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# PLATELET RICH PLASMA FOR PERIPHERAL NERVE REGENERATION. A SYSTEMATIC REVIEW

**Ahmed Hassan Usman[1*], Talha Khalid[2], Muzammil Iqbal[3], Mustabshir Hussain[4], Hassan Raza[5], Sania Maqbool[6*]**

[1*]Junior Registrar Trauma & Orthopaedics at University Hospital, Birmingham
[2]Senior House Officer, Paediatric Neurosurgery Department, The Children's Hospital, Lahore
[3]SHO, Plastic Surgery Department, Shaikh Zayed Hospital, Lahore
[4]SHO, Cardiology Department, Shaikh Zayed Hospital, Lahore
[5]Medical Officer, Gujranwala Medical College and Teaching Hospital, Gujranwala
[6*]Lecturer, Department of Physical Therapy, Lahore College for Women University LCWU, Lahore

***Corresponding Author:** Dr. Hassan Raza, Dr. Sania Maqbool
*E-mail(s): razahassan597@gmail.com & saniamaqbool28@gmail.com

## ABSTRACT

### Background

Platelet-rich plasma (PRP) injections have recently been marketed as a form of autologous cell therapy under the banner of regenerative medicine despite limited scientific evidence on its use for treating peripheral nerve lesions (ED).

### Aim

To evaluate the evidence on PRP treatment for nerve lesions and determine the current trends in provision of this treatment.

### Methods

A critical review of the literature on PRP using the MEDLINE, EMBASE, COCHRANE, PUBMED databases.

### Outcomes

This systematic review focuses on the clinical use of, regulation of, and evidence for PRP in the treatment of peripheral nerve lesion.

### Results

There are a huge number of published peer-reviewed articles demonstrating clinical outcomes pertaining to the use of PRP for nerve lesions in human. The technique and clinical application for PRP is currently patented, with a global total of 71different research studies and literature findings positive used of PRP for nerve lesions.

### Conclusion

Despite a global presence of PRP clinics and ongoing active marketing and public interest in regenerative medicine, no scientific evidence has been published to establish an evidence-based risk-benefit profile for PRP use for ED in humans.

**Keywords**: peripheral nerve; entrapment; regeneration; platelet-rich plasma; dextrose.

## INTRODUCTION:

PRP, an autologous biological product with a high concentration of growth factors, has been employed to support tissue regeneration and wound healing. To achieve the restorative effects, it has been suggested that the platelet concentration in PRP and its derivatives should be three times higher than in whole blood .But the addition of white blood cells (WBCs) to platelets in PRP results in the release of pro-inflammatory cytokines at the site of the injury, resulting in an intensified inflammatory response. (1)

Pure platelet-rich plasma (P-PRP), leukocyte- and platelet-rich plasma (L-PRP), platelet-rich fibrin rich in leukocytes (P-PRF), and platelet-rich fibrin deficient in leukocytes (P-PRF) are only a few of the many PRP preparation variations available. Second-generation PRP is the name given to platelet concentrates that are high in fibrin (PRF).(2)

A growing number of musculoskeletal problems are being treated using regenerative medicine procedures, which entail regenerating human cells, tissues, or organs to restore normal function. The two most popular regenerative injection regimens in this regard are dextrose and platelet-rich plasma (PRP), and several in vitro and in vivo investigations have demonstrated their potential usefulness in fostering tissue repair.(3) Restoring nerve continuity with microsurgical tension-free anastomosis or autogenous nerve transplantation is currently the best treatment for nerve damage. Slow nerve regeneration and incomplete surgical functional recovery are not improved by this therapeutic strategy. Thus, the emphasis of current study is on the regeneration and healing of peripheral nerve damage.(4) Nerve injuries can result in detrimental functional outcomes. Currently, autologous nerve graft offers the best outcome for segmental peripheral nerve injury.(5)

Due to the significant growth factors present in platelet-rich plasma (PRP), which can summon differentiated cells to the injured area and boost mitotic activity and angiogenesis, PRP plays a significant role in tissue regeneration. PRP consequently affects tendon, ligament, muscle, and bone regeneration. Additionally, PRP has demonstrated efficacy in mending wounds in plastic surgery.(6)

There is some indication that platelet-rich plasma (PRP), which contains a variety of growth factors and can help with peripheral nerve regeneration, may have a biological impact on Schwann cells (SCs).(7) In vivo tissue engineering techniques including molecular intervention and scaffolding have recently shown promising results.

Platelet-rich plasma (PRP) and fibrin scaffolds produced using this technology are showing increasing evidence in both preclinical and clinical contexts that they contain significant adjuvant therapeutic promise.(8)

A biological adjuvant in peripheral nerve injuries (PNIs) and neuropathies, platelet-rich plasma (PRP) products have significant therapeutic potential as a neuroprotective, neurogenic, and neuroinflammatory therapeutic modulator system and as an enhancer of sensory and motor functional nerve-muscle unit recovery.(9)

Regrowing damaged axons, myelination, restoring synaptic connections, and regaining physiological capabilities are all examples of nerve regeneration. PRP, which contains growth factors that affect wound healing and is generated from the patient's own blood, is utilized in a variety of surgical specialties, including oral and maxillofacial surgery. Growth factors and proteins are released from the alpha granules of platelets when they are triggered either ex vivo or in vivo.(10)

Poor functional results, inadequate nerve repair, and the loss of sensory and motor function are all common consequences of PNI. Partial healing, muscle atrophy, persistent discomfort, and extreme weakening follow .In order to reinnervate and reach distal motor endplates; axons frequently need to regenerate over vast distances at a sluggish rate of 1-3 mm per day.(11)

Diverse PRP preparations may have diverse clinical results due to heterogeneity in preparation methods with varying spin cycles and additional activators. Numerous investigations in basic science have determined that PRP has the ability to control the neuroinflammatory environment and aid in the remodeling and healing of neural tissue.(2)

Autologous platelet-rich plasma (PRP) therapy has been identified as a viable adjuvant therapy for accelerating the recovery from tissue damage and surgical wounds. PRP is created by sequentially centrifuging entire blood, and when activated, it can release a wide variety of antimicrobial proteins,

cytokines, and growth factors.
The ability of PRP to eliminate necrotic tissue, eradicate infections, and accelerate wound healing is due to these bioactive chemicals. PRP is becoming more and more popular as a supplement to treat or prevent chronic bone or wound infections as well as postoperative infections.(12)

## METHODOLOGY:

The objective of this literature review was to focus on conditions of medical peripheral nerve injuries or lesions and consolidate the available evidence of PRP for practicing physicians. To identify the evidence, a search was conducted in the different databases like MEDLINE, EMBASE, COCHRANE, PUBMED for ‘‘platelet-rich plasma,’’ ‘‘platelet releasate,’’ ‘‘platelet gel,’’ ‘‘platelet-rich fibrin,’’ or ‘‘PRP’’ and ‘‘nerve lesions ,’’ ‘‘nerve injuries,’’ ‘‘peripheral nerves’’ ‘‘PRP for nerve pathologies,’’etc. The 547 identified search items were investigated further to include those that specified the method of autologous PRP or PRF preparation and delivery

Given the paucity of large, prospective studies available but also in efforts to limit bias, a sample size of\20 patients and rates of patient dropout [15% were set as exclusion criteria. Other exclusions were nonhuman research, studies not available in English, studies of postsurgical wounds, and studies investigating homologous PRP or other stem-cell products added into the PRP. The reference lists of relevant articles were also searched for potentially appropriate publications. In total,71 studies investigating ulcers were identified that fulfilled the inclusion criteria. Because of the heterogeneity of studies and widely variable outcome measures, comparison between PRP treatments and subsequent statistical analysis could not be performed. The quality of each individual study was evaluated and levels of evidence were assigned accordingly.

**Table II. Review of Articles**

| Author (year); study design | Intervention | Outcomes and Follow-up | Conclusion |
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| Sulong Wan et al (2022)[1]: Therapy for peripheral Nerve Regeneration. A critical review | Injectable platelet-rich fibrin with connective tissue graft for the treatment of deep gingival recession defects | Patients who received a single dose of PRP had better postoperative (Boston carpal tunnel questionnaire, BCTQ) and neuroelectrophysiological recovery | This article summarizes the literature in recent years to illustrate the effect of PRP on peripheral nerve regeneration from mechanism to clinical application, and prospects for the application of PRP to peripheral nerve |
| Sowa Y. et al (2022)[2] ; Further Evidence That Platelet-Rich Plasma Promotes Peripheral Nerve Regeneration Through Enhancing Schwann Cells Function | The hSCs were cultured with various concentrations of PRP in 5% FBS/DMEM. Cell viability, microchemotaxis, flowcytometry, and quantitative RT-PCR assays were performed to assess proliferation, migration, cell cycle, and neurotrophic factor expression of the hSCs, respectively. hSCs were co-cultured with neuronal cells to assess their capacity to induce neurite extension. Neutralizing antibodies for platelet-derived growth factor-BB (PDGF-BB) and insulin-like growth factor-1 (IGF-1) were added to the culture to estimate contribution of these cytokines to the hSC stimulation by PRP. | An addition of PRP at 5% strongly elevated proliferation, migration, and neurotrophic factor production of hSCs. Both PDGF-BB and IGF-1 may be involved in mitogenic effect of PRP on hSCs, while PDGF-BB may also play an important role in the migration-inducing effect of PRP. Neutralization of both PDGF-BB and IGF-1 cancelled promoting effect of PRP on neurite-inducing activity of hSCs. | The present findings may suggest the optimal concentration of PRP for hSC stimulation as well as potential mechanisms underlying the activation of hSCs by PRP, which may be quite useful for the PRP therapy for peripheral nerve regeneration. |
| **3.Mourad S. I.et al (2022); (3)**Efficacy of platelet-rich fibrin and tacrolimus on facial nerve regeneration: an animal study | Thirty healthy 7-week-old albino rats were used. The left FN was damaged by crushing in all rats. Three random groups of rats were formed: group 1, untreated; group 2, treated with PRFM; group 3, treated with PRFM plus topical tacrolimus. Functional recovery and histological and | At 4 weeks, blinking reflex recovery was more rapid in group 3 than in groups 2 and 1 (4.30 +/- 0.48, 3.40 +/- 0.52, and 2.20 +/- 0.42, respectively); the difference was statistically significant (P = 0.001). Histologically, group 3 showed more apparent | Immunohistochemical caspase-3 evaluation of the axon area revealed a significant difference between group 2 (PRFM alone; 8.67 +/- 0.029) and group 3 (PRFM plus topical tacrolimus; 4.42 +/- 0.028) (P = 0.001). Group 3 showed the greatest positive staining in the myelin sheath. |

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| | immunohistochemical evaluations were performed 4 and 8 weeks later | normal FN structures than the other groups. | Based on the results of this animal study, clinical studies should be performed to determine whether the combination of PRF and tacrolimus also improves the outcome of nerve regeneration in humans |
| 4.Pandunugrahadi Muhammad et al (2022)**([4]);** The Optimal Timing of Platelet-Rich Plasma (PRP) Injection for Nerve Lesion Recovery: A Preliminary Study | This is an experimental in vivo research using male New Zealand white rabbits in the randomized control group posttest only design. Samples were divided into 5 groups (1 control group and 4 treatment groups). The control group without PRP injection and treated groups injected immediately after nerve injury, 3 days, 7 days, and 14 days afterward. Nerve regeneration was evaluated by the histology specimen sacrificed on day 21. Inflammation cells and endoneurium vacuoles were counted as mean percentage of five nerve fragments in each injured nerve sample specimen | Inflammation cells and vacuole cells increased significantly when PRP was administered 3 days after injury (group 2) (respectively, 14 +/- 6.7 and 56.6 +/- 11.6) compared to all treatment groups ($p < 0.005$) (control group, respectively, 6 +/- 2.6 and 15.7 +/- 9.5). On the other hand, significantly lower endoneurium vacuoles and inflammation cells were found on "the day 14" sample group (respectively, 5 +/- 1.3 and 5.2 +/- 1.6) compared to all other groups ($p < 0.005$). | This study found that the best time for injecting PRP for nerve regeneration is 14 days after injury. |
| 5.Das S. JMS et al (2020) [(5);] A clinical study of single intraneural platelet-rich plasma injection in peripheral nerve repair. A case study | A hospital based Non-Randomized control trial was conducted in a tertiary hospital setup in Manipur, India, for a period of 2 years. This study was done on 12 patients who underwent peripheral nerve repair. Materials and method The selected sample will be divided into two groups. Control group was treated with direct tension-free epineural microsurgical repair and the treatment group was treated with direct tension-free epineural microsurgical repair along with intraoperative infiltrating the nerve stumps perineurally and intraneurally with a single dose of autologous PRP injection | A total of 12 patients were included in the study, who were divided into 2 groups i.e., Case group and Control group, with 6 patients in each. The two groups were comparable with regards to patient characteristics, nerve injured and time interval to surgery. The patients in the case group, had significant improved outcome, when compare to control group, in terms of subjective (quickDASH) and objective tests (2-point discrimination, sensory recovery, motor strength and nerve conduction studies). | In this study we found that intraoperative PRP injection can improve the clinical outcome after nerve repair in traumatic nerve injury |
| 6. Senturk Fatma **et al (2020) (6);** Effects of titanium prepared platelet rich fibrin on facial nerve regeneration: an experimental study | Twenty-seven New Zealand male rabbits were used in this study, divided into three experimental groups. Group 1, the sham group (n=7); Group 2, the suture group (n=10); and Group 3, the suture+T-PRF group (n=10). In Group 1, the facial nerve trunk was dissected, and no additional surgical intervention was performed. For Group 2, a transection was made to the facial nerve trunk and the nerve endings were sutured together. In Group 3, nerve endings were sutured after transection, and a titanium-prepared platelet-rich fibrin membrane was wrapped in a tube around the damaged area | Subjects in Group showed improvement in whisker movement and ear drop one week earlier than Group 2. In Group 3, the nerve stimulation threshold required to trigger the compound muscle action potential had returned to values similar to the preoperative control values (11.31+/-2.16V) by 5 weeks postoperatively (12.51+/-3.97V), (p=0.249)., | Titanium-prepared platelet-rich fibrin administration contributed to partial nerve healing both on a functional and an electrophysiological level. |
| 7.Feng B et al (2020) [(7);] Efficacy of autologous epineurium small gap coaptation combined with platelet-rich plasma, nerve growth factor, and nerve fragments in the repair of damaged peripheral nerves | Fifty rabbits were randomly divided into five groups. The control group was treated using the traditional suture method. The remaining four groups were treated using the autologous epicardial small gap model. The autologous | The nerve conduction velocity in experimental group D was higher than in other groups. Compared to other groups, the nerves of the experimental group had small gaps, as well as no collapse or displacement. | PRP can significantly improve the microenvironment in the small gap and promote peripheral nerve regeneration and functional |

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| | epithelium bridged the small gap in experimental group A, and 0.4 mL of nerve growth factor was injected into the small gap. Growth factor was administered in experimental group B, and an appropriate amount of shredded nerve fragments were added into the small gap in experimental group C. Meanwhile, 0.4 mL of PRP was injected into the small gap in experimental group D. Neuroelectrophysiological and histological assessments were performed 12 weeks after surge | The diameter of the regenerative nerve was consistent with that of the normal nerves. In the experimental group, a higher number of myelinated nerve fibers were observed in the small gap, and the arrangement was more regular. Extensive angio-genesis was observed among the nerve fibers. More mature Schwann cells proliferated, and the cytoplasm was clear. Mitochondrial swelling was not obvious, and the epicardium and fascia were intact. | |
| 8.Vares Peyman et al (2020)(8) ; Effects of Platelet-Rich Fibrin/Collagen Membrane on Sciatic Nerve Regeneration | the effects of leucocyte/platelet-rich fibrin (L-PRF) with or without a collagen membrane as a supporter on crushed sciatic nerve healing in a rat model. Recovery of motor function and electrophysiologic measurements were evaluated at 4 weeks | The whole number of myelinated axons, peripheral nerve axon density, average nerve fiber diameter (mum), and G-ratio were analyzed and compered among the groups. Functional, electrophysiological, and histological evaluations showed no significant difference among the groups with the exception of the L-PRF with collagen membrane groups that showed relatively positive effects | Alternative treatment approaches to improve the regeneration ability of damaged peripheral nerves are currently under investigation. |
| 9.Zhu Yaqiong et al (2020) [(9)] ; Platelet-Rich Plasma Combined with Low-Dose Ultrashort Wave Therapy Accelerates Peripheral Nerve Regeneration | The synergistic effects of serial ultrasound-guided PRP injections combined with low-dose USWs radiation on peripheral nerve regeneration in a crush injury model. Fifty rabbits were equally and randomly divided into normal control, model, USW, PRP, and PRP+USW groups. The neurological function, electrophysiological recovery, and histological and morphological evaluation of regenerated nerves, as well as a targeted muscle recovery assessment, were performed to investigate the regenerative effect. | PRP+USW group had the better early axonal regeneration and displayed the earliest positive compound muscle action potential among the treatment groups. At postintervention week 12, a histological evaluation showed similar expression of the S-100 protein in the PRP+USW and normal control groups. Moreover, the morphological assessment revealed a significant increase in the myelinated nerve fiber density and diameter and myelin sheath thickness compared with the USW and PRP groups | The volume in the PRP+USW group, and an ultrasound examination of the targeted muscle showed the best improvement in stiffness and perfusion parameters at 12 weeks after crush injury. Thus, serial ultrasound-guided PRP injections combined with low-dose USW radiation exert a synergistic effect on accelerating functional axon recovery and decreasing atrophy of the target muscles in a crush injury model. |
| 10.Samadian Hadi et al (2020)(10) ; Sophisticated polycaprolactone/gelatin nanofibrous nerve guided conduit containing platelet-rich plasma and citicoline for peripheral nerve regeneration: In vitro and in vivo study | We construct an electrospun nerve guide conduit (NGC) based on polycaprolactone (PCL) and gelatin filled with citicoline bearing platelet-rich plasma (PRP) gel as a treatment for PNI. The NGCs fabricated from PCL/Gel polymeric blend using the electrospinning technique. The characterizations demonstrated that the fabricated nanofibers were straight with the diameter of 708+/-476nm, the water contact angle of 78.30+/-2.52degree, the weight loss of 41.60+/-6.94% during 60days, the tensile strength of 5.31+/-0.97MPa, and the young's modulus of 3.47+/-0.10GPa. | The in vitro studies revealed that the PCL/Gel/PRP/Citi NGC was biocompatible and hemocompatible. The in vivo studies conducted on sciatic nerve injury in rats showed that the implantation of PCL/Gel/PRP/Citi NGC induced regeneration of nerve tissue, demonstrated with histopathological assessmentsAn addition of platelet-rich plasma at 5% strongly elevated proliferation, migration, and neurotrophic factor production of human | Moreover, the sciatic function index (SFI) value of -30.3+/-3.5 and hot plate latency time of 6.10+/-1.10s revealed that the PCL/Gel/PRP/Citi NGCs recovered motor and sensory functions. Our findings implied that the fabricated NGC exhibited promising physicochemical and biological activates favorable for PNI treatment. |

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| | | Schwann cells. | |
| 11.Sowa Y.et al (2019)[11] Involvement of PDGF-BB and IGF-1 in Activation of Human Schwann Cells by Platelet-Rich Plasma | Human Schwann cells were cultured with various concentrations of platelet-rich plasma in 5% fetal bovine serum/Dulbecco's Modified Eagle Medium. Cell viability, microchemotaxis, flow cytometry, and quantitative real-time polymerase chain reaction assays were performed to assess proliferation, migration, cell cycle, and neurotrophic factor expression of the human Schwann cells. | Both PDGF-BB and IGF-1 may be involved in mitogenic effect of platelet-rich plasma on human Schwann cells, and PDGF-BB may also play an important role in the migration-inducing effect of platelet-rich plasma. | This study may suggest the optimal concentration of platelet-rich plasma for human Schwann cell stimulation and potential mechanisms underlying the activation of human Schwann cells by platelet-rich plasma, which may be quite useful for platelet-rich plasma therapy for peripheral nerve regeneration. |
| 12.Li L. Saudi et al (2019) [12] Platelet-rich plasma can release nutrient factors to promote facial nerve crush injury recovery in rats | We have designed a novel two-component matrix (SPRPix) for the encapsulation of directly reprogrammed human neural precursor cells (drNPC). The matrix is comprised of 1) a solid anisotropic complex scaffold prepared by electrospinning a mixture of recombinant analogues of the spider dragline silk proteins - spidroin 1 (rS1/9) and spidroin 2 (rS2/12) - and polycaprolactone (PCL) (rSS-PCL), and 2) a "liquid matrix" based on platelet-rich plasma (PRP). The combination of PRP and spidroin promoted drNPC proliferation with the formation of neural tissue. | Differentiation of drNPCs generated large numbers of βIII-tubulin and MAP2 positive neurons as well as some GFAP-positive astrocytes, which likely had a neuronal supporting function. Interestingly the SPRPix microfibrils appeared to provide strong guidance cues as the differentiating neurons oriented their processes parallel to them. Implantation of the SPRPix matrix containing human drNPC into the brain and spinal cord of two healthy Rhesus macaque monkeys showed good biocompatibility: no astroglial and microglial reaction was present around the implanted construct | The human drNPCs survived for the 3 month study period and differentiated into MAP2 positive neurons. Tissue engineered constructs based on SPRPix exhibits important attributes that warrant further examination in spinal cord injury treatment. |
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## RESULTS:

| **Author (year); study design** | **RESULTS** |
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| 1.Sulong Wan et al (2022)[1];<br>Evaluation of platelet Rich Plasma Therapy for peripheral Nerve Regeneration. A critical review | In the aspect of peripheral nerve injury, the number of related literature is increasing yearly. Although most studies are still based on animal experiments and *in vitro* studies, the clinical application of PRP in the treatment of peripheral nerve injury is also increasing. There is substantial evidence of the effectiveness of PRP in promoting nerve regeneration. Studies focusing on combining PRP, stem cell into tissue engineering nerve in the treatment of nerve defects are also on the increase and the technology is expected to replace nerve transplantation. |
| 2. Sowa Y. et al (2022)[2] ;<br>Further Evidence That Platelet-Rich Plasma Promotes Peripheral Nerve Regeneration Through Enhancing Schwann Cells Function | The present findings may suggest the optimal concentration of PRP for hSC stimulation as well as potential mechanisms underlying the activation of hSCs by PRP, which may be quite useful for the PRP therapy for peripheral nerve regeneration. |
| 3.Mourad S. I.et al (2022); (3)<br>Efficacy of platelet-rich fibrin and tacrolimus on facial nerve regeneration: an animal study | At 4 weeks, blinking reflex recovery was more rapid in group 3 than in groups 2 and 1 (4.30 ± 0.48, 3.40 ± 0.52, and 2.20 ± 0.42, respectively); the difference was statistically significant ($P$ = 0.001). Histologically, group 3 showed more apparent normal FN structures than the other groups. Immunohistochemical caspase-3 evaluation of the axon area revealed a significant difference between group 2 (PRFM alone; 8.67 ± 0.029) and group 3 (PRFM plus topical tacrolimus; 4.42 ± 0.028) ($P$ = 0.001). Group 3 showed the greatest positive staining in the myelin sheath. Based on the results of this animal study, clinical studies should be performed to determine whether the combination of PRF and tacrolimus also improves the outcome of nerve regeneration in humans. |
| 4.Pandunugrahadi Muhammad et al (2022)**[4];**<br>The Optimal Timing of Platelet-Rich Plasma (PRP) Injection for Nerve Lesion Recovery: A Preliminary Study | Inflammation cells and vacuole cells increased significantly when PRP was administered 3 days after injury (group 2) (respectively, 14 ± 6.7 and 56.6 ± 11.6) compared to all treatment groups () (control group, respectively, 6 ± 2.6 and 15.7 ± 9.5). On the other hand, significantly lower |

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| | endoneurium vacuoles and inflammation cells were found on "the day 14" sample group (respectively, $5 \pm 1.3$ and $5.2 \pm 1.6$) compared to all other groups (). *Conclusion.* This study found that the best time for injecting PRP for nerve regeneration is 14 days after injury. |
| 5.Das S. JMS et al (2020) [5];<br>A clinical study of single intraneural platelet-rich plasma injection in peripheral nerve repair.<br>A case study | A total of 12 patients were included in the study, who were divided into 2 groups i.e., Case group and Control group, with 6 patients in each. The two groups were comparable with regards to patient characteristics, nerve injured and time interval to surgery. The patients in the case group, had significant improved outcome, when compare to control group, in terms of subjective (quickDASH) and objective tests (2-point discrimination, sensory recovery, motor strength and nerve conduction studies). Conclusion: In this study we found that intraoperative PRP injection can improve the clinical outcome after nerve repair in traumatic nerve injury |
| 6.Santruk Fatima **et al (2020) (6);**<br>Effects of titanium prepared platelet rich fibrin on facial nerve regeneration: an experimental study | Subjects in Group showed improvement in whisker movement and ear drop one week earlier than Group 2. In Group 3, the nerve stimulation threshold required to trigger the compound muscle action potential had returned to values similar to the preoperative control values (11.31 ±2.16V) by 5 weeks postoperatively (12.51 ±3.97V), ($p$ = 0.249). Titanium-prepared platelet-rich fibrin administration contributed to partial nerve healing both on a functional and an electrophysiological level. |
| 7.Feng B et al (2020) [7];<br>Efficacy of autologous epineurium small gap coaptation combined with platelet-rich plasma, nerve growth factor, and nerve fragments in the repair of damaged peripheral nerves | The nerve conduction velocity in experimental group D was higher than in other groups. Compared to other groups, the nerves of the experimental group had small gaps, as well as no collapse or displacement. The diameter of the regenerative nerve was consistent with that of the normal nerves. In the experimental group, a higher number of myelinated nerve fibers were observed in the small gap, and the arrangement was more regular. Extensive angiogenesis was observed among the nerve fibers. More mature Schwann cells proliferated, and the cytoplasm was clear. Mitochondrial swelling was not obvious, and the epicardium and fascia were intact.PRP can significantly improve the microenvironment in the small gap and promote peripheral nerve regeneration and functional recovery. |
| 8.Vares Peyman et al (2020)(8) ;<br>Effects of Platelet-Rich Fibrin/Collagen Membrane on Sciatic Nerve Regeneration | It was observed that by week 4, the L-PRF/collagen membranes had higher mean axon counts per nerve compared with the other groups ($P < 0.05$) The L-PRF /collagen membrane group also demonstrated a trend toward significantly higher axon counts than other groups. Similar results were seen when analyzing nerve fiber diameter. More importantly, there is statically difference between the L-PRF/collagen membrane and other groups |
| 9.Zhu Yaqiong et al (2020) [9] ;<br>Platelet-Rich Plasma Combined with Low-Dose Ultrashort Wave Therapy Accelerates Peripheral Nerve Regeneration | Our results showed that the PRP+USW group had the better early axonal regeneration and displayed the earliest positive compound muscle action potential among the treatment groups. At post-intervention week 12, a histological evaluation showed similar expression of the S-100 protein in the PRP+USW and normal control groups. Moreover, the morphological assessment revealed a significant increase in the myelinated nerve fiber density and diameter and myelin sheath thickness compared with the USW and PRP groups. The morphometry of the target muscles indicated the lowest reduction in the percent volume in the PRP+USW group, and an ultrasound examination of the targeted muscle showed the best improvement in stiffness and perfusion parameters at 12 weeks after crush injury. Thus, serial ultrasound-guided PRP injections combined with low-dose USW radiation exert a synergistic effect on accelerating functional axon recovery and decreasing atrophy of the target muscles in a crush injury model. |
| 10.Samadian Hadi et al (2020)(10) ;<br>Sophisticated polycaprolactone/gelatin nanofibrous nerve guided conduit containing platelet-rich plasma and citicoline for peripheral nerve regeneration: In vitro and in vivo study | The *in vivo* studies conducted on sciatic nerve injury in rats showed that the implantation of PCL/Gel/PRP/Citi NGC induced regeneration of nerve tissue, demonstrated with histopathological assessments. Moreover, the sciatic function index (SFI) value of $-30.3 \pm 3.5$ and hot plate latency time of $6.10 \pm 1.10$ s revealed that the PCL/Gel/PRP/Citi NGCs recovered motor and sensory functions. Our findings implied that the fabricated NGC exhibited promising physicochemical and biological activates favorable for PNI treatment. |
| 11.Sowa Y.et al (2019)**(11)**<br>Involvement of PDGF-BB and IGF-1 in Activation of Human Schwann Cells by Platelet-Rich Plasma | The results of this study concludes that the factors other than PDGF-BB and IGF-1 played a no negligible role in the effect of platelet-rich plasma (group e versus group d versus group c) (Fig. 5).1 However, we are skeptical about the authors' views on clinical use of plateletrich plasma, especially in long allografts.1 In Figure 5, group c (NG108-15 cells plus human Schwann cells without platelet-rich plasma), neurite length appears significantly increased compared to group b (NG108- 15 cells plus 5% platelet-rich plasma without human Schwann cells). This indicates that |

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| | human Schwann cells are important for neurite growth by themselves, and for platelet-rich plasma to be effective, human Schwann cells need to be present. Long autografts and allografts are known to have senescence of human Schwann cells in the center of the grafts and would therefore render the platelet-rich plasma ineffective. |
| 12.Li L. Saudi et al (2019) [12] Platelet-rich plasma can release nutrient factors to promote facial nerve crush injury recovery in rats | Platelet-rich plasma promotes the recovery of vibrissae movement, eyelid closure, and electrophysiological function in a rat model of nerve crush injury. Hematoxylin and eosin staining, toluidine blue staining, and electron microscopy showed significant recovery of Schwann cells and axons in the PRP group. Polymerase chain reaction results showed that PRP releases growth factors, which include nerve growth factor and brain-derived neurotrophic factor. Immunohistochemistry also demonstrated higher levels of S-100 protein expression in the PRP group compared to the other groups. |

In the results evaluated in study no.3 depicts that P = 0.001 at 4 weeks between Group 1 (control) and Group 2 (PRF). P = 0.001 at 4 weeks between group 1 (control) and group 3 (PRF with tacrolimus). P = 0.001 at 4 weeks between group 2 (PRF) and group 3 (PRF with tacrolimus). Set at P 0.05 for statistical significance. P = 0.059 indicates a significant difference between the groups.

At 4 weeks, the post hoc test (Tukey) found statistically significant differences (P = 0.001) between groups 1 and 2. Additionally, statistically significant differences between groups 1 and 3 and groups 2 and 3 were found (P = 0.001 and P = 0.001, respectively). In another study no.4 the difference between the control and other treatment groups was substantial. The results of a post hoc analysis using the Mann-Whitney test are shown in Table 2. In group 2 (3 days after injury), the post hoc analysis revealed a much higher amount of inflammatory cells than in any other group, indicating that this is the poorest period for PRP injection to stimulate nerve regeneration.

**Table 1**

Inflammation cells found on histopathologic analysis on each treatment groups.

| | Treatment group (*N*) | Mean ± SD (%) | *P* value |
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| Inflammation cells in mean percentage area of 5 nerve bundle fragments | Control (7) | 6 ± 2.6 | 0.001[a] |
| | Group 1 (7) | 16 ± 11.6 | |
| | Group 2 (7) | 29 ± 3.3 | |
| | Group 3 (7) | 14 ± 6.7 | |
| | Group 4 (7) | 5 ± 1.3 | |

Table 1 lists the number of cells associated with inflammation that were found on the samples. Group 2 has the largest number of inflammation cells (29 3.3), followed by group 1 (16 11.6), group 3 (14 6.7), the control group (6 2.6), and group 2 has the lowest number of inflammation cells (29 3.3).

Post hoc analysis comparing various groups of treatment with respect to endoneurium vacuoles found on histopathologic analysis.

| Treatment groups | Mean ± SD | *P* value |
|---|---|---|
| Control and immediately after injury | 15.7 ± 9.5 and 33.6 ± 29 | 0.149[a] |
| Control and 3 days after nerve injury | 15.7 ± 9.5 and 56.6 ± 11.6 | 0.002[a*] |
| Control and 7 days after nerve injury | 15.7 ± 9.5 and 39.6 ± 25.3 | 0.003[b*] |
| Control and 14 days after nerve injury | 15.7 ± 9.5 and 5.2 ± 1.6 | 0.023[b*] |
| Immediately after injury and 3 days after nerve injury | 33.6 ± 29 and 56.6 ± 11.6 | 0.023[a*] |
| Immediately after injury and 7 days after nerve injury | 33.6 ± 29 and 39.6 ± 25.3 | 0.774[a] |
| Immediately after injury and 14 days after nerve injury | 33.6 ± 29 and 5.2 ± 1.6 | 0.020[a*] |
| 3 days and 7 days after nerve injury | 56.6 ± 11.6 and 14 ± 6.7 | 0.003[a*] |
| 3 days and 14 days after nerve injury | 56.6 ± 11.6 and 5.2 ± 1.6 | 0.002[a*] |
| 7 days and 14 days after nerve injury | 39.6 ± 25.3 and 5.2 ± 1.6 | 0.003[b*] |

[a]Mann–Whitney. [b]Independent sample test. *Significant difference ($p < 0.05$).

In the results of the study mentioned above depicts that during the procedures, four subjects—two from each of Groups 1 and 2—died. No other issues were noticed. The investigation of those subjects' study findings continued for several weeks after their passing. CMAP amplitude values brought on by stimulation above the threshold. Distinctly different from Group 1 (p 0.05) in comparison. Significantly different from the week before surgery (p 0.05).Clearly distinct from the left side (p 0.05).

Table 1 The right side warning threshold values of the experimental groups (mean ± SD, volt).

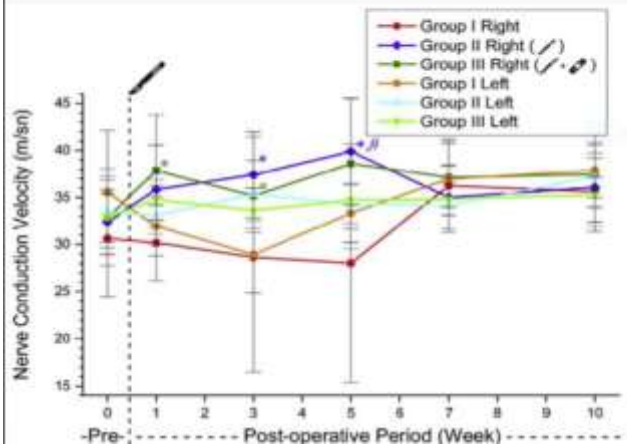
| | Group 1 | | Group 2 | | Group 3 | |
|---|---|---|---|---|---|---|
| | Right | Left | Right | Left | Right | Left |
| Preoperative | 10.64 ± 3.47 | 12.02 ± 5.13 | 8.64 ± 2.04 | 10.21 ± 4.39 | 11.31 ± 2.16 | 10.85 ± 3.96 |
| 1st week | 10.21 ± 3.34 | 10.46 ± 2.46 | 19.32 ± 7.02 | 9.07 ± 3.70 | 23.72 ± 4.99 | 9.61 ± 2.10 |
| 3rd week | 10.09 ± 3.58 | 8.57 ± 1.93 | 18.34 ± 4.76 | 6.94 ± 3.08 | 26.57 ± 9.92 | 7.52 ± 3.07 |
| 5th week | 8.53 ± 1.50 | 8.20 ± 3.01 | 17.68 ± 6.45 | 8.56 ± 2.95 | 16.59 ± 4.19 | 8.24 ± 2.36 |
| 7th week | 8.74 ± 2.52 | 8.67 ± 4.03 | 15.36 ± 4.14 | 8.53 ± 2.82 | 15.75 ± 3.06 | 7.55 ± 2.37 |
| 10th week | 7.82 ± 3.25 | 8.86 ± 3.43 | 11.43 ± 2.88 | 7.21 ± 2.80 | 12.51 ± 3.97 | 7.54 ± 3.73 |

Table 2 Comparison of the right side postoperative warning threshold values with preoperative values within the groups (p-value).

| | Preop-postop 1st week | Preop-postop 3rd week | Preop-postop 5th week | Preop-postop 7th week | Preop-postop 10th week |
|---|---|---|---|---|---|
| Group 1 | 1.000 | 0.999 | 0.780 | 0.865 | 0.609 |
| Group 2 | <0.001 * | 0, 001 * | 0.004 * | 0.051 | 0.839 |
| Group 3 | <0.001 * | <0.001 * | 0.249 | 0.438 | 0.996 |

* Significant differences $p < 0.05$.

Figure 5 The nerve conduction velosity in the experimental groups. * Significantly different compared to Group 1 (p<0.05). # Significantly different compared to the preoperative week (p<0.05).




In the study mentioned above depicts the results that Groups A, B, C, and D all had considerably faster sciatic nerve conduction velocities than the control group did (P 0.01).In the meantime, group D's sciatic nerve conduction velocity was higher than that of groups B and C's (P 0.01 in both cases) (Table 1).

**Table 1.** Comparison of neurophysiological examination 12 weeks after operation

| Group | N | Conduction velocity (m/s) | F | P |
|---|---|---|---|---|
| Control | 10 | 8.38±2.04 | 93.66 | < 0.01 |
| A | 10 | 12.81±1.78 | | |
| B | 10 | 19.63±3.19 | | |
| C | 10 | 24.66±2.91 | | |
| D | 10 | 29.61±3.68 | | |

The homogeneity test of variance: the variance is homogeneous (P=0.304). One-way ANOVA results: F=93.66, P < 0.01 (significant difference).

In the study no.8 mentioned above here concludes that there were significant differences between the groups that had collagen membrane/L-PRF. After 4 weeks following surgery, it was discovered that the SFI values of the grafted groups with collagen membrane/L-PRF had a substantial impact on functional recovery.

**Table S1. The SFI values for control, collagen membrane alone and with to L-PRF, and L-PRF groups. Error bars: +/- 2SE.**

| Samples | Before surgery | Day 1 | Day 7 | Day 14 | Day 28 |
|---|---|---|---|---|---|
| **Control** | -3.61±7.04 | -76.44±12.03 | -62.64±21.20 | -49.75±8.11 | -43.25±3.37 |
| **L-PRF** | -6.24±7.14 | -74.87±8.59 | -62.10±12.22 | -40.36±9.85 | -20.80±3.02 |
| **Collagen membrane** | -6.45±3.31 | -78.22±5.88 | -61.76±9.08 | -41.93±7.91 | -19.81±4.18 |
| **Collagen membrane/L-PRF** | -9.67±3.07 | -79.30±4.85 | -61.51±8.57 | -35.42±5.22 | -8.70±2.66 |

**Table S2. Electrophysiologic measurements among groups.**

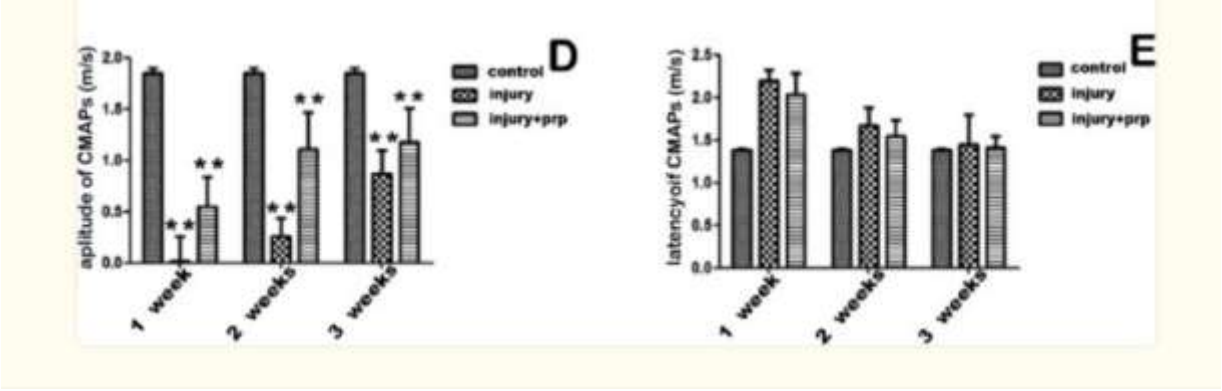
| Samples | N | C | L-PRF | M | M/L-PRF |
|---|---|---|---|---|---|
| **Amplitude (mV)** | 56.4±1.1 | 12.8±1.2 | 28.8±2.1 | 22.8±1.1 | 35.6±1.3 |
| **Latency (s)** | 1.2±0.1 | 2.7±0.2 | 2.9±0.1 | 2.8±0.2 | 2.1±0.1 |

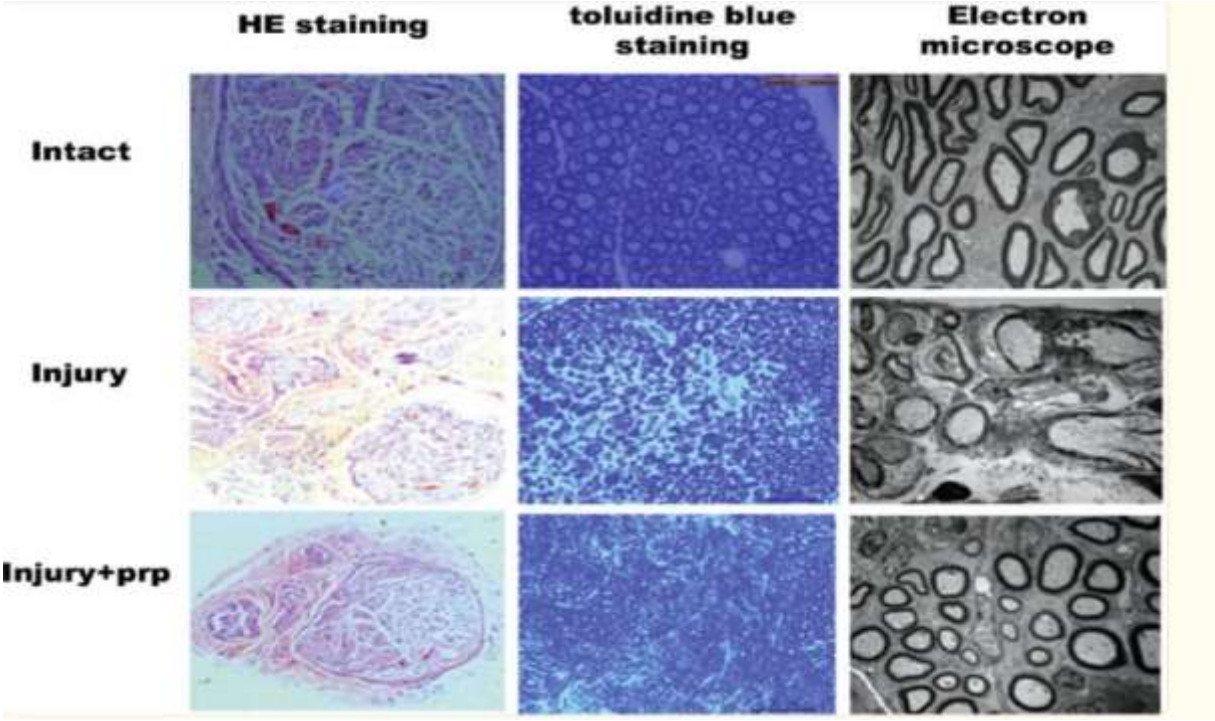
Abbreviations: the non-treated nerve (N), the damaged nerve (C), the L-PRF, the collagen membrane (M), the collagen membrane/L-PRF (M/L-PRF). Significant difference (P< 0.05).
In the study mentioned above depicts that According to the results, autograft had the best outcomes, followed by PRP/Cit filled NGC, which was highest. At both 4 and 12 weeks after surgery, the implantation of PCL/Gel NGCs dramatically improved SFI, as seen in Fig. 4. At 4 weeks after implantation, citicoline reduced SFI from 72.4 to 2.2 to 60.3 to 4.1, and at 12 weeks after surgery, it decreased from 50.5 to 3.5 to 30.3 to 1.9

Table 1
Characterization results of the fabricated PCL/Gel nanofibers.

| Sample | Water contact angle (°) | Weight loss (%) | | Porosity (%) | Mechanical properties | |
|---|---|---|---|---|---|---|
| | | 30 days | 60 days | | Tensile strength (MPa) | Young's modulus (GPa) |
| PCL | 103.77 ± 2.36 | 8.63 ± 1.43 | 13.13 ± 1.12 | 52.57 ± 6.69 | 6.17 ± 6.35 | 3.40 ± 0.85 |
| PCL/Gel | 78.30 ± 2.52 | 27.33 ± 1.90 | 41.60 ± 6.94 | 51.27 ± 6.27 | 5.31 ± 0.97 | 3.47 ± 0.10 |

In the last study the results confined that Electromyography was performed on three groups of animals 7, 14, and 21 days following surgery. Shown are representative data for each group of three rats. The time from nerve stimulation to muscle depolarization is represented by the incubation period on the graph. Following surgery, CMAPs were seen in the 3 groups. The D) amplitude and E) latency of CMAPs at 1, 2, and 3 weeks after surgery were used to electrophysiologically evaluate the facial nerves of the rats in all groups. PRP stands for platelet-rich plasma, **p0.01.






Analysis of S-100 expression using immunohistochemistry. S-100 expression was discovered in the cytoplasm of damaged facial nerves by immunohistochemical labelling. S-100 expression was minimal in the control group's face nerves. Facial nerves and Schwann cells that had been damaged have significant levels of S-100 expression. S-100 expression levels did, however, decline after three weeks, with injury+PRP group levels of S-100 being lower than injury group levels.

**CONCLUSION:**

Peripheral nerve lesions continue to be a costly problem in modern healthcare, and PRP offers a promising alternative. PRP has been reported to improve both healing rates and symptoms, thus it could be used as an additional therapy to reduce the need for systemic drugs with undesirable side effect profiles.

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