REVIEW ARTICLE
Reducing and Eliminating Neuropathic Pain

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Neuropathic pain is initiated or caused by a primary lesion or dysfunction in the central and/or peripheral nervous systems, including infection, trauma, metabolic abnormalities, and nerve compression, and is typically accompanied by hyperalgesia and allodynia. Neuropathic pain can be mild to excruciating, debilitating, difficult to manage, cause depression, decrease the quality of life, require extremity amputations, and has a variety of clinical symptoms. It effects up to 5% of the population, 70% of patients with advanced cancer and inflammatory pathologies, and 95% of patients with spinal cord injuries. The primary treatments of neuropathic pain are antidepressants, anticonvulsants, local anesthetic/topical agents, and opioids. The rapidly evolving symptom- and mechanism-based approaches to the treatment of neuropathic pain holds promise for improving the quality of life of patients with neuropathic pain. However, pharmacological treatment of the symptoms are difficult because of the limited understanding of the underlying causes of the pain, and the systemic levels of multiple side effects induced by various agents at an effective dose. Further, neuropathic pain is often refractory to conventional analgesic treatments, with most patients obtaining only partial relief with these agents, and with tolerability or side effects often limiting their use. Alternative treatments to pharmacology include peripheral or neuraxial nerve blockade, and implanted cortical or spinal cord stimulators. However, the great need remains for development of new and more effective approaches to reducing neuropathic pain. This review examines various approaches currently used for treatment of neuropathic pain and potential new and more effective approaches.

Key words: Chronic pain, Nerve injury, Peripheral nerve trauma

Neuropathic pain is defined as chronic pain initiated or caused by a primary lesion or dysfunction in either the central or peripheral nervous systems, including infection, trauma, metabolic abnormalities, and nerve compression. It is characterized by spontaneous burning pain and/or ongoing pain with accompanying hyperalgesia and allodynia (1-2). Traumatic peripheral nerve injury also increases the excitability of nociceptors in and around nerve trunks and involves components released from nerve terminals (neurogenic inflammation) and immunological and vascular components (pro-nociceptive mediators) from cells resident within or recruited into the affected area (3-4).

Neuropathic pain is difficult to manage, devastating, debilitating, causes depression, decreases quality of life, and has a variety of clinical symptoms. It has been estimated that up to 5% of the population suffers, 70% of patients with advanced cancer and inflammatory pathologies, and about 95% of patients with spinal cord injuries suffer neuropathic pain (5-7).

The primary agents used to treat neuropathic pain are antidepressants, anticonvulsants, local anesthetic/topical agents, and opioids (8-10). The efficacy of these treatments, excepting opioids, was discovered serendipitously. The rapidly evolving symptom- and mechanism-based approach to the treatment of neuropathic pain holds promise for improving the quality of life of patients with neuropathic pain.

The pharmacological treatment of the symptoms of painful neuropathy is difficult, because of the limited understanding of the underlying causes of the pain, and the systemic levels of multiple side effects induced by various agents at an effective dose. Further, neuropathic pain is often refractory to conventional analgesic treatments, with most patients obtaining only partial relief with these agents and the tolerability of side effects is often limiting (11-12). Although most pharmacological agents have been used alone, some have been found to be more effective when combined. In addition to pharmacological interventions, there are alternative treatments including peripheral or neuraxial nerve blockade, implanted spinal cord stimulators.

There is an extensive and exciting literature dealing with the biophysics of pain receptors, and the mechanisms

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of their activation and inactivation. Discussing this area is beyond the scope of this review. Therefore, we have restricted ourselves to an examination of some, but not all of the many and varied pharmacological and cellular approaches being pursued to reduce or eliminate neuropathic pain. What is clear is that although many techniques are effective, few are ideal. Still, novel compounds and new regimens are emerging for drug treatment to influence activity-dependent long-term changes in pain transducing and suppressive systems (pain matrix). However, work that is far more extensive is required to develop an approach with consistent, permanent and effective analgesic effects.

Neuropathic Pain

Complete or even partial peripheral nerve injury leads to the sensitization of nociceptors in the skin to mechanical and heat stimuli (13-14). This nociceptor sensitization can contribute to neuropathic pain (13, 15). Despite many decades of drug development, effective therapies for reducing neuropathic pain remain elusive thus, neuropathic pain, caused or initiated by a primary lesion in the peripheral or central nervous system, can result in a dramatic reduction in the patient's quality of life. The expression neuropathic pain covers a heterogeneous group of conditions including peripheral neuropathy, complex regional pain syndrome, trigeminal neuralgia and central pain. Neuropathic pain poorly responds to conventional analgesics. However, with appropriate therapy, a significant proportion of patients experience a substantial pain reduction.

The term "spinal neuropathic pain" describes chronic neuropathic pain resulting from the aggravation of spinal nerve roots by scar tissue, and is different from the pain of spinal cord injury (16). Spinal neuropathic pain involves longstanding back and radicular pain (nerve root pain, predominantly in the limbs) caused by scar or inflammatory tissue around the nerve roots. The cause of the pain is at least in part due to spinal cord adhesions that compromise biomechanics of the nerve. Since movement can generate additional pain, physiotherapy for such patients may induce increased pain. Therefore, physical therapy for such patients must be tailored to their situation (16).

Elimination of Neuropathic Pain by Target Reinnervation

For years it has been hypothesized that reduction in neuropathic pain following a nerve trauma is in part correlated to the extent of neurological recovery, with the greater the recovery the greater the reduction or elimination of neuropathic pain (17-22). However, neuropathic pain can persist even following good nerve re-innervation, or when there is no apparent loss of neurological function (21-23). In the case of peripheral neuropathies or amputations in which there is no peripheral target to reinnervate, how can the neuropathic pain be reduced or eliminated? Therefore, questions remain as to whether there is really a correlation between the extent of neuropathic pain and the extent of nerve reinnervation, and how can neuropathic pain be reduced or eliminated in the many types of cases in which it exists.

Peripheral plus Central Nervous System Involvement in Neuropathic Pain

A unilateral nerve section and ligation leads to a bilateral decrease in nociceptive threshold (24). This bilateral development indicates the both the central and peripheral nervous systems are involved in the establishment and maintenance of chronic pain (25-26).

Mediators and Blockers of Neuropathic Pain
Nerve Hyperexcitability

Nerve injury frequently triggers hyperexcitability and the ectopic initiation of action potentials in primary afferent axons leading to neuropathic pain (22-23). Primary afferent hyperexcitability results from injury causing modifications of sodium channel turnover in neural membranes, and sodium channels to accumulate in preterminal axolemma, neuroma end bulbs and DRG somata (27-29). These changes appear to occur because of the myelin removal and the loss of the targets the axons innervate, which restrict sodium channel accumulation, which in turn prevents afferent hyperexcitability in injured nerve (27).

Sodium Channel Blockers

The voltage-gated sodium channels that underlie the action potential are main targets for clinically useful drugs in the pain therapy, especially because they have therapeutic efficacy with doses are far below those that impair nerve impulse propagation or cardiovascular function (30-32). Lidocaine and tramadol, both sodium channel blockers, provide pain relief against neuropathic pain in patients with spinal cord injury (33-34). Intravenous lidocaine administration is also effective for opioid refractory pain and is well tolerated (35). However, direct NMDA receptor antagonists and high-affinity channel blockers show limited therapeutic potential (36).

Tetrodotoxin-resistant and tetrodotoxin-sensitive Na+ channels contribute to the abnormal spontaneous firing in dorsal root ganglion neurons, which is associated with neuropathic pain (37). The actions of the anti-nociceptive agent ralfinamide results from its inhibition of tetrodotoxin-resistant and tetrodotoxin-sensitive sodium currents in rat dorsal root ganglion neurons (37).

Efforts have also focused on glycine/d-serine co-agonist function, including partial glycine agonists, pain in the antagonist dose range, for the treatment of neuropathic (36). An alternate approach to partial glycine agonists is to inhibit the uptake carriers for glycine and thus potentiating the lifetime of synaptic glycine (36).

Glial Cells

Activated glial cells (microglia and astroglia) in the spinal cord play a major role in mediating enhanced pain states by releasing proinflammatory cytokines and other substances thought to facilitate pain transmission (38-46). Intrathecal administration of minocycline, a selective inhibitor of microglial cell activation, inhibits low threshold mechanical allodynia (42, 47). However, its ameliorating influences are short-lived, suggesting that microglial activation is involved in initiating, rather than maintaining, enhanced neuropathic pain responses (47).

Nerve transection leads to CNS neuroimmune activation and subsequent cytokine expression (48-50), which leads to the stimulation of membrane-bound microglial Toll-like receptor 4 (TLR4) and painful neuropathy (51). This it turn leads to hypersensitivity in a mouse and rat model of neuropathy, which is prevented by blocking TLR4 (51).

Activation of extracellular signal-regulated kinase (ERK), a mitogen activated-protein kinase (MAPK), in dorsal horn and DRG neurons contributes to inflammatory pain by transcription-dependent and -independent means and with different time courses (52).

5HT / Serotonin

The intrathecal injection of a chronically applied, low local dose of 5-hydroxytryptamine (serotonin) near the dorsal horn reverses the development of chronic neuropathic pain (53-54). This activation cooperates with nociceptive stimulation, paradoxically causing analgesia, and inverse tolerance develops so that the resulting analgesia increases (54). This action against nociceptive pain is as effective as large doses of high-efficacy mu-opioid receptor agonists.

Opiates

Opioids are typically reserved for moderate to severe pain that cannot be relieved by the non-steroidal anti-inflammatory drugs (NSAIDs). Opioids are often used in combination with other adjuvants or other analgesic agents. The advantage of opioids is the lack of a ceiling effect of the pure mu opioid agonists. Their disadvantages are a series of mechanism-based opioids-related side effects (e.g., nausea, drowsiness, constipation) and the potential issue of their abuse and misuse. Each patient needs to undergo a comprehensive evaluation and receive education on the treatment. The physician must be well conversant with the differential diagnosis and definitions of physical dependence, tolerance, pseudotolerance, aberrant behaviors, addiction, and pseudoaddiction. No specific opioid drug is intrinsically "better" than the others are. Opioid rotation refers to the switch from one opioid to another when the degree of analgesia obtained is limited by the persistence of adverse effects or the occurrence of clinically relevant tolerance (55).

Transdermal vs. Oral Delivery

As chronic pain increases special consideration is required with respect to drug delivery, drug interactions and adherence. In particular, patients with chronic neurological diseases often require multiple administrations of drugs during the day to maintain constant plasma medication levels, which in turn increases the likelihood of poor adherence. Transdermal delivery of opioids fentanyl, morphine and buprenorphine play an important role in the management of neuropathic pain (56-57) with their benefits comparable to those seen with oral formulations.

NMDA + Opioids

There are mixed results from many pre-clinical and clinical studies as to whether the addition of N-methyl-D-aspartate (NMDA) receptor antagonists, such as dextromethorphan (DM), to opioid analgesics, such as morphine (MS), enhances the analgesic effects and prevent the tolerance that may result from chronic opioid administration. A recent large study determined that no statistically significant differences between treatment groups in any primary or secondary efficacy variables were demonstrated, suggesting that adding the NMDA antagonist, dextromethorphan, to opioids does not add any clinical benefit (58).

The available drugs to treat neuropathic pain have incomplete efficacy and dose-limiting adverse effects. Gabapentin and morphine are effective analgesics in patients with painful diabetic neuropathy or post therapeutic neuralgia (59-60). However, when combined they achieve better analgesia at lower doses of each drug than either as a single agent (60-62).

In some patients with long-lasting or recurrent pain, severe enough to markedly reduce their quality of life, and for whom no other more effective and less risky therapy is available, opioid analgesics may reduce intensity of pain, increase functioning and improve quality of life for prolonged periods. The type of pain and pain history of the patients do not predict reliably the chance of long-term success or risk of complications from opioid therapy. However, the outlook for successful long term opioid therapy is better in a patient with a stable psychosocial situation having nociceptive type pain that is markedly relieved by a

moderate dose of a long lasting oral or transdermal opioid, than a patient from a complex and unstable psychosocial background having neuropathic type pain that is relieved only partly by a higher dose of a potent opioid.

Following sciatic nerve ligation, some pain-related brain nuclei of neuropathic pain model rats show a significant increase in the opioid receptor like 1 receptor (ORL(1) mRNA expression, which last for 2 weeks. Nociceptin/ orphanin FQ (N/OFQ), the endogenous ligand of ORL(1), plays an important role in nociceptive transmission of neuropathic pain through its receptor.

Ketamine + Morphine

Low doses of epidural ketamine combined with morphine and bupivacaine increases their mean duration of satisfactory analgesia without severe adverse effects and restores quality of life when traditional therapy fails (63-64). Ketamine plus morphine is also recommended when morphine alone is no longer effective (64).

Methadone

Methadone appears to have unique properties, including N-methyl-D-aspartate antagonist activity, which may make it especially useful in the management of intractable neuropathic pain (65-67).

Proenkephalin A

Local overproduction of proenkephalin A-derived peptides in trigeminal ganglion sensory neurons evokes a potent antiallodynic effect through the stimulation of mainly peripherally located opioid receptors (68-69). This finding suggests that targeted delivery of endogenous opioids may serve to treat some severe forms of neuropathic pain.

Anti-depressants and Anti-Epileptics

Antidepressants and antiepileptic drugs are useful in the treatment of neuropathic pain (70-71). Tricyclic antidepressants are the most cost-effective agents, but second-generation antiepileptic drugs are associated with fewer safety concerns in elderly patients (72). Recent evidence suggests that duloxetine and pregabalin have modest efficacy in patients with fibromyalgia (73).

Neuropathic pain conditions are characterized by pathological changes in sensory pathways, which favor action potential generation and enhanced pain transmission. Although sometimes difficult to treat with conventional analgesics, antiepileptics can relieve some symptoms of neuropathic pain (74).

Antidepressants that variously affect both noradrenalin and serotonin levels have more potent and efficacious antinociceptive effects than serotonin reuptake inhibitors (SSRIs) (as exemplified by citalopram), against a range of pain-like behaviors in an animal model of neuropathic pain (75-76).

Anti-Convulsants

Pregabalin and Gabapentin are anticonvulsant drugs used for the treatment of adults with peripheral neuropathic pain and inflammatory pain in animal and human studies. They result in significant decreases in pain scores in about 50% of the patients (77-78). Gabapentin administration was associated with sedation and anxiolysis but not lightheadedness, dizziness, nausea, or vomiting (78).

Calcium Channels

Hyperexcitability of axotomized dorsal root ganglion neurons is thought to play a role in neuropathic pain (79-80). Numerous changes in ionic channels expression or current amplitude are reported after an axotomy. One of the most significant changes is an increased intracellular calcium concentration, which leads to increased excitability of axotomized sensory neurons (81). Pregabalin, a new drug that interacts with the alpha(2)-delta protein subunit of the voltage-gated calcium channel, is an efficacious in reducing calcium channel-induced pain (82).

Anti-inflammatories

Spinal cord glia and glial pro-inflammatory cytokines are important contributors to neuropathic pain. Acetaminophen and anti-inflammatories are first-line drugs for mild to moderate pain (83-84). The anti-inflammatory cytokine interleukin-10 (IL-10) suppresses the production of pro-inflammatory cytokines and intrathecal administration of IL-10 transiently prevents and reversing neuropathic pain (83-84). Similarly, peripheral nerve injury results in a significant increase in IL-6 protein and messenger RNA in the rat spinal cord associated with and neuropathic pain (85). Administration of antibodies that neutralize interleukin-6 block the pain (85).

Monoamine Uptake Inhibitors

Chronic intrathecal administration of the selective uptake inhibitors of the monoamines noradrenalin and serotonin (antidepressants) provide antiallodynic effects against neuropathic pain due to ligation of spinal nerves (75, 86-88).

Vanilloid Receptor

The vanilloid receptor 1 (VR1) is highly localized on nociceptive neurons and their peripheral and central processes (89). Potent and selective antagonists of the vanilloid receptor 1 (VR1) effectively relieve acute and chronic inflammatory pain and post-operative pain (90-91).

Resiniferatoxin (RTX), an excitotoxic VR1 agonist, kills VR1-positive neurons (92-93). Intraganglionic RTX infusion ablates VR1-positive neurons and selectively eliminates hyperalgesia and neurogenic inflammation without affecting tactile sensation and motor function (92).

Neurotrophic Factors
CGRP and NGF
The calcitonin gene-related peptide (CGRP) is involved in neuropathic pain (94-96), and is up-regulated in a small population of large- and medium-sized primary sensory neurons after peripheral nerve injury. In adult animals, the expression of CGRP is regulated by nerve growth factor (NGF). After nerve injury, NGF is up-regulated at the injury site for several weeks, and this up-regulation contributes to the onset of neuropathic pain (94).

Anti-NGF therapy profoundly reduces bone cancer pain and the accompanying increase in markers of peripheral and central sensitization (97).

BDNF Sequestering
The binding of spinally released BDNF to the TrkB receptor following nerve ligation results in the development of a neuropathic pain (39, 98-99). However, the thermal hyperalgesia and tactile allodynia are completely suppressed by repeated intrathecal injection of the TrkB protein, which sequesters endogenous brain-derived neurotrophic factor (BDNF) (99).

GDNF
Glial cell line-derived neurotrophic factor (GDNF) both prevents and reverses sensory abnormalities that develop in neuropathic pain models, without affecting pain-related behavior in normal animals (100-101). GDNF acts by reducing ectopic discharges within sensory neurons after nerve injury. This may arise because of the reversal by GDNF of the injury-induced plasticity of several sodium channel subunits (100). Chronic nerve constriction injury in the rat results in significant increases in protein and mRNA levels of GDNF and GFRalpha-1 in the dorsal root ganglions (DRG), and of GDNF protein in the spinal dorsal horn (102). These increases are further enhanced by electro-acupuncture, which leads to potent analgesia of neuropathic pain (103).

Tumor necrosis factor-alpha (TNF-?) and norepinephrine (NE)
Following trauma, and with the onset of neuropathic pain, brain neurons show increased levels of tumor necrosis factor-alpha (TNF), and the TNF inhibits norepinephrine (NE) release dependent on alpha(2)-adrenergic activation(44). However, the enhanced inhibition of NE release by TNF at the peak hyperalgesia (day-8) changes to a facilitation of NE release at later times, which parallels the decreased neuron production of TNF (74). Chronic antidepressant drug administration also lead to similar results (74). Therefore, adrenergic drugs inhibit increased pain sensitivity (hyperalgesia) by decreasing TNF production, thereby inducing increased NE release (104-105). Thus, while TNF directs the development of hyperalgesia, it is also involved in the resolution of pain, which points to a possible mechanism for management of chronic pain.

Neurotransmitters
Action potentials generated in nociceptors and injured nerve fibers release excitatory neurotransmitters at their synaptic terminals such as L-glutamate and substance P and trigger cellular events in the central nervous system that extend over different time frames. Short-term alterations of neuronal excitability, reflected for example in rapid changes of neuronal discharge activity, are sensitive to conventional analgesics, and do not commonly involve alterations in activity-dependent gene expression.

GABA
The gamma-amino butyric acid (GABA) transporter inhibitor has anti-thermal hyperalgesia and anti-tactile allodynia effects in neuropathic rats (106-107).

Nociceptin/orphanin FQ N/OFQ receptor antagonist
Nociceptin, also called orphanin FQ (N/OFQ), is the natural ligand of the opioid receptor-like 1 receptor (ORL-1), and is classified as the fourth member of the opioid family of receptors and named OP(4). Systemic and spinal administration of the nociceptin receptor antagonist JTC-801 exerts anti-allodynic and anti-hyperalgesic effects in rats (108). This suggests that the nociceptin system is involved in the modulation of neuropathic pain and inflammatory hyperalgesia (108-109).

Glutamate
Changes in glutamatergic neurotransmission within the spinal cord, resulting from the expression and efficacy of glutamate transporters following nerve injury, contributes to hyperalgesic and allodynia (110-112). This results from spinal nerve ligation producing attenuated glutamate uptake activity in the deep dorsal and ventral horn, the projection regions of excitatory, pain transmitting primary afferent neurons that utilize glutamate as an excitatory neurotransmitter (111).

Peripheral and central metabotropic glutamate receptors (mGluRs) play a role in pain nociceptive synaptic transmission during inflammatory or neuropathic pain

states (106, 113-114). Therefore, mGluR5 antagonists provide a therapeutic treatment of post-operative pain (106, 114-116).

Acetylcholine

Neuronal acetylcholine receptor (nAChR) agonists have anti-allodynic effect (117-118). However, spinal nerve ligation is associated with a marked down regulation of functional nAChRs in DRG somata in parallel to development of allodynia (119).

Adrenoreceptor

Systemic administration of the alpha1-adrenoreceptor (AR) antagonist prazosin attenuates in a dose-dependent manner cold allodynia in a rat tail model of neuropathic pain (120). However, the pain is exacerbated by alpha2-AR antagonist yohimbine (106).

Peripheral axotomy induces the expression of plasminogen activators in dorsal root ganglia (DRG) neurons, which play crucial roles in generating neuropathic pain (121-122). The plasminogen activator inhibitor-1 and -2 (PAI-1 and PAI-2) mRNA, endogenous inhibitors of tPA and uPA, are induced in the DRG following sciatic nerve transection and may act in an autocrine manner to modulate extracellular proteolytic activity after nerve injury (121).

Cannabinoid: CB1 and CB2-cannabinoid-receptor agonist

Cannabinoids are potent therapeutic agents in chronic pain management. Central and systemic administration of natural, synthetic and endogenous cannabinoids produce antinociceptive and antihyperalgesic effects in both acute and chronic animal pain models. Much of the existing data suggest that the analgesic effects of cannabinoids are mediated via neuronal CB1 receptors, CB1-receptor stimulation modulates the activity of the vanilloid receptor 1 (VR1) transient receptor potential in cultured rat DRG cells. CB1 analgesia could act by inhibiting either capsaicin-induced Ca(2+) influx, or potentiating capsaicin-induced substance-P release through involvement of a cyclic-AMP-dependent PKA pathway (59).

However, there is increasing evidence for a role for peripheral CB2 receptors, which are expressed preferentially on immune cells (123). Chronic pain models associated with peripheral nerve injury, but not peripheral inflammation, induce CB2 receptor expression in a highly restricted and specific manner within the lumbar spinal cord and the appearance of CB2 expression coincides with the appearance of activated microglia (123). Selective cannabinoid CB2 receptor agonists reduce neuropathic pain and inhibit acute inflammatory responses. These influences are without eliciting central nervous system-mediated side effects, associated with non-selective cannabinoid agonists, since the CNS lacks CB(2) receptors (124-126).

Alternative Techniques

Surgical interventions used to reduce neuropathic pain include nerve resection (127), neuroma removal (128-131), and dorsal root lesions (131-137). However, further studies are required to examine the efficacy combinations of several methods using analgesics, surgery and introduction of compounds such as neurotrophic factors in reducing neuropathic pain.

Caloric Intake

Long-term caloric restriction leads to significant hypoalgesia (138).

Electrical Stimulation

An alternative treatment to pharmacological interventions to reduce neuropathic pain is electrical stimulation of peripheral nerves (136, 139-142), in the brain (136, 143-145), and the spinal cord (145-152).

Electrical stimulation of the spinal cord stimulation provides a significant (>50%) and long-lasting (>1 year) reduction in chronic neuropathic pain in the majority of patients tested (124, 136, 152-153). Spinal cord stimulation also reduces by half the number of patients who require opiate analgesics (151-152).

Frequency-modulated electromagnetic neural stimulation results in a significant reduction in painful diabetic neuropathy (150).

Electrical stimulation of the motor cortex produces significant transient inhibition of the responses of spinal cord dorsal horn neurons to higher intensity mechanical stimuli without affecting their response to an innocuous stimulus (154-155). Although the magnitude and duration of the benefit are highly variable, with a significant percentage of patients losing pain relief over time, intensive reprogramming can recapture the benefit of MCS in patients who have lost pain control (155).

New Alternatives for Alleviating Neuropathic Pain

Although many pharmacological approaches reduce or eliminate neuropathic pain, each alone has its limitations. More extensive studies are required to examine the efficacy combinations of several analgesics and other compounds acting in concert. However, pharmacological treatment of the symptoms of painful neuropathy is difficult because of the limited understanding of the underlying causes of the pain, and the multiple and sometimes incapacitating

side effects of agents at their effective doses. Since neuropathic pain is often refractory to conventional analgesic treatments, most patients obtain only partial relief with these agents, and their tolerability is often limiting, alternative non-pharmacological approaches to treating neuropathic pain are still required.

We recently completed a small IRB-approved clinical study examining a novel approach for reestablishing neurological function following peripheral nerve trauma (unpublished results). The technique induced significantly more neurological recovery than the clinical "gold standard" using sensory nerve grafts. However, in addition to inducing restoration of sensory and motor function, the technique also reduced or eliminated the neuropathic pain in each patient, including two who were suffering excruciating neuropathic pain.

The technique involves the resection of the central nerve stump to the point where the nerve appears anatomically normal to visual inspection. Similarly, the distal nerve stump is trimmed until it looks to visual inspection to be free of scar tissue. Although trimming the nerve ends creates a longer nerve gap, it is essential to remove the scar tissue, which otherwise inhibits axon regeneration. A sheet of resorbable bovine pericardium collagen is then sewn into a tube slightly larger than the diameter of the nerve to be repaired. The nerve ends are then secured with sutures about 3-mm into the ends of the collagen tube. The collagen tube is then filled with a 3-dimensional fibrin matrix of autologous platelet-rich fibrin. The fibrin provides a matrix through which to regenerate, while the platelet-released factors that promote axon regeneration.

All the patients recovered from minimal to complete neurological function. In addition, 88% of the patients had a complete elimination in the neuropathic pain they suffered prior to the surgery, while one patient had his excruciating neuropathic pain reduced to tolerable.

Part of the elimination of neuropathic pain may have resulted from the damaged axons establishing appropriate neurological connections. However, we found no apparent correlation between the extents of neurological recovery and the reduction or elimination of neuropathic pain. In the case of one patient with excruciating neuropathic pain, his pain was reduced to tolerable, even though his neurological recovery was the least of all the patients. These results indicate that, although increasing neurological recovery may influence the reduction or elimination of neuropathic pain, additional other aspects of the technique probably played the major role in reducing and eliminating the neuropathic pain.

As stated earlier, neuropathic pain is in part attributed to neuroma and scar tissue formation of the proximal nerve stump. In addition to inducing neuropathic pain neuroma and scar tissue prevents axon regeneration (156). Such scars are produced by invading fibroblasts and this migration of fibroblasts is blocked by collagen tubularization (157). Therefore, we hypothesize that part of the reduction in neuropathic pain results from the collagen tube bridging the nerve gap reducing fibroblast invasion, neuroma and scar formation and thus the hyperexcitability of the lesioned axons.

The neuropathic pain may also be reduced by the platelet-released neurotrophic and wound healing factors. These factors could act directly on the severed axons and their growth cones to reduce the excitability of the damaged nociceptive axons. Such a reduction in excitability would reduce or eliminate spontaneously evoked action potentials that propagate along the axons of the nociceptive neurons and give rise to pain.

An alternative mode of action is that the platelet-released factors may be picked up by the damaged axons and be
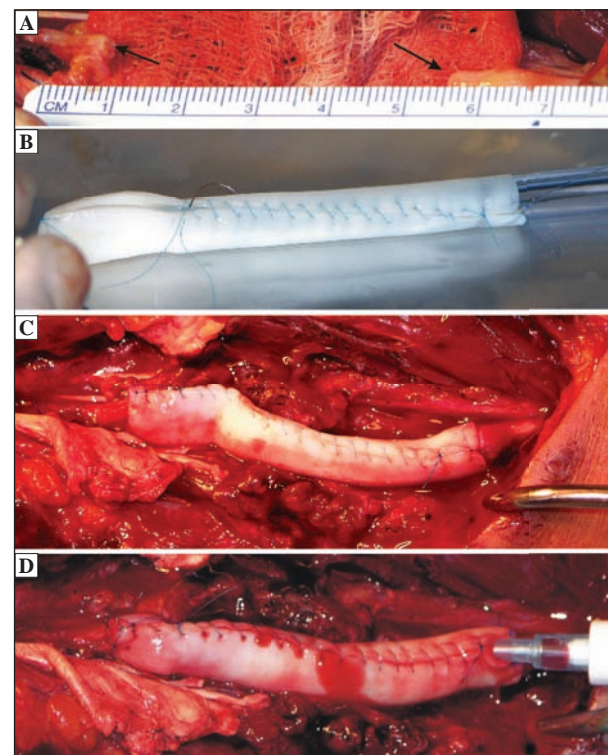

Figure 1. Photographs of the repair of an ulnar nerve using the repair technique described in this review, which leads to a reduction/elimination of neuropathic pain. A. The ulnar nerve after the damaged nerve tissue was removed leaving a 5-cm gap. B. sewing a collagen sheet into a tube with a diameter slightly larger than the nerve to be repaired. C. Securing the ends of the nerve about 3 mm into the ends of the collagen tube with sutures. D. Injecting autologous platelet-rich fibrin into the tube bridging the nerve ends.

transported to the somas of the nociceptive neurons where they reduce the neuron's hyperexcitability. This could be accomplished by reestablishing the normal balance of calcium and sodium channels in the cell membrane, thereby increasing the neuron's threshold for excitation. The factors may function by acting on various targets, such as ion channels, G-protein coupled receptors, purinergic receptors, and chemokine receptors, and downstream regulators of protein phosphorylation.

Eliminating Neuropathic Pain in Amputees

The data from the patients on whom we applied our new nerve repair technique indicate that neuropathic pain was reduced or eliminated even when there was only marginal target reinnervation and neurological recovery. Therefore an exciting aspect of these findings is that even excruciating neuropathic pain can be reduced/eliminated when the technique is applied many years post nerve trauma. Thus, as stated above, we hypothesize that the pain reduction or elimination results from the fibrin and the platelet-released factors acting singly or when combined, directly on the resected axons. This suggests that application of a variation of this technique might also reduce or eliminate the neuropathic pain of amputees. Approaches that might be effective are resectioning the nerve stump followed by applying autologous platelet-rich fibrin in an open or closed collagen tube, or its direct the application to the resectioned nerve stump without any collagen tube.

Testing whether application of platelet-rich fibrin is effective in reducing or eliminating neuropathic pain is a simple clinical study that is begging to be tested. It is also critical that the study be performed because of the large numbers of individuals who undergo amputations due to the current lack of a technique to repair long peripheral nerve gaps, and then suffer neuropathic pain. Such amputations are presently taking place in very large numbers, especially in individuals involved in present military conflicts.

Conclusion

We have seen the pain of patients suffering years of chronic excruciating neuropathic pain eliminated following a single application of platelet-rich fibrin to the central end of transected nerves. It is also remarkable that the neuropathic pain never reoccurred, even up to 4 years following the nerve repair surgery. Thus, application of this simple technique may make it possible to eliminate a lifetime of treatment with potent opioid and other pharmacological agents, with their attending side effects and even lack of effectiveness. Application of this technique may also be beneficial in reducing or eliminating other types of neuropathic pain. Clearly, it is vital to continue to study the application of additional techniques, such as electrical stimulation of the lesioned region of a nerve, administration of neurotrophic or other factors for their ability to reduce or eliminate neuropathic pain, when applied singly or in combination with platelet-rich fibrin.

Resumen

El dolor neuropático es iniciado, o causado por una lesión primaria o disfunción en el sistema nervioso central y/o periferal. Esto incluye infección, trauma, abnormalidades metabólicas y compresión nerviosa; y está acompañado típicamente por hiperalgesia y alodinia. El dolor neuropático puede ser de leve a alta intensidad y causar problemas de debilidad motora, depresión, afectar la calidad de vida, amputaciones de extremidades, y una variedad de síntomas clínicos. Esta condición, afecta hasta un 5% de la población general, a un 70% de los pacientes con cáncer en estadios avanzados y patología inflamatoria, y a 95% de los pacientes con lesiones en la espina dorsal. Los tratamientos primarios para el dolor neuropático incluyen el uso de antidepresivos, anticonvulsantes, anestésicos locales/agentes tópicos y opioides. Los tratamientos basados en la sintomatología del dolor neuropático evolucionan rápidamente y poseen la promesa de mejorar la calidad de vida de estos pacientes. Sin embargo, el tratamiento farmacológico de los síntomas es difícil por el conocimiento limitado de las causas que llevan al dolor, y los múltiples efectos secundarios de varios agentes en sus dosis efectivas. Más aun, el dolor neuropático es frecuentemente refractario a tratamientos analgésicos convencionales, con la mayoría de los pacientes obteniendo solo un alivio parcial con estos agentes, y con tolerancia o efectos secundarios que limitan su uso. Los tratamientos alternos a los farmacológicos incluyen bloqueo periferal o neuralgial e implantes de estimuladores corticales o espinales. Sin embargo, existe una gran necesidad de nuevos y más efectivos acercamientos para reducir el dolor neuropático. Este artículo examina varios acercamientos utilizados actualmente para el tratamiento del dolor neuropático, y además de posibles y más efectivos tratamientos.

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