

Prevention and Management of Painful Neuroma

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Abstract

Painful neuroma is a common sequela of peripheral nerve injury which is usually resistant to pharmacologic treatment and requires surgical intervention. The widely accepted methods of neuroma management prevent regrowth of nerve fibers, thus precluding any functional repair. The present study reviews the currently used methods and experimental approaches to prevent and cure neuromas developing after peripheral nerve injury. The main recommendations are as follows. Special care should be taken to minimize scar formation when operating on peripheral nerves. The laser or scissors transection methods should be used to cut the nerve rather than electrocoagulation or cryoneurolysis. Direct nerve reconstruction, or, if a gap occurs, nerve grafting, should be performed immediately after nerve injury. Surgical resection of recurrent neuroma followed by implantation of the nerve into the muscle or capping the nerve stump with epineural graft seems to be the most effective method of prevention.

Key words: neuroma, prevention, treatment, neuropathic pain, peripheral nerve

Introduction

Peripheral nerves are known to be capable of repairing their structure and restoring their function after injury, but complete recovery after peripheral nerve lesion rarely occurs in the clinical setting.⁷⁾ Recovery is most often impaired by persistent functional loss and by neuropathic pain. Neuropathic pain usually develops just after injury and may persist for weeks or even years, and is highly unpleasant and resistant to most therapeutic strategies, so clearly reduces the quality of life.⁵¹⁾

The mechanisms underlying neuropathic pain are not fully understood but are likely to be complex and include both central and peripheral mechanisms.²⁴⁾ The first symptoms can be attributed to local inflammatory reaction that can irritate the nerve endings.^{35,36)} Nerve transection triggers a cascade of various cellular and humoral events leading to clearing of the injury site. Macrophages and mast cells invade the lesion site, and produce inflammatory cytokines and factors promoting connective tissue scar formation.^{20,39,51)} Some of these cytokines and other factors, like histamine or serotonin, are widely accepted to be responsible for pain produc-

tion.⁴²⁾ However, the inflammatory reaction only lasts for a few weeks, whereas neuropathic pain is chronic, possibly due to the ectopic activity of sensitized C fibers, extra-recruitment of nociceptors, and abnormal spontaneous activity in regenerating nerve sprouts.^{6,31,35,36,51)} Recently, much attention has focused on neuromas and microneuromas developing at the injury site as the probable cause of neuropathic pain.²⁰⁾ Neuromas also often develop after diagnostic nerve biopsies.³⁾ Therefore, neuromas should be considered as a serious clinical problem, unresolved despite much progress in microsurgery and neuroscience.

Neuroma is a bulb-shaped thickening created by improperly and irregularly regenerating nerve fibers.¹¹⁾ The pathogenesis of neuroma development after nerve injury is not clear, but several mechanisms are widely accepted to be involved.⁵¹⁾ During wallerian degeneration, neurotrophic factors produced in the distal nerve stump diffuse and attract nerve fibers from many different directions.³⁹⁾ Moreover, the forming connective tissue scar additionally disperses these fibers.^{11,12,14)} Haphazardly arranged nerve fibers are known to produce abnormal activity that stimulates central neurons.⁴⁷⁾ This ongoing activity can be enhanced by mechanical stimulation, for example, from the constantly rebuilt scar at the injury site.^{31,35)} Up till now, the

best and practically only method of neuroma treatment has been surgical removal.^{11,16)} However, an extra-surgical procedure is required and the outcome is rarely satisfactory, as a piece of nerve has to be cut off and, most likely, replaced by graft. This may induce another neuroma and trigger multiple interventions.^{38,44,45,48)} Therefore, the techniques of neuroma prevention are currently under investigation.¹⁷⁾

The ideal technique of nerve repair should provide rapid and complete regeneration without side effects. Alas, despite much progress in neuroscience and microsurgery, the methods introduced so far are usually neither effective nor painless. Moreover, as reviewed in this article, some may even enhance neuropathic pain. It should be also noted that there are many nerve regeneration enhancement techniques, in which neuroma and pain development have not been studied.⁷⁾

Current Clinical Approaches

Nerve fiber outgrowth is widely considered to be identical with neuroma formation. The accepted clinical practice is to cover the nerve stump with a cap to prevent both neuroma development and regeneration. These caps can be autologous (formed of muscle, vein, fascia, bone canal, fatty tissue, etc.) or synthetic, made of silicone or collagens and other materials.^{11,13,23,28,32,37,39,45,47)} Implantation of the transected nerve into the muscle prevents neuroma formation and is used in clinical practice.^{13,32,45)} Experimental studies, however, revealed that under these conditions a different type of neuroma develops containing less connective tissue and formed mainly by sensory neurons. These neuromas, although smaller, are reported to be painful.³²⁾

Nerve fiber growth can also be hindered pharmacologically, by alcohol, steroids, formalin, pepsin, nitrogen mustard, hydrochloric acid, or phenol injection to the injury site or by selective dorsal root ganglion cell destruction.^{5,11,13,32,38,45)} Repeated procaine injection into neuroma has been recommended.⁴⁰⁾ Nerve stump ligation, electrocoagulation, or freezing also decreases the size of neuromas formed after injury.^{3,6,10,33,45)} Recently, some laser methods were proved to be effective for the prevention of neuroma formation.^{29,50)} Some techniques of neuroma formation prevention, like neurocampsis or wrapping the nerve stump with metal foil, have never been introduced into clinical medicine due to minor or no efficacy.^{13,32,44,45)} Others, like epineural flap technique and epineural grafting to cap the proximal nerve stump, are rarely used in clinical practice. Epineural graft seems to be

most effective (Fig. 1).⁴⁹⁾ However, all of these methods assume reduction in quality of life by preventing any restoration of nerve function.

An interesting technique of neuroma treatment was presented in 1976, which assumed the neuroma pain was due to the irritating influence of the surrounding scar and proposed a method of translocating the neuroma to an intact place.¹²⁾ However, the results were controversial as only post-amputation neuromas responded well to this technique. Nevertheless, this finding clearly shows that scar formation should be minimized in surgery of the peripheral nerves.

Experimental Approaches

In order to elaborate new techniques of neuroma prevention and treatment, various experimental approaches have been established in recent years (Table 1).^{8,10,14,21,22,48)} The most common one is sciatic nerve transection in rats.⁵⁰⁾ In this paradigm, neuroma formation at the end of nerve proximal stump can be observed as soon as 2 weeks following injury.^{21,32,51)} Studies on neuroma in animals required the elaboration of an experimental model of neuropathic pain. Autotomy is a term introduced for the behavior of self-mutilation of the denervated limb and is referred to the experimental equivalent of neuropathic pain.^{6,46)} Recently, some self-mutilating behaviors in humans were also suggested to be autotomy.⁵¹⁾ Neuroma in animal models is usually accompanied by marked autotomy.^{4,50,51)} Studies on autotomy in animals have provided additional data about neuropathic pain and neuroma development as well as possible treatment.⁶⁾

Special attention has been paid to neurotrophic factors, which regulate nerve fiber growth. Local blocking of nerve growth factor (NGF) activity by application of antibody against trkA receptor (trkA-IgG) to the sciatic nerve transection site prevents both traumatic neuroma formation and neuropathic pain development in rats.¹⁷⁾ In our studies, NGF did not induce neuroma formation when applied in excess to the injury site, whereas brain-derived neurotrophic factor (BDNF) strongly enhanced haphazard growth of nerve fibers and autotomy. Inactivation of BDNF by specific antibody in our experiment resulted in decrease in neuroma and neuropathic pain development (unpublished observations). BDNF is up-regulated by NGF after nerve lesioning.^{1,42)} BDNF concentration within the sensory neurons can also be increased by exogenous administration of NGF and decreased by anti-NGF antibodies.^{18,31,35,41,43)} Most neurons that respond to NGF treatment by increasing BDNF levels also

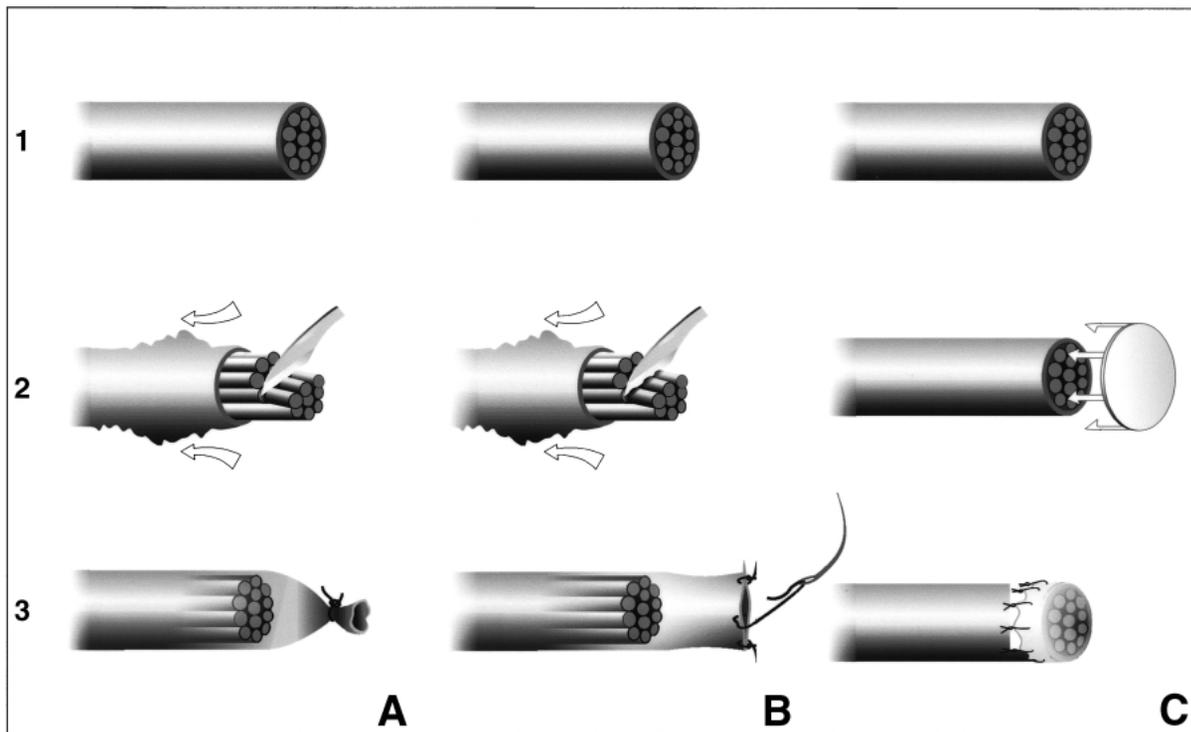


Fig. 1 Schematic presentation of consecutive steps of various nerve stump capping methods: 1, nerve transection; 2, nerve stump preparation (A and B, nerve sheath must be slid off, then a piece of the nerve is removed to prepare a sleeve-like fragment of epineurium; C, cap can be formed of any autologous tissue, sutured to the epineurium); 3, the end of epineurium can be tied up (A) or sutured (B and C).

Table 1 Some of recently used surgical approaches in prevention of posttraumatic neuroma formation

Author (Year)	Technique or method	Species	Outcome
Gorkisch et al. (1984) ¹⁰⁾	centrocentral nerve union with autologous graft	human	good
Wood and Mudge (1987) ⁴⁸⁾	direct primary coaptation of two proximal nerves	human	good
Gonzalez-Darder et al. (1987) ⁹⁾	microfascicular ligation	rats	poor
Low et al. (1999) ²²⁾	end to side anastomosis of transected nerves	rats	good
Low et al. (2000) ²¹⁾	implantation of a nerve ending into a vein	rats	good
Kakinoki et al. (2003) ¹⁴⁾	nerve stump insertion into vein	rats and human	excellent

express *trkA*.^{30,31,34)} It is likely that NGF inactivation attenuated neuroma development and autotomy by prevention of BDNF up-regulation. These results indicate possible clinical applications for neurotrophins and their antibodies in neuroma and neuropathic pain management.

To develop a safe method to enhance neuronal regeneration, we applied various mixtures of neuroactive substances by means of autologous connective tissue chambers sutured to the proximal stump of the nerve in rats (Fig. 2).^{19,26,27)} We found that clothing the proximal stump of a transected nerve with a dead-ended connective tissue chamber

filled with fibrin significantly reduced autotomy behavior and prevented neuroma formation as well as promoted nerve fiber outgrowth.¹⁹⁾ It is likely that the chamber walls created a barrier for the inflammatory cytokines diffusing from the surrounding tissues. Moreover, the fibrin network could have formed a convenient scaffold for regenerating, directing, and promoting parallel arrangement of fibers. These results strongly support the hypothesis that adverse surrounding conditions are at least partly responsible for painful neuroma formation. We have also investigated the role of peripheral nerve extracts in nerve regeneration.²⁶⁾ Such

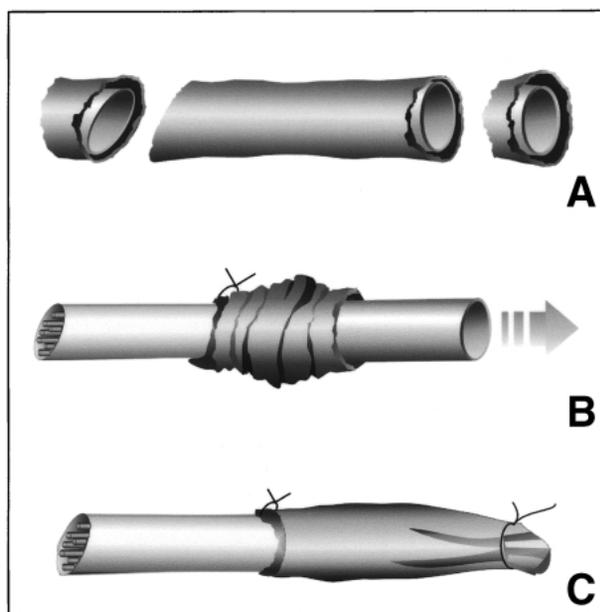


Fig. 2 Consecutive steps of connective tissue chamber processing and implantation: **A**, silicone tube, implanted subcutaneously, becomes covered with connective tissue; **B**, the tissue surrounding the tube is sutured to the proximal stump of transected nerve, then the tube is removed; **C**, the free end of the chamber is tied up.

extracts enhance both regeneration and autotomy as well as promote neuroma development.¹⁹⁾ Inactivation of BDNF or NGF in these extracts reduced autotomy.²⁷⁾ Recently, the BDNF influence on nerve repair as well as pain sensations was shown to be dose-dependent.²⁾

Nerve injury may not be accidental, but may result from medical procedures, so the effect of different ways of nerve transection on neuroma formation were studied. Neuromas developed more often after cryoneurolysis and electrocoagulation than after scissors cut or tight ligation of the nerve in rats. The lowest incidence of neuroma was observed when CO₂ laser transection was performed.⁵⁰⁾

Recently, a new but very simple modification of nerve surgery has been under investigation. Oblique, instead of perpendicular, transection and suturing of the nerve markedly improves functional outcome and morphological features of regeneration.¹⁵⁾ In previous studies, we found not only better regeneration but also decreased neuroma formation after oblique nerve cutting.²⁵⁾ The differences were especially striking when the oblique transection was performed for nerve grafting. The possible explanation of this phenomenon is that the longer fibers

provide a kind of growth pathway for the shorter fibers.

The last but not least issue we would like to discuss is whether the chronic phase of neuropathic pain after peripheral nerve injury can be exclusively attributed to neuroma formation. Our studies revealed that nerve fibers fitted with autologous connective tissue chambers filled with fibrin regenerated with no neuroma. However, we observed autotomy behavior in the same animals starting on the 5th day after nerve injury and persisting till the end of the 7-week follow-up period. In order to elucidate the mechanisms of that phenomenon, we blocked BDNF activity in the chambers and found marked autotomy decrease. Interestingly, extra-BDNF applied to the chambers resulted in both neuroma formation and autotomy increase (unpublished observations). The discrepancies between neuroma development and autotomy were also noted in an investigation of the influence of anesthesia on neuropathic pain model.⁹⁾ Autotomy was markedly minor if the nerve transection was preceded by local anesthesia. Neuroma formation was not changed by this procedure. Therefore, we presume that neuroma is not the only source of chronic pain after peripheral nerve injury.

Nevertheless, the avoidance of neuroma formation is a necessary, if not the only, condition to eliminate neuropathic pain. The present review of experimental data presents different promising approaches for neuroma prevention and treatment. The clinical efficacy remains to be evaluated.

Clinical Recommendations

Various surgical procedures have been used for neuroma treatment and prevention, but none has been widely accepted as the standard management. The main problem is that the studies published so far are often based on small groups of patients, so further intensive efforts should be undertaken to establish the effectiveness and safety. However, the following points can be recommended as applicable to neuroma management at present. Special care should be taken to minimize scar formation when operating on peripheral nerves. The laser or scissors transection methods should be used to cut the nerve rather than electrocoagulation or cryoneurolysis. Direct nerve reconstruction, or, if a gap occurs, nerve grafting, should be performed immediately after nerve injury. Surgical resection of recurrent neuroma followed by implantation of the nerve into the muscle or capping the nerve stump with epineurial graft seems to be the most effective method of prevention.

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Commentary

The prevention or eventually the management of neuromas is a challenging task that will be encountered by most neurosurgeons now and then, and will present many difficulties. This concise review is an excellent presentation of the somewhat limited options we have. Simple techniques such as the use of scissors appear to emerge superior to cryosurgery or electrocoagulation. The authors are to be congratulated on this summary for focussing our attention on prevention rather than treatment.

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Painful neuroma is a common sequela of peripheral nerve injuries due to various causes, and is usually resistant to medication. To remove the intractable pain, surgical intervention to the injured nerve is necessary. As authors stated in this paper, the mechanism underlying neuropathic pain secondary to neuroma is not fully understood, and there are no widely accepted standard managements of painful neuromas because of the lack of fundamental experiments treating this problem and clinical studies on large numbers of patients. Nowadays, after the ampu-

tation of the painful peripheral nerve neuromas, coverage of the proximal nerve end with vascularized soft tissue, nerve stump transplantation into the vein, implantation of the proximal nerve stump into the muscle, coverage with the atelocollagen tube, and so on, have been tried in clinical practice. But it is difficult to get complete pain relief. The authors are recommending clinically applicable management from the review of literature regarding this difficult problem and their experiments.

In Japan, this problem is rarely treated in the department of neurosurgery, but mainly in the department of orthopedics or plastic surgery. This paper will emphasize the importance of prevention and management of painful neuroma to young neurosurgeons in Japan.

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