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ORIGINAL RESEARCH

Clinically Reducing/Eliminating Chronic Neuropathic Pain by Bridging Peripheral Nerve Gaps with an Autograft within a PRP-Filled Collagen Tube

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Purpose: Peripheral nerve trauma is associated with 50–79% of individuals developing chronic neuropathic pain. No technique reliably induces long-term chronic neuropathic pain reduction/elimination.

Patients and Methods: This study compared the influence of bridging peripheral nerve gaps with an autograft vs an autograft within a platelet-rich plasma- (PRP) filled collagen tube (PRP repair) on the level of long-term chronic neuropathic pain.

Results: Pre-surgery, all 11 autograft repair subjects suffered chronic neuropathic pain of 4–10 (mean 8.6±4.2), with 81.8% of 8–10. Following repairs, pain reduction started when axons started reinnervating targets. The pain decreased to 0–6 (mean 0.27 ± 0.3), with 18.2% having long-term pain reduction and 81.8% long-term pain elimination. Pre-surgery, of the 15 PRP repair subjects, 60% suffered chronic pain of 4–10 (mean 7.7 ± 1.4), with 66.7% pain of 8–10. Pain reduction began within two weeks, and within two months, 11% of the subjects had maximum pain reduction and 89% long-term pain elimination. The pain never increased or occurred over the following 1.1–15.4 years.

Conclusion: Chronic neuropathic pain is normally reduced/eliminated when axons reinnervate targets, including by using targeted muscle reinnervation (TMR). However, bridging nerve gaps with an autograft within a PRP-filled collagen tube reduces/eliminates pain far faster because axon regeneration and target reinnervation are not required, only that platelet-released factors act on the peripheral axons. In addition, the PRP technique induces pain reduction several times greater than TMR, and although TMR is only effective when applied less than four months post-trauma, PRP is effective when applied at least up to 3.25 years post-trauma. This is the first clinical demonstration that PRP induces long-term pain reduction/elimination by factors acting only on peripheral axons, while they are regenerating and does not require target reinnervation. This study sets the stage for testing whether bridging gaps with only a PRP-filled collagen tube has the same effects.

Plain Language Summary: Chronic neuropathic pain is a severe problem following peripheral nerve trauma. However, no technique provides reliable long-term pain reduction/elimination. This paper shows that combining platelet-rich plasma with an autograft within a collagen tube induces rapid long-term chronic neuropathic pain reduction in 11% and elimination in 89% of the subjects. Thus, this is the first study showing the ability of PRP to reliably reduce/eliminate chronic neuropathic pain.

Keywords: nerve repair, pain elimination, peripheral nerve trauma, platelet-rich plasma

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Introduction

Peripheral nerve trauma results in 50–79% of people developing chronic neuropathic pain,[1–3] with 7–10% of the population living with chronic neuropathic pain.[4] Predictors of persistent neuropathic pain following a nerve repair include pre-operative neuropathic pain,[5–8] increasing the duration of the repair delay,[5,9] and the failure of injured axons to reinnervate targets.[10]

The first line of neuropathic pain treatment involves pharmacotherapy and local anesthetics.[11] However, only 30–40% of patients achieve adequate pain relief,[12] while another study found only 30% of patients experience about a 30% pain reduction,[13] and only 17%[13] achieve significant, but not long-lasting, pain relief.[13,14] Further, their use is limited by side effects and non-responsive patients. In addition, although combinations of simultaneous medications increase pain relief, combinations are infrequently prescribed.[15]

Neuroma formation is a leading cause of neuropathic pain. Their clinical removal reduces pain, but provides long-term pain relief to <50% of subjects,[16–18] but new neuromas and pain may redevelop.[8,19–22] Therefore, the best technique for preventing neuropathic pain is preventing neuroma formation, such as by capping the nerve stump in a collagen tube,[18] or securing it to an allograft or autograft,[23,24] both standard techniques for restoring function across a nerve gap[25] or other materials.[26]

Autografts, allografts, and conduits do not directly reduce chronic neuropathic pain.[1,2,23,27,28] Rather, they allow axon regeneration leading to target reinnervation, which underlies pain reduction/elimination, but only to 20.59%, 37.5%, and 19.44% of nerves, respectively.[29] Similarly, following lower extremity amputations, the resulting pain is reduced by implanting nerve stumps in bone,[30] or by nerve capping.[16,30] However, they do not induce long-term chronic neuropathic pain reduction.[31]

The most effective technique for preventing or reducing chronic neuropathic pain or post-amputation neuroma pain is to prevent neuroma formation by creating a peripheral nerve interface (RPNI) or targeted muscle reinnervation (TMR).[10,19,32–35] Both reduce phantom limb pain in 45–80% and neuroma pain in 75–100% of patients.[19] They function by providing the regenerating axon targets to reinnervate, which are hypothesized to provide axons factors that suppress pain. However, these techniques cannot be used when the ultimate goal is to both reduce chronic neuropathic pain and restore nerve function.

An alternative tool for reducing pain in animal models is applying platelet-rich plasma (PRP) to nerves evoking chronic neuropathic pain, which induces short- to mid-term pain reduction but not elimination.[36–40] Clinically, a single PRP application may provide analgesia,[41–50] but multiple applications may also be required[51–54] and pain suppression is of only of short to mid-term duration.[36–40,48]

This study compared the efficacy of bridging nerve gaps with an autograft vs an autograft within a PRP-filled collagen tube on the level of neuropathic chronic pain.

Materials and Methods

Bridging Nerve Gap with an Autograft within a PRP-Filled Collagen Tube

Peripheral nerve injury sites were examined under a microscope, and the proximal nerve stump trimmed to where clear nerve fascicles were seen, and no scarring was seen in the distal stump/s. The autograft stumps and the nerves to be repaired were loosely secured with a single suture, leaving a 1–2 mm gap. For the PRP repairs, the autograft was surrounded by a PRP-filled collagen tube. Subjects who presented requiring a nerve repair were enrolled.

Preparing and Injecting Platelet-Rich Plasma

PRP was prepared using the Zimmer Biomet Gravitation Platelet Separation III (GPS III) kit (Zimmer Biomet, Warsaw, IN). Under general anesthesia and before any surgical interventions, 55 cc of whole blood were drawn from a peripheral vein into a 60-cc syringe containing 5 cc of citrate-based anticoagulant and mixed. The blood was injected into a GPS III tube, and the tube spun in a Zimmer Biomet centrifuge at 3.200 rpm for 15 minutes, yielding ca. 6 cc of PRP.

The PRP was drawn from the GPS III tube into a 10-cc syringe and 0.6 cc bovine thrombin (Baxter, Deerfield, IL) into a 1 cc syringe. The syringes were attached to a FribriJet 10:1 ratio Applicator Assembly, SA-1001, mixer with

a FribriJet SA-3673 blending catheter (Nordson Medical, Westlake, OH). The catheter was inserted into the collagen tube, and the two syringe plungers pressed simultaneously, mixing and injecting the contents into the collagen tube. PRP was injected until it began to flow out the distal end of the collagen tube, ensuring the space between the autograft and collagen tube was filled with PRP. The fibrin polymerized in <20 seconds and the subjects were closed. Six cc was sufficient for 1–2 nerve gap repairs.

Collagen Tubes

Before the availability of United States Food and Drug Administration- (FDA)-approved collagen tubes, they were created by sewing a 2×8 cm collagen sheet (Veritas, Synovis Life Technologies, Inc., St. Paul, MN) into a tube around the autograft Figure 1. Subsequently, 5 cm long FDA-approved NeuroMend collagen tubes (Collagen Matrix, recently renamed Regenity Biosciences, Oakland, New Jersey) were used Figure 2. These tubes have a horizontal slit, which allows them to be opened, and the autograft slipped inside, followed by their self-closing with a 25% overlap. The nerve coaptation sites were positioned 1–2 mm inside the tubes to ensure they were surrounded by PRP. Bridging gaps >5 cm requires multiple NeuroMend tubes with overlapping ends.

Subject Inclusion Criteria and Relevant Dates

Individuals were considered for inclusion in this study who presented to the clinical of the peripheral nerve surgeon who were 18–75 years old, with an upper extremity nerve with a gap ≥3 cm. Recruitment, surgeries, data collection: November 2006–December 2024.

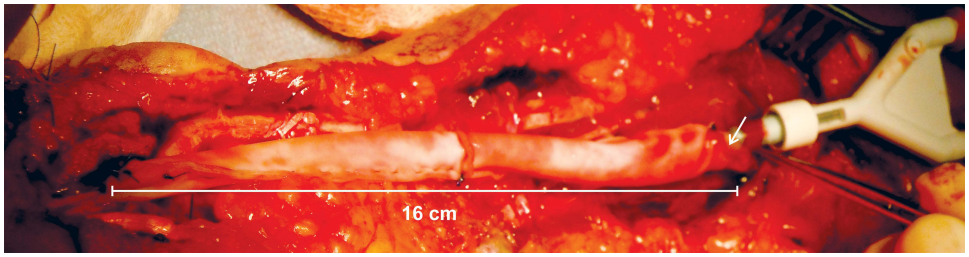

Figure 1 Repair of a 16 cm nerve gap with an autograft within a collagen tube. The arrow indicates the proximal end of the collagen tube where the PRP is being injected.

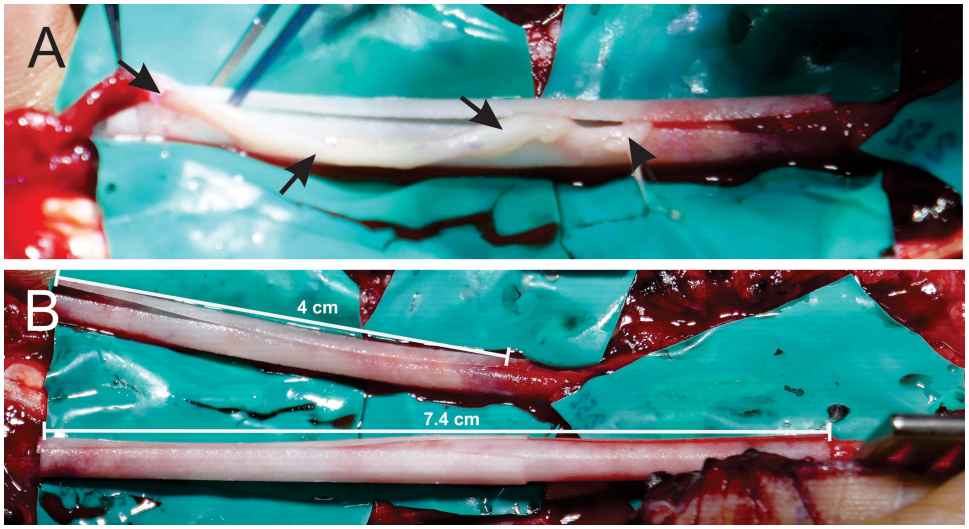

Figure 2 (**A**) The collagen tubes were opened and the autograft with attached proximal and distal nerve stumps were slipped inside, marked by arrows. (**B**) Repairing a 4 cm and 7.4 cm nerve gap using NeuroMend collagen tubes before injecting PRP.

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Statistical Analysis

Post-hoc power analysis was performed using the two-sided paired *t*-test on the level of pre- and post-surgical pain at the 0.05 level of statistical significance, using the GPower statistical software version 3.1.9.7. The estimated statistical power of the analysis of the changes in recovery of sensory and motor function was 100%.

Pain Evaluation

Each subject evaluated their level of neuropathic pain before and after surgery. The evaluation used the validated 11-point qualitative pain assessment linear pain scale from 0 to 10, where 0 = no pain and 10 = worst pain possible.[55,56]

Demographics of Subjects, Nerves, and Injuries

The autograft repair group involved 11 subjects, one female and 10 males, 19–71 (mean 42.3 ± 16.3) years old, with 16 upper extremity 2–8 (mean 2 ± 2) cm long gaps, and repair delays of 2 weeks to 1.5 (mean 0.22 ± 0.05) years Table 1. All the nerves were mixed: median (37.5%), radial (6.3%), and ulnar (56.3%). The injuries were caused by sharp objects 81.2% and penetrating trauma (18.8%) and were located at the elbow (12.5%), forearm (50%), and wrist (37.5%).

The PRP repairs were performed on 15 subjects, one female and 14 males, aged 24–71 (mean 41.4 ± 26.2) years old, 25 upper extremity peripheral nerve gaps 3–16 (mean 6.7 ± 9.2) cm long, and repair delays of 1.5 weeks - 3.25 years (mean 1.0 ± 1.3). The nerves were 8% pure motor, 32% pure sensory, and 60% mixed. The injuries were caused by gunshots (24%), sharp cuts (ie, glass, knife) (24%), and penetrating traumas (ie, auto accidents, saws) (52%) Table 1. The trauma locations were the elbow (4%), forearm (12%), wrist (64%), and palm (20%). The time between nerve repair and

Table 1 Demographics of Repairs

Demographics	Autograft	PRP	Autograft	PRP	Autograft	PRP	Autograft	PRP
Gender and number	Female/male 1/10	Female/male 1/14						
# of repaired nerves	16	25						
Type of nerves	Median 37.5%	Median 25%	Ulnar 56.3%	Ulnar -	Radial 6.3%			
Nerve function	Mixed 100%	Pure motor 8%		Pure sensory 34.6%		Mixed 57.7%		
Trauma locations	Elbow 12.5%	Elbow 4.2%	Forearm 50%	Forearm 12.5%		Palm 20.8%	Wrist 37.5%	Wrist 66.7%
Causes of trauma	Gunshots -	Gunshots 24%	Sharp cuts 25%	Sharp cuts 24%	Penetrating traumas 18.8%	Penetrating traumas 52%		
Gap lengths	Range 2–8 cm mean 2±2	Range 3–16 cm mean 6.7±9.2						
Repair delays	Range 2 wk - 1.5 yr mean 0.22±0.05 SD	Range 1.5 wk - 3.25 yr 1±1.3 SD						
Subject ages	Range 19–71 yr mean 43.2±16.3 SD	Range 24–71 yr mean 41.4±26.2 SD						
Subjects with pre-surgical pain	100%	60%						
Pre-surgical pain level	Range 4–10 yr mean 8.6±4.2 SD	Range 4–10 yr mean 7.7±1.4 SD						
Post-surgical pain level	Range 0–4 mean 0.27±0.3 SD	Range 0–6 mean 0.67						
Pain reduced	18.2%	11%						
Pain eliminated	81.8%	89%						

final neurological exams from which the recovery data are reported was 1.1–15.4 (mean 5.4 ± 3.9) years. No subjects dropped out of the study.

Results

Chronic Neuropathic Pain

Pre-operatively, 100% of the autograft repair subjects suffered chronic neuropathic pain of 4–10 (mean 8.6 ± 4.2), with 81.8% suffering pain of 8–10. Each subject's pain began to decrease about the time the regenerating axons reinnervated their targets. The pain was reduced to 0–4 (mean 0.27 ± 0.3) for 18.2% of the subjects and eliminated for 81.8%. These pain levels did not change over the following 3 years of follow-up.

For the PRP repair subjects, pre-operatively, 60% suffered chronic neuropathic pain of 4–10 (mean 7.7 ± 1.4), and 66.7% pain of 8–10. Each subject's pain began to decrease within the two weeks of surgery, and by two months, the mean pain was reduced to 0–6, mean 0.67, with 11% having their pain reduced and 89% eliminated. The pain levels did not change over the following 1.1–3.75 years. For the PRP repairs, electrophysiological and physical studies found that long-term chronic neuropathic pain reduction/elimination occurred while the axons were regenerating and before any axons had reinnervated targets.

Correlations Between the Extent of Pain Relief and Subjects' Three Independent Variables

For the autograft repair subjects, the paired *T*-test established a significant difference between the pre- and post-surgical pain scores, $p = 0.001$. Linear regression analysis determined there was no correlation between the degree of reduction in pain score and increasing repaired gap length ($p = 0.28$), repair delay ($p = 0.55$), and subject age ($p = 0.10$).

For PRP repair subjects, the paired *T*-test established a significant difference between the pre- and post-surgical pain scores for the PRP repair subjects, $p = 0.00$. Linear regression analysis determined there was no correlation between the degree of pain reduction scores with the increasing gap length ($p = 0.88$), repair delay ($p = 0.64$), and subject age ($p = 0.09$).

Discussion

Peripheral nerve trauma results in 50–79% of individuals developing chronic neuropathic pain,[1–3] with 7–10% of the population living with chronic neuropathic pain.[4] Predictors of persistent neuropathic pain following a nerve repair include pre-operative neuropathic pain,[5–8] increasing the duration of the repair delay,[5,9] and the failure of injured axons to reinnervate targets.[10] Thus, reducing chronic neuropathic pain normally requires performing repair surgery within several months of trauma, which is often this is not possible.

Clinically, the first-line treatment for neuropathic pain is pharmacotherapy, using anticonvulsant drugs, tricyclic antidepressant drugs, or serotonin and noradrenaline reuptake inhibitors,[57–60] and local anesthetics.[11,61] However, they provide adequate pain control to 17%[13] to 30–40%[12] of patients, and their effects are not long-lasting.[13,14] Further, while combinations of medications simultaneously improve pain relief, they are rarely prescribed.[15]

Efficacy of TMR and RPNI

In animal models, neuropathic pain behavior persists until the injured axons reinnervate targets,[10] obtain target-derived factors and stop regenerating.[62] This finding is consistent with the efficacy of TMR and RPNI in reducing/eliminating chronic neuropathic pain in 71–100% of subjects.[19,63] Clinically, RPNI and TMR surgery reduce neuroma pain in 56–100% of patients,[19,63,64] and post-amputation neuroma pain[19,32–34,65,66] and phantom limb pain in 45–80%. However, the efficacy of TMR decreases when applied >3 months following trauma,[67] and neither technique can be used if the ultimate goal is to reduce pain and restore nerve function.

Efficacy of PRP

In animal models, applying PRP to nerves evoking neuropathic pain induces short- to mid-term pain reduction but not elimination.[36–40,68] Clinically, PRP reduces neuropathic pain by up to 70% in 87% of patients[69] when applied to a nerve

crush site,[50,70] nerves during carpal tunnel release surgery,[71,72] and following perineural injections due to leprosy-induced pain.[36] Clinically, by 4 months after applying PRP to a post-thoracotomy pain site, the pain was reduced from 8.5 to 3 in 90% of patients, although opioid consumption did not decrease significantly.[73]

In the present study, autograft repairs induced long-term neuropathic pain reduction from a mean of 8.6 ± 4.2 to 0.27 ± 0.3, an 8.3-point reduction, with 18.2% undergoing pain reduction and 81.8% long-term pain elimination. Following the PRP repairs, the pain decreased from a mean of 7.7 ± 1.4 to 0.67± 0 a 7-point reduction, with 11% of the subjects having their pain reduced and 89% eliminated, regardless of the pre-surgery chronic neuropathic pain level.

The European Federation of Neurological Societies guidelines consider a ≥2-point pain reduction successful.[12] While TMR reduces residual and phantom limb pain by an average of 3.7 and 3.6 points, respectively,[10,56] PRP induced a 7-point pain reduction, almost two times that of TMR.[32,74]

These results show that, for pain reduction/elimination, PRP repairs are superior to TMR because they do not require target innervation, and the process is far faster. An additional benefit is that, while TMR efficacy decreases with increasing repair delays, PRP repairs reduce/eliminate pain, even with repair delays of up to 3.25 years.

Single vs Multiple PRP Applications

In some studies, a single PRP application induced incomplete pain suppression[41–49,72] lasting 3[69] to 6 months,[48] while in others, multiple PRP applications are required for good pain suppression.[45,51–54,75] Nevertheless, in all cases, the pain suppression was only short to mid-term duration.[36–40,48] In the present study, only a single PRP application was required to induce long-lasting pain suppression.

Chronic Neuropathic Pain Reduction with Increasing Values of the Three Independent Variables

Studies report that the extent of post-nerve repair chronic neuropathic pain reduction decreases with (1) increasing high pre-surgery pain, (2) increasing nerve repair delay,[5,9] (3) increasing gap length,[76] and (4) increasing age.[77] In the present study, while both autograft and PRP repairs reduced/eliminated chronic neuropathic pain, there was no correlation ($p = 0.21$) between high pre- and post-surgery persistent pain levels, and the amount of post-surgery pain did not change with statistically significance with increasing gap length, repair delay, or subject age.

Cessation of Chronic Neuropathic Pain

Chronic neuropathic pain is closely associated with abnormal spontaneous electrical activity of regenerating dorsal root axons.[78–80] This observation led to the hypothesis that neuropathic pain is associated with regenerating axons.[78] This hypothesis is supported by the finding that rat chronic pain behavior is blocked by applying semaphorin 3A, and growth associated protein (GAP) 43 knockdown, which stop axon regeneration and silence nociceptive neuron spontaneous electrical activity.[78]

Consistent with previous studies, autograft repairs lead to neuropathic pain beginning to decrease only about the time axons began reinnervating targets and stopped regenerating. However, following PRP repairs, the pain began to decrease within two weeks, reaching its maximum reduction/elimination within two months, and subsequently did not change. Thus, long-term pain reduction/elimination occurred while the axons were regenerating, and long before any axons innervated targets, which suggests, but does not prove, that platelet-released factors reduced/eliminated the chronic neuropathic pain.

Greater Efficacy of PRP in This Study vs Others

Most studies testing the efficacy of PRP on axon regeneration and pain use PRP with a platelet concentration increased 2.7–8.5-fold.[81–84] The PRP in the present study was prepared using the Zimmer Biomet GPS III centrifuge system and has a 9.3-fold increase in platelet concentration and a 5-fold increase in leukocyte concentration (Zimmer Biomet Data on File. Validation Report, GPS III Platelet Concentrator, Test new design for GPS III Buoy re-design, OT000183, 2007).

The present results showing reliable pain reduction/elimination by PRP with a 9.3-fold increase in platelet concentration are supported by a recent study showing that 4 months after PRP application, post-thoracotomy pain was reduced from 8.5 to 3 in 90% of subjects, although opioid consumption did not decrease significantly.[73] We hypothesize that the higher PRP concentration and leukocytes underlie the good and long-term analgesic efficacy of PRP in this vs other studies.[85–87] Also potentially contributing to the greater efficacy of PRP in this vs other studies is using a larger PRP volume, ca. 4–6 cc vs 0.1–0.5 cc, respectively.

We propose that contributing to the present good analgesic effects of PRP is due to surrounding the PRP with a collagen tube. This is consistent with the demonstration that surrounding PRP applied to a rat nerve injury site with a collagen membrane increased functional recovery compared to PRP without a collagen tube.[88] This result suggests that the collagen tube reduces the diffusion of platelet-released factors away from the site, which allows them to act for longer at a higher concentration of platelet-released factors.

Limitations

One limitation of this study is its relatively small sample size and should be repeated on a larger sample size. In addition, the study shows that the technique eliminated pain in one female subject. Further studies are needed to determine whether there is any gender-induced variability in pain response between females and males.

Conclusions

This study shows that autograft repairs induce long-term pain reduction in 18.2% of subjects and long-term pain elimination in 81.8%, and PRP repairs induce long-term pain reduction in 11% and elimination in 89%. Autograft repairs begin to reduce/eliminate chronic pain only when the regenerating axons begin to innervate targets. However, following PRP repairs, pain begins to decrease within two weeks and reached maximum reduction/elimination within two months, while the axons were regenerating and before any target reinnervation. The results suggest, but do not prove, that platelet-released factors induce the pain reduction/elimination by only acting on peripheral axons, without the need for any CNS actions. New studies are required to determine whether bridging nerve gaps with only a PRP-filled collagen tube also induces long-term pain reduction/elimination.

Ethical Practice

This study was performed under a protocol approved by the IRB of the Medical Sciences Campus, University of Puerto Rico, and in accordance with the World Medical Association Declaration of Helsinki (JBJS 79-A:1089-98, 1997), and each subject was informed about the purpose of the study and its potential risks and benefits.

Consent Statement

All Subjects signed IRB-approved Written Consent Forms.

Adverse Events

No subject suffered any adverse events, such as increased pain or infection.

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Disclosure

The authors report no conflicts of interest in this work.

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