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Role of Platelet Rich Plasma in Peripheral Nerve Repair

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Abstract:

Peripheral nerve injuries (PNIs) represent a significant clinical challenge, often resulting in impaired sensory and motor function, chronic pain, and long-term disability. Despite advances in microsurgical techniques, full functional recovery remains suboptimal in many cases. This has led to the exploration of adjunct therapies that can enhance the regenerative process. One promising approach is the use of Platelet-Rich Plasma (PRP), an autologous concentrate of platelets suspended in a small volume of plasma. PRP is rich in growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-b-eta (TGF-β), vascular endothelial growth factor (VEGF), and nerve growth factor (NGF), all of which play crucial roles in tissue healing, angiogenesis, and nerve regeneration. These bioactive molecules can stimulate Schwann cell proliferation, enhance axon growth, and reduce inflammation and apoptosis, creating a more favorable microenvironment for nerve repair. Several preclinical and clinical studies have demonstrated that PRP application—whether as an injection, gel, or scaffold—can accelerate nerve regeneration, improve functional outcomes, and reduce recovery time when used alongside surgical repair or grafting techniques. As a biocompatible, cost-effective, and minimally invasive therapy, PRP holds considerable potential in the management of PNIs. However, further research is needed to optimize its formulation, dosing, and delivery methods to maximize clinical efficacy.

Keywords: Peripheral nerve injuries**,** Platelet-Rich Plasma, nerve growth

.Introduction:

Peripheral nerve fibers, the most delicate and fragile structure of our body, are prone to get damaged easily by crush, compression, or trauma. Their damage manifests as abnormalities in the brain's communication with the target organs and muscles. Peripheral nerve injuries (PNIs) fall amongst the most pivotal issue regarding the health status because of their higher prevalence. These injuries affect motor activity and also cause the loss of sensation in the respective part of the body **(1).**

Plasma rich in growth factors (PRGFs) consists of a pool of growth factors (GFs), microparticles, and other bioactive mediators many of them trapped, through fibrin heparan sulfate-binding domains, in a three-dimensional transient fibrin matrix **(2)**

Alpha granules of platelets contain growth factors with mitogenic and chemotactic characteristics, such as PDGF, TGF-β, IGF-1, FGF and VEGF. Although they are not classical neutrophic factors, the effect of these GFs on nerve regeneration has been extensively studied. IGF-1 receptors exist in axons of peripheral nerve cells, nerve endings, SCs and cell bodies of the motor neurons. IGF-1 initiates the formation of bud growth, supports the forward extension of the nerve and inhibit apoptosis in motor, sensory and sympathetic neurons **(3).**

PRP is effective when applied following the ideal surgical nerve repair in a nerve transection model and was ineffective in cases of insufficient surgical repair The intra-operative use of autologous biological substances such as PRPs obtained from peripheral veins is low-cost, fast, single-stage technique that may enhance the nerve reparative procedure and the final functional outcome **(4).**

The results of the experimental animal study showed that enrichment of PRP or MSCs on nerve repair resulted in better functional recovery of the sciatic nerve with better structural indexes on regenerated nerve mainly on the distal part of the repair, indicating that biological adjuvant therapies may play a role in the peripheral nerve regeneration **(5).**

Degeneration and regeneration

The peripheral nerve injury elicits a cascade of changes in physiological as well as the metabolic level at the injured site and several changes also happen in the soma of injured neuron. A neuron is divided into two segments as distal and proximal to the site of injury and both are significantly different from each other **(6)**. The distal part suffers the Wallerian degeneration (WD) while the proximal part goes through the retrograde degenerative changes as well as instigates the process of regeneration. The process of WD initiates within 24-48 hours following injury and emerges at the distal end of the abrasion in case of severe nerve injury **(7).**

Wallerian degeneration is a cascade of stereotypical events in reaction to injury of nerve fibers. These events consist of cellular and molecular alterations, including macrophage invasion, activation of Schwann cells, as well as neurotrophin and cytokine upregulation **(8).**

. The skeleton of the axon disintegrates along with the myelin sheath and the remaining debris is cleared by infiltrated macrophages. Both peripheral and central nerve injury can lead to Wallerian degeneration, but subsequent regeneration differs between the nerve types. In the periphery, the nerve fibers can regenerate and reinnervate the tissues via growth factors produced by Schwann cells **(9).**

The pathophysiology of Wallerian degeneration is described in **(figure 1).**

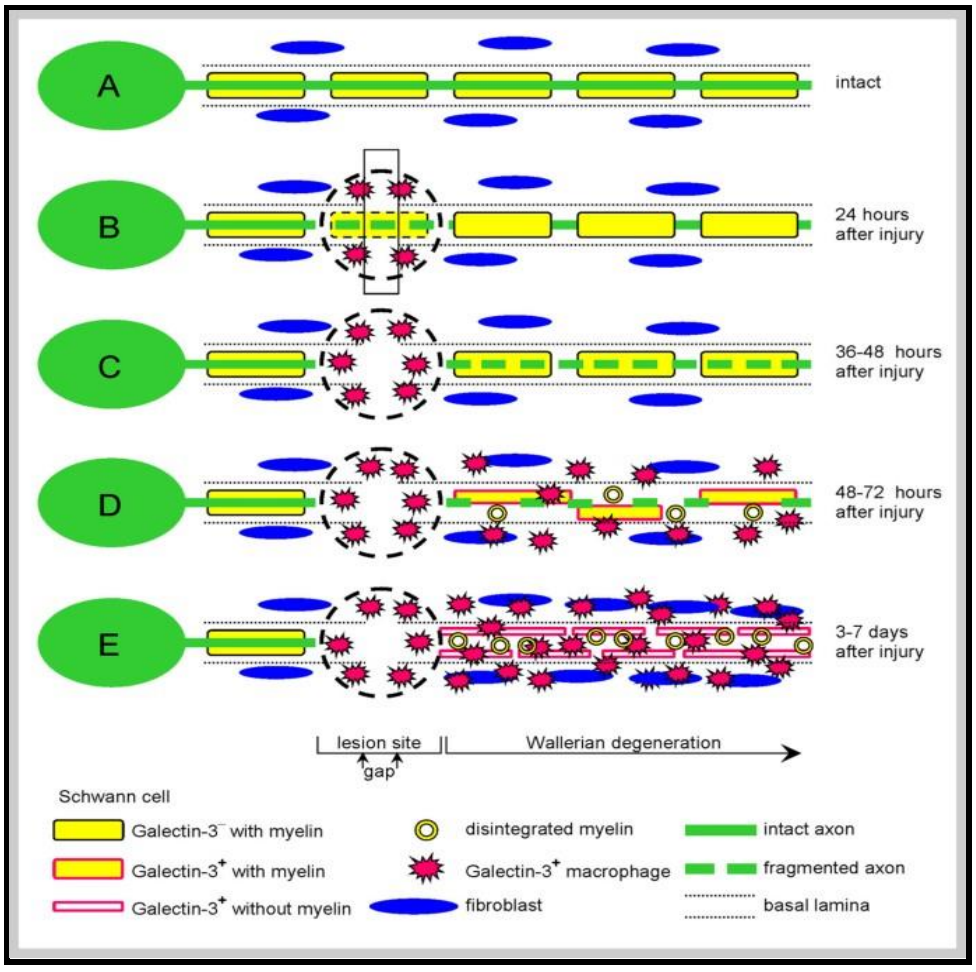

Figure (1): A schematic representation of some of the cellular characteristics of (A) intact and (B through E) injured PNS nerves that undergo normal Wallerian degeneration **(10).**

Schwann cells phagocytose axonal and myelin debris until empty endoneurial tubes remains. Macrophages are recruited to the area releasing growth factors, which stimulate Schwann cell and fibroblast proliferation. Schwann cells fill the empty endoneurial tubes in organized longitudinal columns called bands of Bungner. This supportive environment is critical for successful axonal regeneration **(11) (Figure 2).**

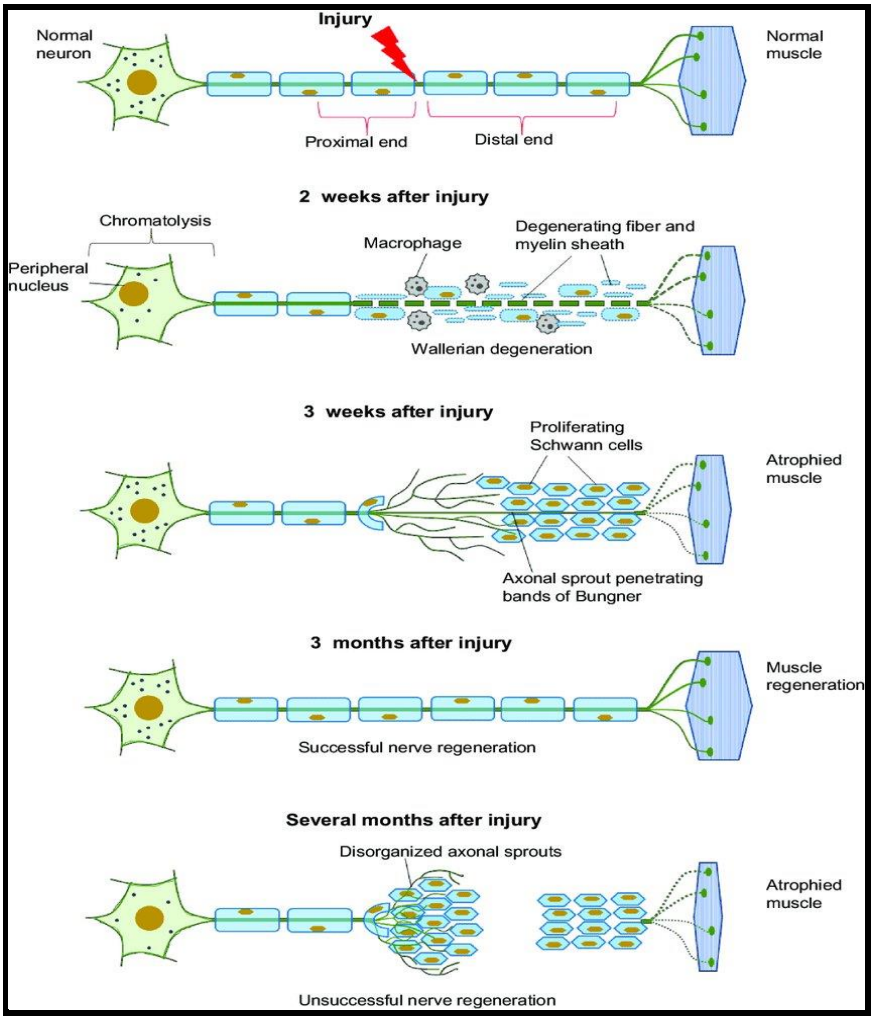

Figure (2): Activated Schwann cells (SCs) and recruited macrophages phagocytose axonal and myelin debris following a nerve injury. Neurotrophic factors stimulate SCs to replicate and extend over arrays of extracellular matrix proteins to form the bands of Büngner, which guide the extending growth cone across the site of injury. Prolonged denervation can result in poor nerve regrowth and target scar formation **(12).**

Regenerating axons sprout from the proximal stump at different times rather than all at once, leading to "staggered" nerve regeneration. Nerve fibers initially grow in random, asynchronous directions before developing a dominant pathway across the injury site **(12).**

This phenomenon, in addition to the slow rate of regeneration (1 mm/day in humans), contributes to a lengthy time requirement for nerve recovery, especially in the setting of a proximal nerve injury. Trophic signaling from nearby Schwann cells support and guide axons from the proximal nerve stump as they grow **(13).**

Growth factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF) have demonstrated the ability to promote neurite outgrowth. By enhancing the extension of regenerating axons, these growth factors may contribute to more targeted and organized reinnervation, reducing the risk of neuroma formation. infused the PLLA/β-tricalcium phosphate (β-TCP) nerve conduit with chitosan (CS)–hyaluronic acid (HA) hydrogel loaded with NGF to achieve the sustained release of growth factors at the site of peripheral nerve injury **(14).**

If the regenerated axons fail to reach the distal end and intertwine with the proliferation of connective tissue, forming a coiled mass known as traumatic neuroma. The prominent symptom is the existence of typical percussion pain and tenderness in the region of pain hypersensitivity (dysesthesia) or neuroma, which can impact the patient's work and daily life, causing significant distress to the patient **(15) (Figure 3).**

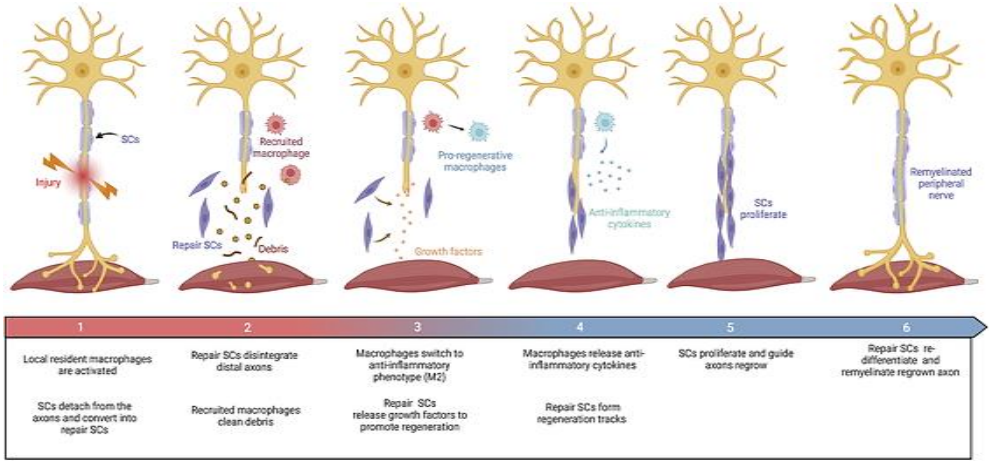

Figure (3): Schematic diagram summarizing the repair process in the PNI. Damage to peripheral nerves: (1) SCs were rapidly responded and converted into repair SCs. Local resident macrophages are activated. (2) Repair SCs disintegrate distal axons and recruit macrophages to clear debris. (3) Repair SCs release growth factors to promote axon regrowth. Macrophages switch to an anti-inflammatory phenotype (M2). (4) Repair SCs form regeneration tracks to guide axon regrowth. Macrophages secrete anti-inflammatory factors under the stimulation of the local injured microenvironment. (5) SCs proliferate and guide axon regeneration. (6) Finally, SCs transform into myelinating SCs and remyelinate the regenerated axon**.(16).**

Mechanism of nerve injury

There are numerous mechanisms of injury for peripheral nerves. The three most common mechanisms of injury for peripheral nerves are stretch related, lacerations, and compressions respectively. Radiation, electricity, injection, crush, cold injury, and intra-neural and extra-neural pathologies could also result in peripheral nerve injuries **(17)**

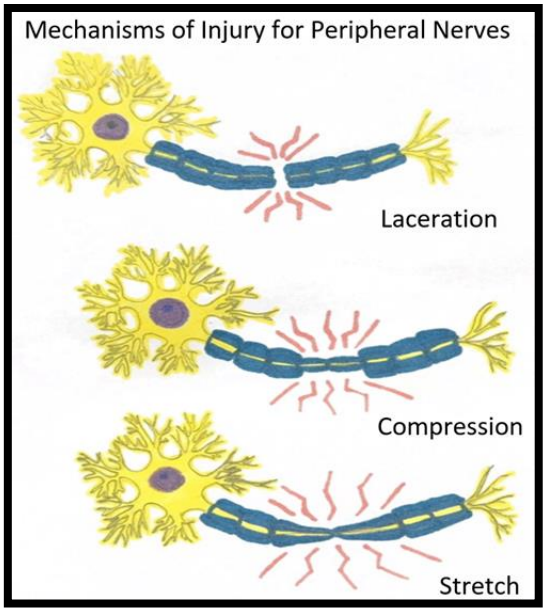

Figure (4): Peripheral nerve injury mechanisms **(17).**

Due to the elastic nature of peripheral nerves, stretch related injuries can occur if a traction force is too strong for the nerves elasticity. If the traction force exceeds the nerves stretch abilities, a complete tear could occur. However, it is more common that the continuity of the nerve is retained during this type of injury **(18).**

Laceration injuries are the second most common types of peripheral nerve injuries. With this mechanism of injury, a nerve is severed partially or fully by some type of sharp object. Most common lacerations are from knives, broken glass, metal shards etc **(19).**

Compression nerve injuries typically affect large-caliber nerves that cross over bony structures or between rigid surfaces. Acute compression (e.g. Saturday Night Palsy) and chronic compression injuries (e.g. carpal tunnel syndrome) are the two main subcategories for compression injuries. Compressive nerve injuries can result in complete functional loss of both motor and sensory function even though the nerve fibers are still intact **(18).**

PRP preparation

PRP is prepared by a process known as differential centrifugation. In differential centrifugation, acceleration force is adjusted to sediment certain cellular constituents based on different specific gravity. There are many ways of preparing PRP. It can be prepared by the PRP method or by the buffy-coat method **(20).**

Procedure

- **PRP method (Figure 5)**
  - Obtain Whole blood (WB) by venipuncture in acid citrate dextrose (ACD) tubes
  - Do not chill the blood at any time before or during platelet separation.
  - Centrifuge the blood using a 'soft' spin.
  - Transfer the supernatant plasma containing platelets into another sterile tube (without anticoagulant).
  - Centrifuge tube at a higher speed (a hard spin) to obtain a platelet concentrate.
  - The lower 1/3rd is PRP and upper 2/3rd is platelet-poor plasma (PPP). At the bottom of the tube, platelet pellets are formed.
  - Remove PPP and suspend the platelet pellets in a minimum quantity of plasma (2-4 mL) by gently shaking the tube **(Figure 5) (21).**

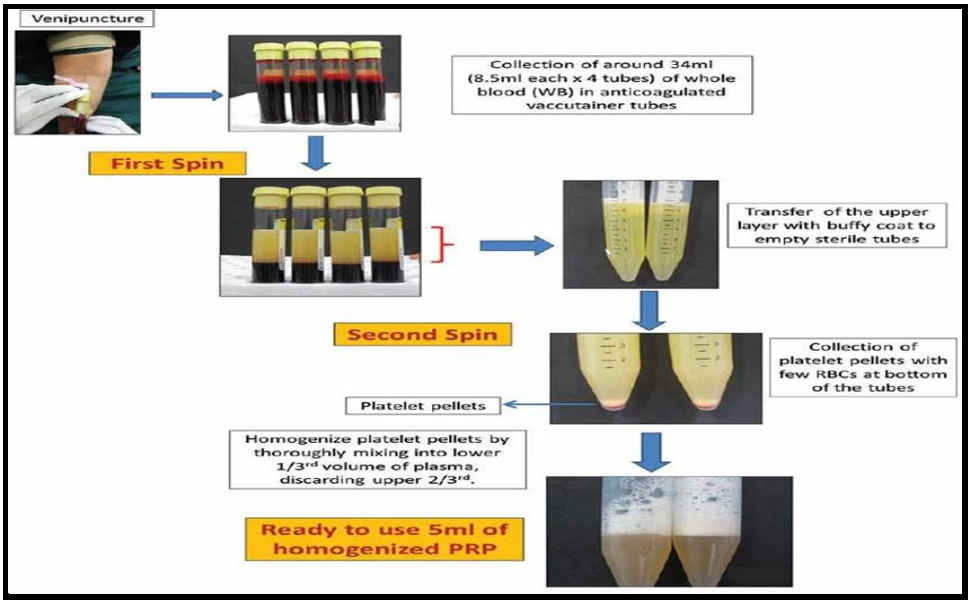

Figure (1): Flow chart describes a double centrifugation process of PRP **(21)**

- **Buffy coat method**
  - WB should be stored at 20°C to 24°C before centrifugation.
  - Centrifuge WB at a 'high' speed.
  - Three layers are formed because of its density: The bottom layer consisting of RBCs, the middle layer consisting of platelets and WBCs and the top PPP layer.
  - Remove supernatant plasma from the top of the container.
  - Transfer the buffy-coat layer to another sterile tube.
  - Centrifuge at low speed to separate WBCs or use leucocyte filtration filter **(22).**

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