injuries*. Edinburgh: E & S Livingstone, 1968.
2. **Thompson JE.** The diagnosis and management of post-traumatic pain syndromes (causalgia). *Aust NZ J Surg* 1979;49:299-304.
3. **Bonica JJ.** Causalgia and other reflex sympathetic dystrophies. In: *The management of pain*. Philadelphia: Lea & Febiger, 1953:913-78.
4. **Lankford LL.** Reflex sympathetic dystrophy. In: Green DP, ed. *Operative hand surgery*. New York, etc: Churchill Livingstone, 1982:539-63.
5. **Shumacker HB.** A personal overview of causalgia and other reflex dystrophies. *Ann Surg* 1985;201:278-9.
6. **Hodges DL, McGuire TJ.** Burning and pain after injury: is it causalgia or reflex sympathetic dystrophy? *Postgrad Med* 1988;83: 815-92.
7. **The International Association for the study of Pain Subcommittee on Taxonomy.** Classification of chronic pain, description of chronic pain syndromes and definitions of pain terms. *Pain* 1986;3:Suppl 28-30.
8. **Seddon SH.** *Surgical disorders of the peripheral nerves*. Edinburgh: Churchill Livingstone, 1975:139-53.
9. **Barnes R.** The role of sympathectomy in the treatment of causalgia. *J Bone Joint Surg [Br]* 1953;35-B:172-80.
10. **Blumberg H, Janig W.** Clinical manifestations of reflex sympathetic dystrophy and sympathetically maintained pain. In: Wall PD, Melzack R, eds. *Textbook of pain*. Edinburgh: Churchill Livingstone, 1994: 685-98.
11. **Rang HP, Bevan S, Dray A.** Nociceptive peripheral neurons: cellular properties. In: Wall PD, Melzack R, eds. *Textbook of pain*. Edinburgh: Churchill Livingstone, 1994:57-78.
12. **Mayer RA, Campbell JN, Raja SN.** Peripheral neural mechanisms of nociception. In: Wall PD, Melzack R, eds. *Textbook of pain*. Edinburgh: Churchill Livingstone, 1994:13-44.
13. **Cuello AC, Polak JM, Pearse AG.** Substance P: a naturally occurring transmitter in human spinal cord. *Lancet* 1976;2:1054-6.
14. **Henry JL.** Effects of substance P on functionally identified units in cat spinal cord. *Brain Res* 1976;114:439-51.
15. **Oku R, Satoh M, Takagi H.** Release of substance P from the spinal dorsal horn is enhanced in polyarthritic rats. *Neurosci Lett* 1987;74: 315-9.
16. **Yamashita T, Cavanaugh JM, Ozaktay AC, et al.** Effect of substance P on mechanosensitive units of tissues around and in the lumbar facet joint. *J Orthop Res* 1993; 11:205-14.
17. **Lembeck F, Gamse R.** Substance P in peripheral sensory processes. *Ciba Found Symp*. London:1982;91:35-49.
18. **Yaksh TL.** Substance P release from knee joint afferent terminals: modulation by opioids. *Brain Res* 1988;458:319-24.
19. **Murakami H, Ishii S, Usui M, et al.** Peripheral nerve resection for the treatment of reflex sympathetic dystrophy. *Rinsho Seikei Geka* 1994;29:193-9.