The Combination of Proteolytic Enzyme Supplementation, Acupuncture, and Osseous Manipulation for the Treatment of Traumatic Peripheral Nerve Injury: A Case Report

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ABSTRACT

This report describes the treatment of peripheral nerve injury in a 43-year-old woman using a combination of proteolytic enzymes, acupuncture, and osseous manipulation as alternatives to conventional care. Her presenting symptoms include complete loss of sensation in the superolateral left thigh and a mass of fibrotic scar tissue in the area of injury. A holistic treatment plan was created to address the underlying mechanisms of the injury. Plant-based proteolytic enzymes, bromelain and papain, were used to address tissue inflammation and reduce scar tissue formation around the nerve, acupuncture was used to regenerate the superficial nerves, and osseous manipulations were provided for structural re-alignment. After 8 weeks of treatment, the patient reported significant reduction in the size of the fibrotic mass and complete resolution of sensory loss. The fibrotic mass of tissue reduced from 6 cm to 1 cm during the treatment course. Proteolytic enzymes have wide-ranging indications; however, they have not been well studied for peripheral nerve injury, which makes this a novel indication for this natural health product. This case report found the use of proteolytic enzymes, and acupuncture, effective in treating peripheral nerve injury and provides grounds for research to treat nerve-related injuries.

Key Words Bromelain/papain, inflammation, anti-inflammatory, anti-fibrinolytic, trauma

INTRODUCTION

Peripheral nerve injuries (PNI) are common conditions with wide-ranging presenting symptoms. Although much is known about the mechanism of injury, very few reliable treatments have been shown to provide full functional recovery. In many cases, nerve and soft tissue damage can cause debilitating symptoms weeks to months after the initial trauma. Untreated tissue damage can lead to chronic pain, loss of nerve function, and other long-term complications, such as compartment syndrome and avascular necrosis. Prompt diagnosis and effective treatment can reduce the risk of complications and improve patient outcomes.[1]

Seddon and Sunderland created a universal language for the classification of peripheral nerve injury.[2,3] They classified the severity of nerve injury into Stages I through V based on the extent of axonal and connective tissue damage. Grade I, also known as neurapraxia, is defined as focal demyelination with limited damage to the axons and connective tissues.[4] Clinical symptoms of neurapraxic injuries include paresthesia but with preservation of autonomic function.[4] Grades II-IV are known as axonotmesis and are defined as direct damage to axons and focal demyelination with continuity of the nerve connective tissue sheath.[5] This stage can present with paresthesia, neuropathic pain, advancing Tinel's sign, and dry skin with loss of sweating due to vasomotor and autonomic dysfunction.[4] Grade V, also called neurotmesis, is the most severe form of PNI. This stage involves complete transection of the axon and connective tissue layers, resulting in discontinuity of the nerve.[5] This stage often presents with severe neuropathic pain, paralysis, anesthesia, and loss of vasomotor and autonomic function.[4] The Seddon and Sunderland classification grades of nerve injury are outlined in Table 1, with Seddon contributing the electrophysiologic diagnosis and Sunderland contributing surgical treatment standards. The gold standard diagnostic techniques to accurately classify PNI include neurophysiology studies of electromyography (EMG) and nerve conduction study (NCS).[4]

PNI can have various etiologies. Traumatic peripheral nerve injuries (TPNIs) can arise from falls, crush injuries, stretching or compression in sports, and as a complication of orthopedic surgery.[4,5] TPNI differs from other forms of neuropathy in

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TABLE 1 Seddon and Sunderland Classification of Nerve Injury[1,2,3]

Stage	Pathology	Clinical signs	Neurophysiologic Findings	Prognosis
I Neurapraxia	Only conduction block	Paresthesia Autonomic function preserved	NCS: CMAP and SNAP show focal conduction block at site of lesion EMG: may show fibrillation, reduced motor unit action potential	Full, spontaneous recovery takes about 3 months
II–IV Axonotmesis	Division of axons with Wallerian degeneration Connective tissue remains intact	Paresthesia Neuropathic pain Worsening Tinel's sign Dry skin, loss of sweating due to autonomic dysfunction	NCS: loss of CMAP and SNAP within 2 weeks EMG: fibrillations	May be a good prognosis, dependent on severity Average spontaneous nerve recovery at rate of 0–3 mm/day May require surgery if severe
V Neurotmesis	Complete transection of nerve	Paralysis Neuropathic pain Anesthesia Dry, red skin with loss of sweating due to complete autonomic dysfunction	NCS: loss of CMAP and SNAP within 2 weeks EMG: fibrillations	Poor prognosis without surgical intervention Surgery required

NCS = nerve conduction studies; EMG = electromyography, CMAP = compound muscle action potential, SNAP = sensory nerve action potential. Table adapted from: Bage T, Power DM. [1]Seddon HJ, Three types of nerve injury, *Brain.* 1943;66(4):237-88, https://doi.org/10.1093/brain/66.4.237; [2]Sunderland S. *Nerves and nerve injuries*. Edinburgh: E & S Livingstone Ltd.; 1968; [3]Bage T, Power DM. Iatrogenic peripheral nerve injury: a guide to management for the orthopaedic limb surgeon. *EFORT Open Rev*. 2021;6(8):607-617. doi: 10.1302/2058-5241.6.200123.

the sudden nature of the event, and recovery is closely associated with the type and severity of injury.[5] Functional recovery is often unsatisfactory, and limited treatment options are available.[5] Therefore, there is an unmet need for alternative non-surgical strategies to promote functional recovery in patients affected by this injury.

Conventional medical approaches to PNI include watchful waiting, pharmacological, electrical, cell-based, and surgical strategies. Surgery is reserved for moderate to severe cases and includes end-to-end neurorrhaphy, nerve grafting, nerve transfer, and conduit repair. However, surgical repair entails several risks, including slow rate of nerve regeneration and sub-optimal functional outcome, as well as being an invasive procedure. Aside from surgery, other evidence-based treatment strategies include physical therapy, electrical stimulation, low level laser therapy, and pharmaceuticals such as corticosteroids and erythropoietin.[5,6]

Many conventional treatments for PNI primarily address the pain aspect of injury, and limited treatments are available when pain is absent, such as in this case. In addition, there are few non-surgical treatment options to treat milder stages of peripheral nerve injury and its sequelae. The accessibility of these options is also limited.[5] Naturopathic medicine has the potential to provide effective, non-invasive treatment options using a root-cause approach.

Acupuncture has been used for centuries to heal a wide variety of diseases. It has become more widely accepted as a means of reducing chronic pain and improving peripheral neuropathies associated with diabetes, Bell's palsy, and carpal tunnel syndrome.[7] Although the use of acupuncture in nerve injury is supported by the literature, there is less quality evidence for the use of proteolytic enzymes in PNI.[8] Plant-based enzymes have not been found to directly regenerate nerves; however, they have been shown to reduce inflammation in soft tissues, which provides a supportive environment for nerve healing.[9] Therefore, the use of proteolytic enzymes as an adjunctive therapy in nerve injury is novel. The purpose of this case report is to document the impact of proteolytic enzymes with acupuncture in a case of peripheral nerve injury.

CASE PRESENTATION

This report describes the case of a 43-year-old female presenting with loss of sensation and a mass of fibrotic scar tissue over the superolateral left thigh. Onset of pain, numbness, and the formation of a hematoma began as the direct result of a fall to the lateral left thigh on March 15, 2023. The patient had slipped on the front steps of her house, lost her balance, and her left leg took the brunt of the impact with other minor injuries to the left elbow and left ankle. Due to the magnitude of the bruising and pain, she presented to the emergency department a few days after the injury. X-rays of the left leg, left elbow, and left ankle were taken; no fractures were identified. No treatment options were provided, and she was told that the injury would resolve without intervention. Pain and bruising resolved on their own. However, the numbness and fibrotic scar tissue remained without improvement. She sought naturopathic care for the lack of sensation in her left leg due to concerns of permanent nerve damage.

A physical exam was performed to assess the severity of her nerve damage. Findings revealed absent sensation of the dermatome innervated by the lateral femoral cutaneous nerve. Two-point discrimination test revealed an area of 12 cm in length and 5 cm in width on the left leg with no sensation. An oval-shaped nodule of soft fibrotic tissue was palpated beneath the left buttock measuring at 6 cm in length and 3 cm in width. The borders were well-demarcated, the skin was slightly elevated and dome-shaped, and the texture was smooth. Muscle function of her left leg was conserved at strength 5/5 in hip flexion, extension, abduction, and adduction movements, and pain was absent. This case report complies with the *CAND Journal* policies on Research Ethics and Informed

Consent. The patient provided full, informed, and written consent for this case report.

Medical History, Medications, Natural Health Products

The patient reported having no current medical diagnoses. She had been successfully working with her general practitioner (GP) on weight loss for the past 6 months towards her goal weight. Her GP had prescribed semaglutide, a long-acting GLP-1 agonist medication, administered subcutaneously once per week. She reported only minor side effects from the medication, including a smaller appetite and mild constipation on the day of the injection. The patient had a history of clinical depression in 2004 that had since resolved. She reported a few minor motor vehicle accidents in childhood that left her with no long-term injuries. She reported no significant musculoskeletal injuries in the past.

Family history revealed her father had passed from amyotrophic lateral sclerosis (ALS) in 2021, her sister was diagnosed with rheumatoid arthritis, and her brother and paternal grandfather had been diagnosed with diabetes mellitus type 2 (T2DM). Her current supplement regimen included self-prescribed vitamin D (1000 IU daily), a broad-spectrum probiotic (15 billion CFU, 1 cap daily), iron (21 mg daily), B-Complex (1 cap daily), magnesium (100 mg daily) and fish oils (375 mg EPA and 250 mg DHA daily).

Biopsychosocial Determinants of Health

The patient reported having a healthy support system, including her husband, two children, close family and friends. She works 5 days per week at a desk job that she finds enjoyable. She has a highly active lifestyle; she attends spin class twice per week, does strength training twice per week, goes for walks three to five times per week, and either attends an aquafit class or free swims once per week. In her spare time, she enjoys gardening, traveling, hiking, walking her dogs, cooking, and spending time with her husband and children. She reported 8 to 10 hours per night of quality sleep. Her stress was well managed with a positive mindset, exercise, and taking time for the activities she enjoyed.

Diagnosis

A definitive diagnosis could not be made due to the lack of GP referral for a nerve conduction study and/or electromyography. However, a working diagnosis of traumatic peripheral nerve injury was made. Based on clinical history, the paresthesia presented in a dermatomal distribution, which suggested PNI of the left lateral femoral cutaneous nerve. The history of hematoma and remaining tissue mass at the site of injury led to the conclusion that there was scar tissue forming as a result of soft tissue damage. Radiographic findings ruled out fracture and avascular necrosis, which allowed us to be more confident in our working diagnosis. In addition, lack of significant cramping pain and pressure in the leg ruled out compartment syndrome, and lack of tingling and shooting pain ruled out sciatica.[10,11] Using the Seddon and Sunderland Classification of Nerve Injury, we concluded that this injury was a mixed neurapraxic and axonotmesis peripheral nerve injury.[12] She experienced a biphasic recovery, where there was immediate spontaneous resolution of pain and bruising, suggesting a neurapraxic component, and a slower recovery of the axon, suggesting an axonotmesis component.[13] Classification of peripheral nerve injury is described in Table 1.

Therapeutic Management

A holistic treatment plan was created to address the root cause of her presenting symptoms. Based on her peripheral nerve injury, we wanted to reduce the inflammation around the nerve, improve blood flow to the local area of injury to promote healing, and ensure surrounding skeletal structures were in alignment following her fall. A combination of targeted supplementation, acupuncture, and osseous manipulations were utilized.

Natural Health Products

On the first visit, a proteolytic enzyme supplement containing plant-derived bromelain and papain was prescribed, 1 capsule twice daily taken at least 30 minutes before or after meals until symptoms resolved. Each capsule contained 9,450,000 food chemical codex (FCC) of protease activity and only contained the enzymes derived from *Carica papaya* (papaya seeds) and *Ananas comosus* (pineapple stem). Proteolytic enzymes, thiol endopeptidases from pineapple stem and chymopapain from papaya, cleave peptide bonds between amino acids through hydrolysis, and are used by the body to break down ingested protein when taken orally.[8] The targeted outcome of using this supplement was to break down the mass of fibrotic scar tissue and reduce connective tissue inflammation around the nerve, hence the indication to take on an empty stomach to avoid the enzymes breaking down food.

Physical Medicine

Weekly acupuncture sessions were recommended, with points chosen to improve blood flow and enhance nerve regeneration. The points were chosen based on a combination of traditional Chinese medicine (TCM) and western medical styles of acupuncture. Specifically, points on the gallbladder (GB) meridian as they benefit sensory deficits in the leg based on TCM theory.[14] In addition, three a-shi points were chosen based on palpation and patient feedback of the area of greatest sensory deficit. A-shi points do not follow a particular TCM meridian. Six 0.25 × 25 mm needles were inserted into GB 30, GB 31, GB 32 acupuncture point locations and a-shi points on the left leg to a depth of 1 cun (about 1 inch or 2.5 cm). The acupuncture points were manually stimulated for 2 to 5 seconds upon insertion, then left in their respective locations for an average of 15 minutes per session. Four acupuncture sessions were completed at an interval of 1 to 3 weeks, based on the patient's availability. Clean needle technique was used.

To provide structural re-alignment, osseous manipulations were utilized. Based on an assessment of the sacroiliac (SI) joint using the long-sit test, observation of a posterior-inferior sacroiliac joint dysfunction of the left hip was made.[15] One high-velocity, low-amplitude osseous manipulation was performed to the left SI joint using a posterior to anterior force vector. The patient had also reported that her left leg and foot were more laterally rotated

compared with her right leg since the fall. To correct this dysfunction, three attempts of a left subtalar adjustment using a superior to inferior force vector and two attempts of an internal rotation acetabular adjustment using an anterior to posterior force vector were performed. She found little to no benefit from the osseous manipulations and therefore we will not comment on their significance in this case.

The primary outcome measure was the distance between points using a two-point discrimination test for sensation. The secondary outcome measure was the size of the fibrotic tissue mass. Due to clinician oversight, no standardized questionnaires or validated measures were used. Lack of access to a nerve conduction study and electromyography meant we had to assume the patient's condition was improving based on our measurements and her reported symptoms, despite not being able to accurately assess changes in nerve morphology and remyelination.

RESULTS AND PATIENT OUTCOMES

On August 11, 2023, after about 1 month of taking the proteolytic enzymes twice daily and one acupuncture session, she reported indigestion and acid reflux after taking the enzymes immediately before a spin cycle class. She was advised to continue the supplement and to avoid doing vigorous exercise within 30 minutes of taking the capsule. Her adverse reaction completely resolved and did not reoccur. Gastrointestinal upset is a known side effect of proteolytic enzymes if taken on an empty stomach and followed by exercise.[8] The patient was adherent to taking this supplement for the duration of her treatment, as assessed by clinical inquiry each visit.

On August 18, 2023, the patient reported improvement in her sensation on the left thigh. A physical exam revealed the distance on the two-point discrimination test had decreased to 9 cm from 12 cm in length measured on the initial appointment on July 14, 2023. On September 15, she reported further improvement in sensation, and the distance between the two points was 4 cm in length.

On September 8, 2023, she reported the fibrotic tissue mass had decreased in size. It measured 3 cm in diameter, down from 6 cm in diameter on the initial appointment.

On October 13, 2023, she reported complete resolution of the loss of sensation on her left leg and the fibrotic tissue mass had decreased in size to 1 cm. She reported being very happy with the results of her treatment. A complete timeline of her treatments can be found in Table 2.

TABLE 2 Treatment Timeline

Date of Visit	Recommended NHPs/Treatments	Physical Medicine Treatment	Patient-Reported Outcomes
July 14, 2023	Plant-derived bromelain and papain, proteolytic enzymes, 1 cap twice daily 30 min away from meals until symptoms resolved	—	—
July 21, 2023	—	Acupuncture: GB 30, GB 31, GB 32 on left side only	Difficulty finding time to take enzymes twice per day away from meals
Aug 11, 2023	—	Acupuncture: GB 30, GB 31, GB 32, 2 a-shi points based on palpation of sensory loss on left side only Osseous manipulation: left posterior-inferior ilium adjustment (posterior to anterior vector)	No change in sensation on thigh Left SI joint pain since the injury Indigestion and acid reflux after taking proteolytic enzymes and attending spin class immediately afterwards. Recommended to avoid vigorous exercise within 30 minutes of taking supplement
Aug 18, 2023	—	Acupuncture: GB 30, GB 31, GB 32, 3 a-shi points based on palpation of sensory loss on left side only Osseous manipulation: left subtalar adjustment (superior to inferior vector), left hip internal rotation adjustment (anterior to posterior vector)	Improved sensation on thigh Mild tolerable pain in left hip post-adjustment lasting for 1 day, resolved spontaneously.
Sept 8, 2023	—	Osseous manipulation: left posterior-inferior ilium adjustment (posterior to anterior vector)	Significant decrease in size of fibrotic tissue mass as observed by the patient
Sept 15, 2023	Recommended Figure-4 stretch, 45 sec hold per side twice daily, to improve hip mobility	Acupuncture: GB 30, GB 31, GB 32, 3 a-shi points based on palpation of sensory loss on left side only Recommended performing lunges to strengthen gluteus muscle group and stabilize SI joint, 10 reps × 2 sets per day	Improved sensation on thigh No noticeable difference in hip joint mobility post-adjustment
Sept 29, 2023	Continue treatments as stated above	—	Improved sensation on thigh noticed while doing aquafit training No change in hip mobility since last hip adjustment
Oct 13, 2023	—	—	Full resolution of lost sensation on left thigh Fibrotic tissue mass decreased in size

NHP = natural health product; GB = gall bladder meridian; SI = sacroiliac.

DISCUSSION

Although peripheral nerve injuries are not life-threatening, they can have a significant effect on a patient's quality of life. This case report describes the use of alternative, non-surgical treatment modalities to address the underlying mechanisms of peripheral nerve injury. In particular, we describe the use of acupuncture and proteolytic enzymes to treat this condition.

Acupuncture has been studied as an effective alternative treatment for peripheral neuropathy.[7] It involves inserting fine needles in particular points to specified depth and angles along meridians to promote healing from disease. Several studies have demonstrated a high density of peripheral nerve endings along acupuncture point meridians, suggesting that acupuncture acts directly on the nervous system.[16] The mechanism by which acupuncture effectively restores PNI-induced neurological deficits involves remodelling of the nervous system via neural regeneration and promotion of axon sprouting through the release of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell-derived neurotrophic factor (GDNF).[16] In addition, acupuncture has been shown to increase blood vessel number, which could increase blood flow and address the tissue ischemia component of PNI.[16]

In addition to the nerve injury in TPNI, muscles and surrounding connective tissue are frequently affected. Muscles have limited capacity for regeneration after injury, and therefore part of the healing results in scar tissue formation. Clinical signs of soft tissue injury include hematoma, edema, and post-traumatic fibrosis.[1] Conventional treatment for this type of injury involves anti-inflammatory techniques using ice, compression, and non-steroidal anti-inflammatory drugs (NSAIDs). However, some research has suggested that NSAIDs may in fact delay the healing of muscle injury.[1]

Proteolytic enzymes may act as a natural alternative to NSAIDs for treating soft tissue inflammation after TPNI. Found naturally in the body as well as in some foods, proteolytic enzymes act to break down protein. Common plant-derived proteolytic enzymes include bromelain and papain. Bromelain is derived from pineapple stalk and has been studied widely in plastic and dental surgery. It was found to be effective in reducing facial swelling and pain following third molar extraction.[9] Papain and chymopapain from papaya seed have been shown to resolve pain and accelerate wound healing in perineal episiotomies.[17] These enzymes can be used for a variety of therapeutic purposes, including as a digestive aid, to reduce blood viscosity, enhance circulation, and reduce swelling and inflammation. This case report identified their use as an anti-inflammatory for traumatic soft tissue injury. The mechanism by which these enzymes work on soft tissue edema and inflammation is largely unknown; however, the theory is that the enzymes denature proteins in the soft tissue resulting in increased permeability of the inflamed tissue, allowing drainage and tissue repair.[8]

Another therapeutic mechanism of proteolytic enzymes is their anti-fibrinolytic activity. Although they have not been studied specifically in PNI, they have been highly effective for wound debridement and in preventing blood clotting.[17] The clotting cascade involves two key mechanisms, platelet aggregation and fibrin formation, to promote wound healing.[18] This was the basis for our decision to use these enzymes in this case. We proposed that the proteolytic enzymes could act to break down the fibrin in the scar tissue and prevent further necrotic debris from accumulating.

LIMITATIONS

This case report has several limitations. One limitation was the prognosis for this patient. Mixed neurapraxic and neurotmesis injuries tend to have a relatively good prognosis. In general, recovery can occur within 3 months for milder injuries and up to 12 months in more severe injuries.[4] Our patient experienced significant improvement in sensation in 2 months of treatment, with treatment being 4 months post-trauma. It is difficult to say whether the patient would have recovered in the same timeframe without intervention based on the natural history of her condition. Second, we did not have access to a nerve conduction study or electromyography to be able to diagnose the injury and monitor treatment effectively and accurately. This limitation forced our reliance on our clinical diagnostic tests to track her treatment progress. In hindsight, we could have used a validated questionnaire or quality-of-life scale, such as the QOLS to better assess patient outcomes over the course of her treatment.[19] Some speculate that oral proteolytic enzymes are destroyed in the highly acidic environment of the stomach. Since we cannot easily assess the extent to which these enzymes reached the target tissue, we assumed that they were playing a part in reducing inflammation and breaking up scar tissue in this patient. Lastly, a major limitation to this report was the small population size associated with a single case report. Therefore, the strength, reliability, and applicability of our results are limited.

FUTURE RESEARCH

Current articles on PNI focus on the mechanism, complications, and limited conventional treatments. There is an evidence gap in research on alternative treatments for TPNI. Future research should focus on higher-quality whole-systems-based treatments, including nutrition, physical rehabilitation, nutraceuticals, and botanical therapies. Such studies would create a more robust research base for our current line of treatment to manage PNI. Furthermore, a validated set of clinical criteria to accurately assess and diagnose PNI should be created in future research.

CONCLUSION

This report demonstrated that alternative treatments for the management of PNI can be effective when they address the underlying mechanisms of injury. Within 8 weeks of treatment with proteolytic enzyme supplementation, acupuncture, and osseous manipulations, complete resolution of sensory loss and significant reduction in the size of the patient's scar tissue was achieved,

although osseous manipulation had no noticeable benefit. This case highlights the importance of addressing nerve degeneration, soft tissue inflammation, and microvasculature compromise in a holistic approach to treating traumatic PNIs. Using a combination of complementary modalities and addressing the root cause of this condition, we can better address this complex form of nerve injury.

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CONFLICTS OF INTEREST DISCLOSURE

We have read and understood the *CAND Journal*'s policy on conflicts of interest and declare that we have none.

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