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A Novel Technique Restores Function while Eliminating Intractable Neuropathic Pain in a 71-Year-Old Diabetic Patient under Challenging Injury Conditions

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Abstract

Background The extent of functional recovery induced in healthy patients by sensory nerve grafts, the clinical "gold standard" technique for repairing peripheral nerves with a gap, is significantly limited by increasing gap length, time between trauma and repair, and patient age. When the values of any two, or all three, variables increase simultaneously, there is little to no recovery. For diabetic patients, even under the best of conditions and without any large variables, the extent of axon regeneration and functional recovery is significantly less, but generally none. Therefore, novel techniques are required that enhance recovery in diabetic patients.

Methods A 12-cm long median nerve gap in the wrist/palm of a 71-year-old male long-term diabetic patient was bridged 1.3 years post nerve injury with a sural nerve graft within a platelet-rich plasma-filled collagen tube.

Results By 2 months post-repair, the patient's level 6 chronic neuropathic pain was permanently eliminated. By 6.75 months, the palm had recovered good sensitivity to stimuli of all sensory modalities, including 4.56 g pressure and less than 15 mm two-point discrimination. Each finger had good motor function of M3–5, with partial to complete sensitivity to stimuli of all sensory modalities and an overall recovery of S3.

Conclusion This technique permanently eliminates severe chronic neuropathic pain while simultaneously inducing good motor and sensory recovery in a long-term diabetic patient, under conditions where recovery is rarely, if ever, seen, even in non-diabetic patients. This technique holds great promise of restoring function to diabetic patients, for whom it is otherwise not possible.

Keywords
- nerve repair
- peripheral nerves
- long nerve gap
- neuropathic pain
- platelet-rich plasma

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Sensory nerve grafts are the "gold standard" technique for repairing peripheral nerves with a gap in animal models[1–3] and clinically.[4] However, their efficacy in restoring reliable good to excellent function is limited by increasing gap length (> 3–5 cm),[5,6] delay between trauma and repair (> 3–5 months),[7,8] and patient age (> 20–25 years old).[7,9] For diabetic animal models and clinically, even under the best of circumstances, functional recovery is significantly less, or none[10–12] and decreases further, or does not develop, with the increasing duration of individual's diabetes.[13] Therefore, novel techniques are required that restore better function to patients with diabetes under all conditions.

Methods

Platelet-Rich Plasma Preparation and Delivery

Prior to surgery, but under general anesthesia, 55 mL of whole blood was drawn from a peripheral vein into a 60 mL syringe containing 5 mL of citrate-based anticoagulant. The blood was injected into a Gravitation Platelet Separation III centrifuge tube (Zimmer Biomet, Warsaw, IN). Centrifugation yielded ca. 6 mL of platelet-rich plasma (PRP). The PRP was drawn into a 10 mL syringe and 1 mL of thrombin into a 1 mL syringe, and both were attached to a 10:1 ratio mixer with a fine catheter attached (Nordson Medical, Westlake, OH). The catheter was inserted into the collagen tube, the two plungers pressed, and their contents injected into the collagen tube. The PRP flowed entirely through and completely filled the space between the sural nerve graft and collagen tube, the fibrin polymerized in less than 20 seconds, and the patient was closed.

Surgery

The nerve trauma site, extending from the wrist into the palm, was exposed, revealing extensive scar tissue and a macerated median nerve. After removing the damaged nerve tissue, there was a 12 cm long nerve gap. The gap was bridged with a sural nerve graft within an autologous PRP filled collagen tube.

Collagen Tube

The nerve graft was surrounded by a long collagen tube constructed of two 5 cm and one 3 cm long NeuroMend collagen tubes (Collagen Matrix Inc., Oakland, NJ) (►**Fig. 1**). The use of PRP was off-label.

Patient

The patient was a 71-year-old male with insulin-dependent type II diabetes, which he had suffered for more than 25 years. He presented following a rotary saw injury to the palm/wrist. Due to the extensive trauma, although an initial repair surgery was performed to reconnect several tendons, no nerve repair was performed, and no nerve repair surgery was scheduled. The patient presented again 1.3 years post-trauma, seeking the restoration of function and the reduction/elimination of his level 6 severe chronic neuropathic pain. Nerve surgery was scheduled. When he presented for the nerve repair surgery, he was going through a period of diabetic crisis.

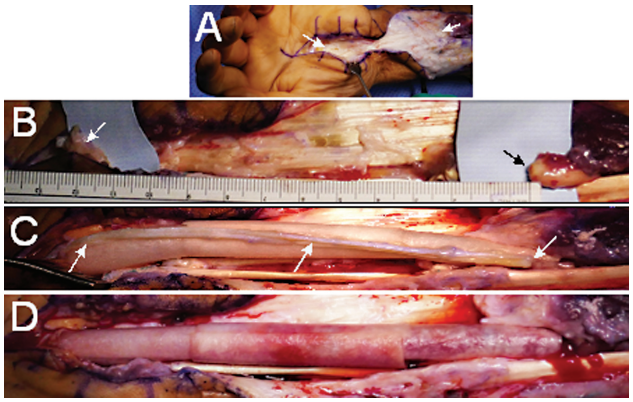

Fig. 1 Nerve injury and repair of peripheral nerve gap. (**A**) The exposed trauma site in the wrist and palm showing extensive scar tissue (*arrows*). (**B**) After removing the scar tissue and the macerated portion of the median nerve, the proximal and distal ends of the median nerve, indicated by *arrows*, were refreshed with a scalpel. (**C**) A 12.5 cm collagen tube was created using two 5 cm long and one 3 cm long collagen tubes with their ends overlapping and placed in the nerve gap. The sural nerve graft is seen lying on top of the collagen tube (*arrows*). (**D**) Completed nerve gap repair after slipping the sural nerve graft into the collagen tube and filling it with autologous PRP. PRP, platelet-rich plasma.

Results

Electrodiagnostic Studies

The median nerve compound motor action potential was recorded from the abductor pollicis brevis muscle with stimulation distal to the site of nerve injury, 8 cm proximal to the active recording electrode. The sensory nerve action potential was recorded from the third digit of the hand with stimulation distal to the site of injury, 14 cm proximal to the recording electrodes. The amplitude of the responses that were obtained was compared with the opposite extremity to determine the degree of axonal loss. In this case severe axonal and secondary demyelination would result in reduced amplitude of the evoked motor response and prolonged distal latency. The ulnar nerve of the involved extremity and median as well as ulnar nerves of the unaffected limb were evaluated to assess for underlying peripheral neuropathy.

At 1.2 years following nerve repair, electrical stimulation of the median nerve evoked action potentials with prolonged latencies of 4.45 versus 3.1 milliseconds compared with the median nerve of the opposite hand. They had decreased amplitudes of 2.72 versus 8.94 mV and conduction velocities of 33.1 versus 56.8 m/s.

Electromyographic studies established that axons of the repaired nerve correctly reinnervated their appropriate four muscle targets: opponens pollicis, abductor pollicis brevis, flexor digitorum profundus to digits 2, 3, and flexor carpi radiali muscles.

Physical Exams

Sensory Recovery

The entire area of the palm normally innervated by the median nerve developed sensitivity to stimuli of all sensory modalities, including light touch, deep pressure, pinprick, heat, cold,

Table 1 Table of extent of recovery of sensitivity to various modalities of sensory stimuli to regions of the hand normally innervated by the median nerve

Stimuli	Proximal palm	Distal palm	Thumb Proximal/ intermediate/ distal	Index Proximal/ intermediate/ distal	Middle Proximal/ intermediate/ distal	Ring Proximal/ intermediate/ distal
Light touch	+	+	+ − −	+ − −	+ − −	+ + +
Pinprick	+	+	+ − −	+ − −	+ − −	+ + +
Heat	+	+	+ − −	+ − −	+ − −	+ + +
Cold	+	+	+ − −	+ + +	+ + +	+ + +
Pressure			− − −	− − −	3.61 3.61 3.61	3.61 3.61 3.61
Vibration	+	+	− − −	− − −	+ + +	+ + +
Proprioception	4.56 g	6.65 g	+ + +	+ + +	+ + +	+ + +
2-Point discrimination	< 15	< 15	0 0 0	> 15 > 15 > 15	> 15 > 15 > 15	> 15 > 15 > 15

vibration, and two-point discrimination of less than 15 mm. The sensitivity to touch was determined by moving the tip of a Q-tip in different directions across the skin. The patient was sensitive to all such movements. ►**Table 1**. The proximal half had pressure sensitivity of 4.56 g and the distal half had pressure sensitivity of 6.65 g.

The most extensive sensory recovery was of the lateral portion of the ring finger, which responded to stimuli of all sensory modalities, including light touch, pressure, pain, heat, cold, and vibration, which extended to the fingertip, including two-point discrimination of greater than 15 mm (►**Table 1**). Other fingers developed varying degrees of sensitivity, although the joints of all the fingers had correct proprioception (►**Table 1**).

Motor Recovery

The repaired median nerve induced a motor force of M3 from the opponens pollicis and abductor pollicis brevis muscles. It induced a force of M5 from the flexor digitorum profundus to digits 2, 3, and flexor carpi radiali muscles.

Tinel Response

A Tinel response was evoked from the middle of the palm.

Chronic Neuropathic Pain

Before surgery, the subject suffered level 6 severe chronic neuropathic pain based on the 11 point analog scale, where 0 is no pain and 10 is excruciating pain. The pain began to decrease during the first two 2 following nerve repair surgery, and was eliminated within 2 months, and did not reappear over the following 1.5 years.

Discussion

Although sensory nerve grafts are the clinical "gold standard" technique for repairing peripheral nerve gaps, under the best conditions, less than 50% of patients recover from good to excellent function.[5,14] Most of this limitation is due to recovery decreasing significantly for gaps greater than 3 to 5 cm in length,[5,6] repairs delay of greater than 3 to 5 months,[15,16] and patients greater than 20 to 25 years old.[17] However, as the values of any two or all three of these variables increase simultaneously, recovery is extremely limited to none.[7,18] Contributing to the decreases are injury-induced changes in neurons,[19,20] Schwann cells,[21,22] and reduced post-injury revascularization.[23,24]

Diabetes

While the functional recovery following the repair of peripheral nerves in healthy individuals is limited, it is significantly more limited in diabetic animal models[25,26] and patients with type I and type II diabetes.[12,27] This is due to specific diabetes-induced limitations[12,27] on neurons,[12,28] Schwann cells,[12,27,29] and on reduced development of post-injury vascularization.[30] Thus, even under the best conditions, particularly for type 2 patients, recovery is normally incomplete[10,12] or none.[10,30]

Electrodiagnostic Results

The regenerated axons of the repaired nerve had action potentials with prolonged delays, significantly reduced amplitudes, and reduced conduction velocities compared with those of the control nerve of the opposite hand. These differences are consistent with the electrical properties of regenerated/regenerating axons[31] and also suggest underlying neuropathies typical of diabetic nerves.

Sensory Recovery

The entire palm recovered topographically correct sensitivity to stimuli of all sensory modalities, including two-point discrimination of less than 15 mm, with the proximal half of the palm having greater pressure sensitivity (4.56 g) than the distal half (6.65 g). While the lateral portion of the ring finger developed sensitivity to stimuli of all sensory modalities, the other fingers developed partial to extensive sensitivity, although the joints of all the fingers developed appropriate proprioception. The presence of a Tinel response in the middle of the palm suggests some axons had only regenerated to that point and that over time they might regenerate further and restore additional function. Thus, sensory recovery was overall good.

Motor Recovery

The repaired nerve innervated all four of its original muscle groups, with two muscles generating M3 force and two M5 forces. Thus, there was extensive motor axon regeneration, high specificity of reinnervation, and good functional recovery.

Pain

Ninety percent of type I and II diabetic patients suffer neuropathic pain associated with diabetic neuropathies, and the pain does not decrease over time.[32,33] Although the present patient suffered severe chronic level 6 neuropathic pain before surgery, the pain began to decrease soon after surgery and was permanently eliminated within 2 months.

PRP Effects in Animal Models and Clinically

The present results show that this novel nerve gap repair technique restores good and extensive motor and sensory function while permanently eliminating severe chronic neuropathic pain in a diabetic patient, despite the values of all three variables that limit axon regeneration being simultaneously large. These are the conditions under which no recovery would normally develop, even in healthy patients. Because such recoveries are not induced by sensory nerve grafts alone, these results indicate that platelet-released factors induced the recoveries. This hypothesis is consistent with the data showing that the application of PRP to injured nerves promotes axon regeneration in animal models[34–37] and clinical studies[38–40] and reduces/eliminates chronic neuropathic pain in animal models[34–37] and clinically.[38,39,41,42] These recoveries indicate that this novel technique induced axon regeneration in this diabetic patient similar to that seen in healthy patients.

Conclusion

These results show that this novel technique can restore good motor and sensory function even in a senior (71 years old) long-term insulin-dependent diabetic patient with a long (12 cm) nerve gap, repaired following a long delay (1.3 years) post nerve trauma. These are conditions under which virtually no recovery is seen even in healthy patients and would never be anticipated in a diabetic patient. Simultaneously, the technique rapidly and permanently eliminated the diabetic patient's chronic neuropathic pain, which is rarely seen in healthy patients, no less diabetic patients. Further applications of the technique to other diabetic patients are required to determine the reliability of this technique for diabetics.

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None.

Conflict of Interest
None declared.

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