
11 Nerve Decompression for Chemotherapy-Induced Neuropathic Pain

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11.1 INTRODUCTION

Despite the limited efficacy of current medical treatments, and the fact that they only treat the pain component of chemotherapy-induced peripheral neuropathy (CIPN), until recently there has been little interest in exploring surgical therapies for this condition. This is not at all surprising, because at first blush, it would seem that there is no rationale for a surgical approach to a systemic side effect of a medication (neurotoxicity). Similar reasoning had previously been applied to other forms of systemic-disease-induced neuropathy, such as diabetic neuropathy. This resulted in a long lag between the recognition of the cause of diabetic neuropathy and the application of a successful surgical treatment to alleviate its effects on the extremities. The lessons learned from the success in the treatment of diabetic neuropathy allowed for investigations into the feasibility of transferring similar techniques into the realm of chemotherapy-induced neuropathy. These surgical techniques have proven to be valuable adjuncts to available medical therapies for this disabling and painful condition.

Chemotherapy-induced neuropathy affects a large percentage of patients who receive chemotherapeutic agents. Not all chemotherapy agents cause neuropathy, but platin-based compounds, taxanes, and vinca alkaloids are the most common offenders, among many (Quasthoff et al., 2002). Even the more rarely used thalidomide, and several other atypical chemotherapeutic agents, have a strong correlation with the development of painful neuropathy. For all of these agents, the affect appears

to be dose dependent and is typically a sensory neuropathy, although a motor component is not unheard of (Rosson, 2006). The neuropathic effects for most of these drugs tend to abate slowly after cessation of therapy, but in many cases they persist long after the drug is discontinued. There is even a clinical phenomenon known as coasting, where a previously asymptomatic patient develops neuropathic symptoms weeks or months after the cessation of therapy. These patients with persistent neuropathic symptoms are in a confusing clinical situation: although they have successful cancer outcomes, the severity of their neuropathy symptoms prevents them from returning to work or partaking in activities they enjoyed prior to their cancer treatment. Further dampening these patients' outlook is the following: for all intents and purposes, there is no current medical treatment of CIPN, but rather, there are only ways to ameliorate the pain. Even when successful at relieving the pain of CIPN, the current medical treatments have troublesome adverse effects.

Like most systemic problems, initial treatments are aimed at systemic amelioration of symptoms. Medicinal treatments such as gabapentin and pregabalin are commonly prescribed along with selective serotonin reuptake inhibitors (SSRIs) such as duloxetine. Opioids are frequently needed. While many of these treatments offer some degree of symptomatic efficacy, they also have attendant adverse effects or potential for misuse and abuse. What they all have in common is that they simply manage, cover-up or make tolerable the pain. They do little or nothing to reverse or treat the underlying cause. Furthermore, while pain is the main symptom that drives the patient to seek help, it is not in fact the symptom that is most threatening to the patient. The resulting lack of protective sensation in the neuropathic extremity is a major cause of ulcers, infections, and subsequent amputations (Aszmann et al., 2004).

11.2 NERVE DECOMPRESSION

11.2.1 BACKGROUND

Dellon published the seminal paper demonstrating the efficacy of nerve decompression on both the symptoms and the natural course of diabetic neuropathy (Dellon, 1992). Not only were the symptoms improved in 85% of treated patients, but treated extremities—unlike the remaining untreated extremities—were no longer experiencing ulcers, infections, and subsequent amputations. This indicated that the decompression was protective against future neuropathy-derived morbidity. This phenomenon was further discussed in a paper in 2004 (Aszmann et al., 2004). To date there are 13 clinical studies demonstrating the efficacy of the nerve decompression approach to the treatment of diabetic neuropathy (reviewed by Melenhorst et al., 2009). Nevertheless, the surgical approach to the treatment of diabetic peripheral neuropathy has its critics (Therapeutics and Technology Assessment Subcommittee, 2006).

Over time, clinicians with experience with the surgical approaches to diabetic neuropathy began to expand their indications for this treatment. First, it was diabetic neuropathy, then it was idiopathic neuropathy, and eventually chemotherapy-induced neuropathy became a valid target for this treatment (Dellon et al., 2003; Valdivia et al., 2005). In fact, this approach has been successfully applied to alcoholic neuropathy,

lead neuropathy, and the neuropathy of Hanson's disease (A.L. Dellon, personal communication). It would seem that the cause of the neuropathy is somewhat irrelevant, as there is some degree of a common pathologic pathway that renders the nerves susceptible to compression at known sites of anatomic narrowing. This allows for nerve decompressions to treat the effects of many variations of neuropathy.

The crux of the problem, and the reason that surgery can be effective, relates to the double-crush phenomenon (Upton and McComas, 1973). The double-crush hypothesis is that separate insults to the peripheral nervous system—neither of which would have caused symptoms on their own—are additive and thus cause significant symptoms, even when the separate insults are relatively minor. This phenomenon has been clearly elucidated in animal models and explains clinically why diabetic patients are more susceptible to compression neuropathies such as carpal tunnel syndrome (Dellon and MacKinnon, 1991).

While the exact mechanism for the development of neuropathy after chemotherapy is not known, there is evidence for direct neuronal toxicity as well as a component of intracellular and extracellular edema as a response to that neurotoxicity. The slow component of axoplasmal transport appears diminished in most forms of CIPN, a pathophysiologic mechanism that is also found in diabetes-induced peripheral neuropathy (Tassler et al., 2000). The resulting stiffening and swelling of the nerves may result in neurocompressive symptoms caused at the known sites of anatomic narrowing (carpal tunnel, tarsal tunnel, etc.). So the direct effect of the toxic agent causes decreased function of the nerve, but more importantly, decreased function leads to stiffness and swelling of the nerve, and in predisposed individuals that results in nerve compression at the anatomic tunnels. This is precisely what the double-crush hypothesis predicts.

A loose analogy would be if a man who wore the same suit and tie every day gained 30 pounds. He would certainly be less healthy for the weight gain, but it would be his belt and his collar (sites of fixed anatomic narrowing) that would be most likely to cause him pain and distress. After loosening his belt, and unbuttoning his collar, he will feel considerably better, even though the underlying problem is still there. So the weight gain is one crush, but the presence of fixed-diameter tunnels provides the second crush that ultimately leads to the distress. Neither crush alone would have caused the problem, but together they result in disease.

11.2.2 BASIC SCIENCE AND CLINICAL DATA

Most of the work in the surgical treatment of neuropathy has been done in the diabetes model, with some additional study in a chemotherapy-induced model. Dellon et al. (1994) found that rats made diabetic with streptozotocin developed a neuropathic walking tract pattern. This pattern could be prevented by pretreating the rats with decompression of their tarsal tunnels. By eliminating one of the "crushes" the animals were rendered asymptomatic. This study was duplicated by Kale et al. (2003). Similar studies were performed in a model of cisplatin neuropathy in adult rats. In that study, rats administered cisplatin developed neuropathic walking patterns, yet rats that had tibial nerve decompressions concurrent with the commencement of cisplatin therapy did not develop these abnormal walking patterns.

This indicated that similar to the diabetic model, tibial nerve decompressions were protective against the development of neuropathic walking patterns in the adult rat (Tassler et al., 2000).

11.2.3 HUMAN DATA

Human clinical data remain sparse despite the fact that the two known papers were published 6 and 8 years ago, respectively (Dellon et al., 2003; Rose et al., 2006). There is one case series of nine patients and one double case report of two additional patients with CIPN who were successfully treated with nerve decompressions. In the case series, six of the nine patients fit the World Health Organization's clinical definition of chemotherapy-induced neuropathy and are the basis of the results and conclusions of the paper. All six of these patients had statistically significant reductions in the visual analog scale (VAS) for pain, and all had varying degrees of improvement in 2-point discrimination in the treated extremity. The second paper is a double case report of two patients with CIPN from thalidomide. Both were treated with nerve decompressions and both had measurable decreases in their VAS pain score and improvement in their 1-point pressure thresholds and 2-point discrimination thresholds. Due to the novelty of this approach to treat the symptoms of CIPN, there remains significant clinical resistance to applying it to patients. Furthermore, third-party payers might not reimburse for such treatment, which in some cases further hinders its application clinically.

11.3 DIAGNOSIS

Chemotherapy-induced neuropathy is fairly obvious and straightforward to diagnose clinically, but in fact there is no test for neuropathy. It is thus a diagnosis of exclusion and a clinical diagnosis. However, the symptom cluster for CIPN varies so much from patient to patient that the only thing consistent is that there is no consistency. Not all patients report pain, and every patient with pain reports it to varying degrees. Some complain of numbness and tingling while others have cramping pain or shooting pains. Some are affected at night, others during the day. Some feel better lying down, some standing up and walking. Some feel like there is something stuck in their shoe (like walking on sand, or that their sock is bunched up) while others notice that they cannot feel all or part of their foot—despite the pain they feel. What drives the diagnosis is that there is a clearly definable cause (chemotherapy) and a clearly correlated onset of symptoms after the commencement of therapy.

Typically the patient will be sent for expensive and painful electromyograms (EMGs) and nerve conduction studies. Unfortunately, electrodiagnostic studies are notoriously unreliable in distal extremity neuropathy diagnosis (Perkins et al., 2002; Quasthoff and Hartung, 2002; Dellon, 2005). Furthermore, expense and patient discomfort preclude these modalities as a screening test, or one that can be used repeatedly to follow the course of disease over time. Dellon and others advocate non-invasive neurosensory testing as a modality to quantify and follow the progression of disease over time, and after surgical therapy (Tassler and Dellon, 1995; Rosson,

2006). Since many CIPN patients do improve over 3 to 6 months following the cessation of the offending treatment, surgical intervention is ideally postponed until this time unless symptom severity dictates a more aggressive timetable. Painless, inexpensive, noninvasive neurosensory testing is an excellent way to follow these patients and document progression, or regression of disease. One clear indication for early consideration of surgery would be significant motor weakness in the affected extremities. Both peripheral sensory and motor nerves can regenerate at any time after injury; however, the motor nerves terminate at motor endplates on the muscle that irreversibly disappear sometime between 6 and 12 months after impulses stop being received at the motor endplate. This physiologic fact makes the timing of intervention with motor neuropathy more critical. Since there is a lag between the time of nerve decompression and the resumption of motor impulses on the order of several months, it behooves the surgeon to consider surgery for motor symptoms well prior to the 6- to 12-month window where the endplates begin to stop functioning forever.

Once a patient is clinically diagnosed with CIPN, he or she may be sent for electrodiagnostic tests to rule out another cause, and possibly illuminate the current disease process, but in most cases clinical examination coupled possibly with noninvasive sensory threshold testing is adequate to make a decision to move forward with treatment, including surgery. One issue that remains is the ability to reliably predict outcomes from surgery preoperatively. Multiple factors determine who will or will not be helped by the surgical decompressions, but currently no reliable test exists to select the best candidates for the procedure. Interestingly, the diabetic neuropathy literature presents evidence that the presence of a positive Tinel-Hoffman sign is a strongly positive predictor of a good outcome (Lee and Dellon, 2004). Anecdotal evidence in the two published human papers regarding the surgical treatment of CIPN indicates that a positive Tinel-Hoffman sign is a good predictor of outcomes in this population as well, but more studies are needed to confirm this (Rose et al., 2006).

Typically, a patient will have a stocking-and-glove distribution of his or her symptoms, but isolated mononeuropathies are reported. A Tinel sign should be present at the site of anatomic narrowing to establish a high chance of clinical success after surgery. The typical sites on the upper extremity to be examined are cubital tunnel, carpal tunnel, Guyon's canal at the wrist, and the radial nerve in the dorsal forearm. On the lower extremity, it is typical to examine the tarsal tunnel, the common peroneal nerve's tunnel just below the lateral condyle of the fibular neck, and the deep peroneal nerve as it passes underneath the extensor halucis brevis tendon in the mid-dorsum of the foot. If Tinel signs are positive at these sites, with symptoms in the distribution covered by that nerve, then surgical decompression has a high likelihood of success.

Prior to surgery, the patient should be examined and worked up to eliminate more central causes for the neuropathic symptoms (e.g., disk compressions, spinal stenosis, etc.). Furthermore, vascular compromise of the lower extremity can alter healing capacity, and can also mimic neuropathy symptoms and should be ruled out prior to surgical intervention. The patients' general health should be evaluated prior to surgery as well.

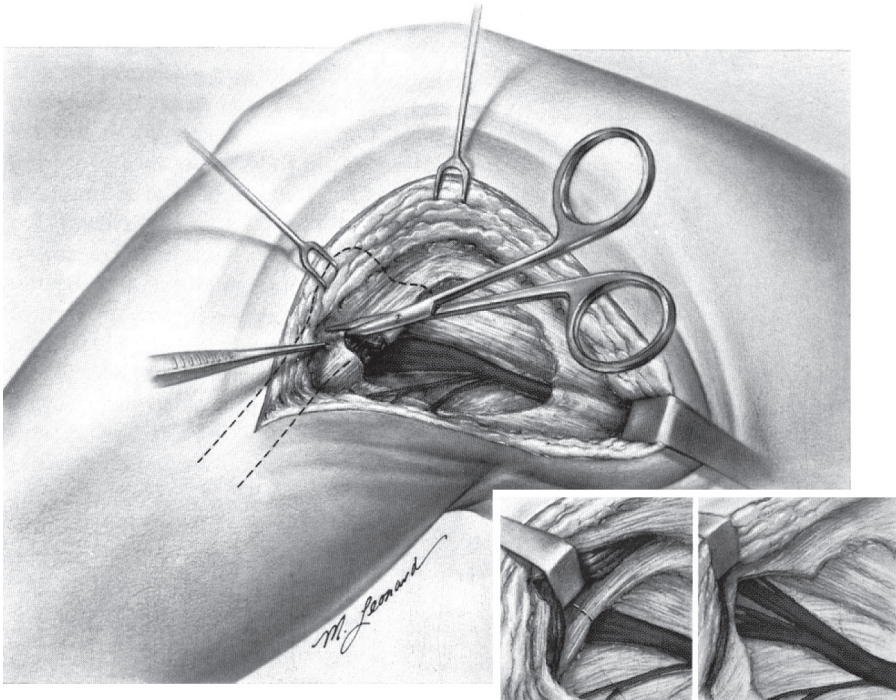


FIGURE 11.1 In the lower extremities common peroneal nerve compression is treated by release of the nerve as it passes through the peroneous longus fascia just inferior to the lateral fibular neck. (Schematic provided by A. Lee Dellon, M.D., Ph.D., Dellon.com. With permission.)

11.4 SURGICAL TREATMENT

In the upper extremity, compressions of the nerves occur in well-described anatomic points, and surgical treatment of the upper extremity is a bit more studied and understood. Neuropathy decompression includes release of the cubital tunnel, carpal tunnel, Guyon's canal, and the radial nerve in the distal forearm. For a glove distribution, all of the sites will be decompressed. If symptoms are more localized, then a focused approach should be used. Whether endoscopic releases offer any benefit in the setting of neuropathy decompressions remains to be demonstrated. Similarly, in the lower extremities common peroneal nerve compression is treated by release of the nerve as it passes through the peroneous longus fascia just inferior to the lateral fibular neck (Figure 11.1).

Deep peroneal nerve decompression is executed by resecting a segment of the extensor halucis brevis tendon as it passes over the deep peroneal nerve in the dorsum of the foot (Figure 11.2).

There is no functional consequence to sacrificing this tendon as the extensor halucis longus tendon is the primary extensor of the great toe. Finally, the tarsal tunnel as well as the four medial ankle tunnels should be decompressed to improve symptoms attributable to the tibial nerve (Figure 11.3).

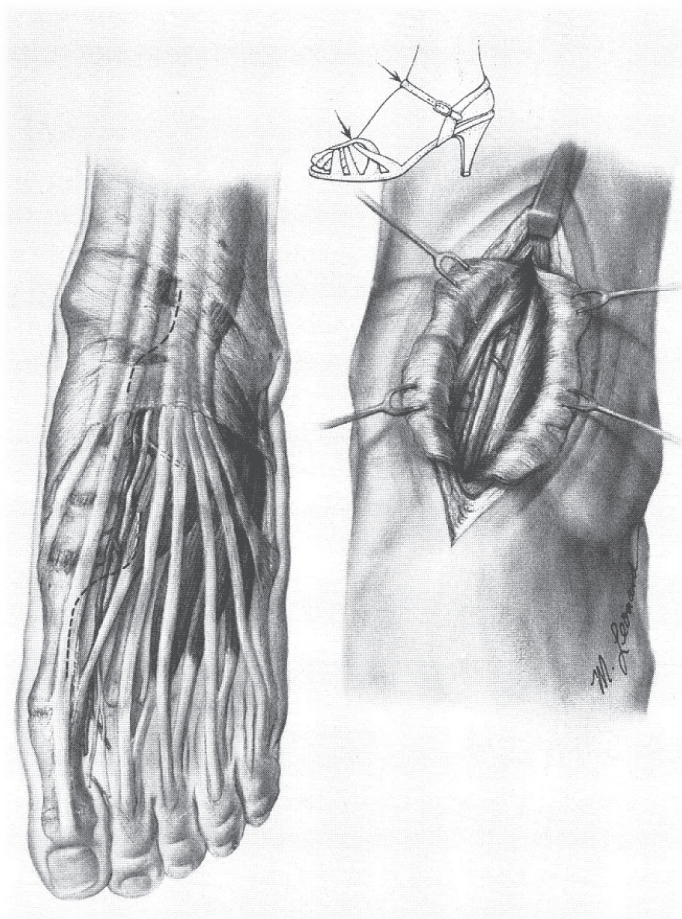


FIGURE 11.2 Deep peroneal nerve decompression is executed by resecting a segment of the extensor hallucis brevis tendon as it passes over the deep peroneal nerve in the dorsum of the foot. (Schematic provided by A. Lee Dellon, M.D., Ph.D., Dellon.com. With permission.)

Traditionally, tarsal tunnel release is the simple opening of the flexor retinaculum over the tibial neurovascular bundle. Results tend to be much more predictable if the T-shaped roof and septum between the medial and lateral plantar nerves (see [Figure 11.3](#), inset) are excised. This results in a common tunnel into the porta pedis of the foot. Surgery is generally performed as an outpatient procedure, with follow-up typically 1 week after the surgery when the bulky but soft dressing is to be removed. To avoid wound healing issues, the patient is instructed to elevate the extremity postoperatively, but he or she is allowed to bear weight and use the extremity gingerly during the healing phase to minimize scarring and reentrapment of the nerves during the healing process. Sutures are removed 3 weeks after surgery since these incisions are over high-stress, active-motion areas.

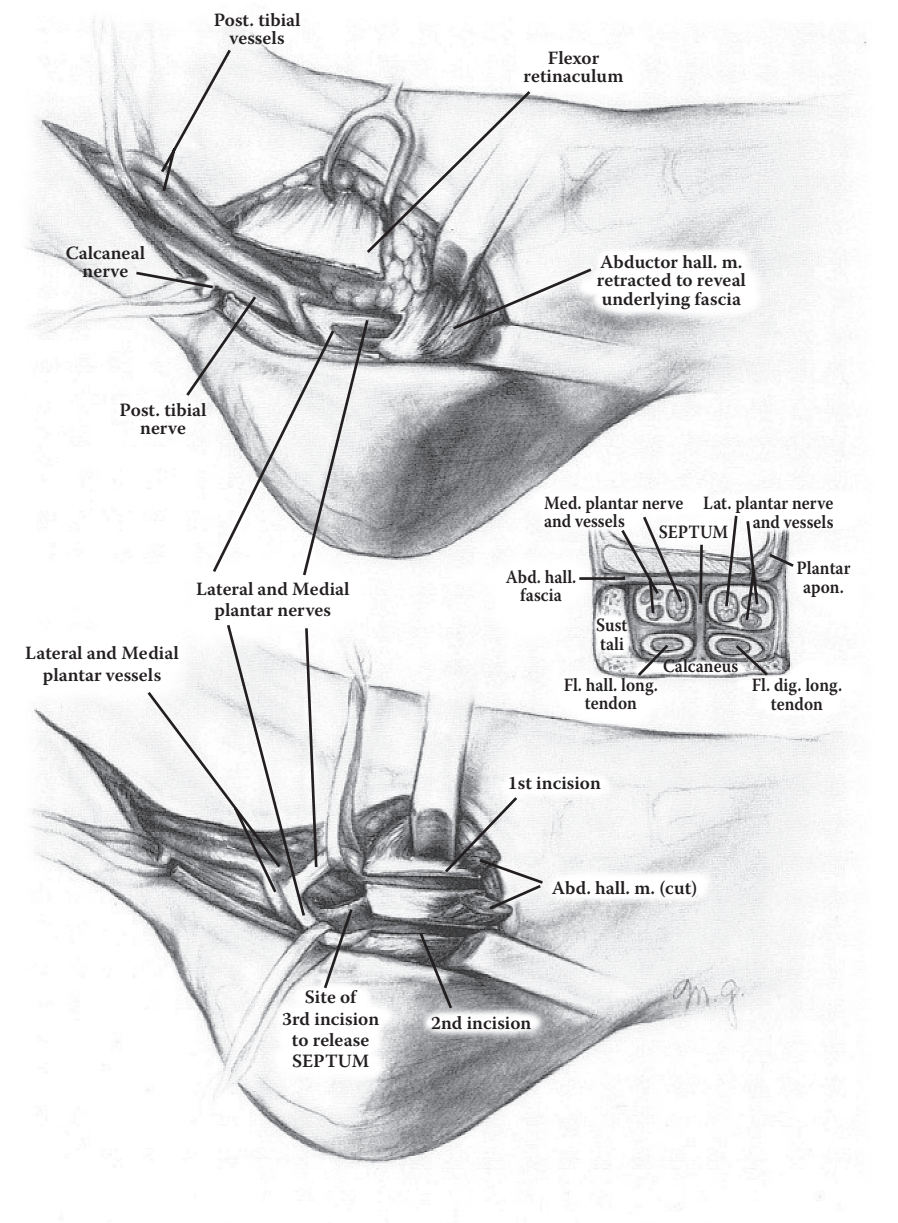


FIGURE 11.3 The tarsal tunnel as well as the four medial ankle tunnels should be decompressed to improve symptoms attributable to the tibial nerve. (Schematic provided by A. Lee Dellon, M.D., Ph.D., Dellon.com. With permission.)

11.5 CONCLUSION

While data are still sparse, there is a small body of human and animal data that support the application of nerve decompression surgery for the relief of CIPN. Patients should be chosen carefully to maximize the chance of a good outcome and minimize complications. Further clinical and basic science studies are needed to confirm definitively the efficacy of this approach and to cement it as a weapon in the armamentarium of the surgeon against this debilitating effect of chemotherapy.

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