
# The Role of Platelet-Rich Plasma in Peripheral Nerve Injuries

# Periferik Sinir Yaralanmalarında Trombosit Zengin Plazmanın Tedavideki Yeri

Sinir Yaralanması ve Trombosit Zengin Plazma / Nerve Injury and Platelet-Rich Plasma

Sevgi Ikbali Afsar, Oya Umit Yemisci, Nuri Cetin
Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, Başkent Üniversitesi, Tıp Fakültesi, Ankara, Türkiye

**Özet**

Sinir rejenerasyon ve reinnervasyon süreci, nöronla ilişkili sayısız faktörü içeren karmaşık bir olaydır. Sinir rejenerasyonunun geliştirilmesi için birçok büyüme faktörü kullanılmıştır. Koagülasyon kaskatında önemli rolleri ile bilinen trombositler, içerdikleri büyüme faktörleri ile doku tamirinde de rol oynamaktadır. Bu büyüme faktörlerinin özelliği, farklılaşmamış hücrelerin kemotaktik ve mitotik özelliklerini arttırarak anjiogenezi başlatması ve dokunun iyileşmesine katkıda bulunmasıdır. Trombosit Zengin Plazma (TZP), tam kanın santrifüj edilmesi ile elde edilen ve suprafizyolojik dozlarda büyüme faktörü içeren plazma komponentidir. Başlıca maksillofasiyal ve kardiyovasküler cerahi olmak üzere tıbbın birçok dalında uzun zamandır kullanılmakta olan TZP, son yıllarda tendon ve kıkırdak doku rejenerasyonunu arttırıcı etkisi ile kas iskelet sistemi hastalıklarında da uygulanmaya başlanmıştır. TZP'nin perferik sinir iyileşmesine olan katkısı ise daha yakın dönemde araştırılmaya başlanmış ve umut verici sonuçlar elde edilmiştir.

**Anahtar Kelimeler**

Trombosit Zengin Plazma; Periferik Sinir Yaralanması; Sinir Rejenerasyonu

**Abstract**

Nerve regeneration and reinnervation process is a complex event involving numerous neuron-related factors. Many growth factors have been used to stimulate nerve regeneration. In addition to their well-know role in hemostasis, platelets also play an important role in tissue repair due to the growth factors they contain. These growth factors initiate angiogenesis by increasing the chemotactic and mitotic characteristics of the undifferentiated cells, thus contributing to tissue healing. Platelet-rich plasma (PRP) which is obtained by centrifugation of whole blood is a plasma component that contains supraphysiological doses of growth factors. PRP has been used in many branches of medicine including maxillofacial and cardiovascular surgery in particular and is currently being used in musculoskeletal system disorders due to its effect on increasing tendon and cartilage tissue regeneration. Evaluation of the contribution of PRP to peripheral nerve healing has started more recently and encouraging results have been obtained.

**Keywords**

Platelet-Rich Plasma; Peripheral Nerve Injury; Nerve Regeneration

DOI: 10.4328/JCAM.3822 Received: 08.08.2015 Accepted: 31.08.2015 Printed: 01.12.2015 J Clin Anal Med 2015;6(suppl 6): 905-8
Corresponding Author: Sevgi Ikbali Afsar, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, Başkent Üniversitesi, Tıp Fakültesi, Bahçelievler, 06490 Ankara, Türkiye.
T.: +90 3122126650 F.: +90 3122157840 E-Mail: ikbaliafsar@hotmail.com

## Introduction

The main objective in the treatment of peripheral nerve injuries is ensuring functional improvement of the nerve by re-establishing structural integrity at the lesion site. Despite the developments in understanding the regeneration mechanisms and technical improvements and modern surgical equipment in microsurgery, functional improvement in peripheral nerves following serious injuries commonly presents unsatisfactory results [1]. This review includes information regarding the role of platelet-rich plasma (PRP) which has an increasingly widespread use in the treatment of peripheral nerve injuries, its biological mechanism of action, and review of the literature for relevant studies.

## The Pathophysiology of Peripheral Nerve Damage

Injury to the peripheral nerve causes wallerian and axonal degeneration distal to the damaged segment. Wallerian degeneration is a pathological process that results when a nerve fiber is cut or crushed, in which the part of the axon separated from the neuron cell's body degenerates distal to the injury. The axonal degeneration is followed by degradation of the myelin sheath. Regeneration process starts following degeneration and regeneration occurs through Schwann cells [2]. Regenerations starts at the distal end of the portion of the nerve fiber proximal to the lesion. Sprouts are sent to the neurolemma of the injured nerve and if it the gap is not too wide it reaches the end, grows into it and advances between the nerve sheaths reinnervating the target tissue growth factors such as nerve growth factor, brain-derived neurotrophic factor, ciliary neurotrophic factor and glial cell-derived neurotrophic produced by Schwann cells play a role in the modulation of healing [3,4]. However, this improvement depends on many factors. Regeneration usually develops slowly and the healing may not be complete. Axonal degeneration develops due to metabolic disorders at the axon of the nerve fibers and this effects commonly result in axon destruction at the distal regions [3].

## Platelet-Rich Plasma

PRP; which is obtained by centrifugation of whole blood is a plazma component containing higher concentration of platelets than the whole blood. In addition to their primary role in hemostasis, platelets play an instrumental role in the initiation and regulation of healing with the growth factors, cytokines and other bioactive factors they contain [5]. They trigger an inflammatory response, chemotaxis, atherothrombosis, coagulation and cellular differentiation regulation with autocrine and paracrine self-activation. They contain three types of granules; alpha, lysosomal and dense core granules. The cytokines, chemokines, clotting factors and growth hormones that are found especially in the alpha and core granules play a main role in hemostasis and injury healing [6,7]. Resting platelets at the injury site are activated with thrombin within a 10-minute period after coagulation and secrete the coagulation and growth factors within their alpha granules [5]. An important point here is that the growth factors become activated prior to their release. If the platelets are damaged during the PRP preparation, activation of the growth factors fail resulting in an ineffective PRP administration. Acid citrate dextrose type A anticoagulant and low gravitational power is therefore necessary during centrifugation [8,9]. Alpha granules of the platelets contain mitogenic and chemotactic growth factors such as insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF) [10]. These factors play a role in cell regulation, differentiation, proliferation, chemotaxis, angiogenesis and matrix synthesis during healing following injury [5]. Their common characteristics are initiating angiogenesis by increasing the chemotactic and mitotic characteristics of the undifferentiated cells and making a positive contribution to tissue healing [1].

## The Characteristics of Growth Factors

PRP contains growth factors in supraphysiological amounts and can be called as a regenerative treatment like stem cell, prolotherapy and nitric oxide treatments. The aim of PRP is to activate the repair mechanisms of the body. Unlike conventional treatments, the general principle is to trigger inflammation rather than suppress it. PRP has been in use for about 30 years. It was first used in 1987 by Ferrari et al [11] to decrease the transfusion of homologous blood products following open heart surgery. Use in maxillofacial and plastic surgery started in the 1990s followed by application in musculoskeletal problems [12]. PRP's effect of accelerating the healing process in tendon, ligament, cartilage and muscle injuries has been demonstrated in various animal trials and clinical studies [13,14]. Although the relevant factors are not classical neurotrophic factors other than IGF-1, their effect on nerve regeneration is being investigated in recent years and promising results have been reported. IGF-1 was reported to play a role as a neurotrophic factor after nerve incisions and increase the protein and lipid synthesis necessary for regeneration in in vivo studies. The positive effects of local IGF-1 administration on the nerve lesion have been shown in several studies [10]. Experimental data show that growth factors such as TGF-β, FGF and PDGF stimulate axonal growth and increase Schwann cell proliferation and mitogenesis [15].

## IGF-1

IGF-I is an important mediator in all stages of healing and especially in the inflammatory and proliferative stages and has many effects such as protein synthesis, myoblast and fibroblast proliferation, and matrix and collagen synthesis stimulation [16]. IGF-I can be secreted in various structures such as Schwann cells, skeletal muscle and capillaries. Its receptors are present especially in the axons, nerve endings and motor neuron cell bodies in the peripheral nervous system [17]. IGF-I has been shown to stimulate initial sprouting and subsequent elongation of axons in the motor, sensory and sympathetic nerves by acting as a neuropathic factor and providing protection from apoptosis [18]. Systemic IGF-1 treatment has been reported to increase muscle reinnervation and prevent motor neuron death after neonatal sciatic nerve axotomy [19], furthermore increased axonal sprouting and axonal regeneration rate have been shown at the damaged nerve following local IGF-I administration [17]. Tiangco et al [20] reported that local IGF-I infusion improves muscle functions quicker than placebo in the end-to-side nerve repair model. IGF-I has also been suggested to play a role in repair after hypoxic ischemic damage in many tissues and also to be of critical importance for myelinization, which will not occur in its absence [17].

## VEGF

VEGF is a potent angiogenic factor. It has been reported to stimulate proliferation and migration of endothelial cells and play a role in angiogenesis and increasing vascular permeabil-

ity. VEGF has also been shown to stimulate axonal sprouting and increase Schwann cell proliferation in experimental studies [21]. VEGF has been reported to play a role in axon growth and Schwann cell proliferation and act as a neurotrophic factor and enhance nerve cell survival through FLK-1 activation. Additionally, VEGF increases the survival of motor neurons with the deletion of the element responsible for hypoxia within VEGF that causes motor neuron degeneration [4].

**TGF- β**

TGF-β is a pro-inflammatory factor which plays a role as an immunosuppressant at the inflammatory phase. It can activate or inhibit growth of many cells in the presence of other growth factors and plays a role in macrophage chemotaxis [22]. It has many biological effects such as enhancing cell migration, fibroblast count and type I and III collagen expression. TGF-β also plays a role in angiogenesis and improves mechanical structure of the tendon during the healing process [5]. TGF-β has been shown to be secreted from the damaged nerve following injury. TGF-β2 and TGF-β3 regulate Schwann cell proliferation and differentiation [23].

**bFGF**

bFGF plays a key role in cell proliferation and migration. It stimulates angiogenesis and capillary endothelial cell proliferation. It is also involved in the formation of granulation tissue [24]. bFGF has been shown to play a role in nerve regeneration. bFGF can be synthesized and secreted from damaged axon, Schwann cell, endothelial cell, fibroblast and macrophages. bFGF and FGF-3 receptors have been shown to be upregulated at the lesion site at L5 sensory neurons and sciatic nerve after peripheral nerve injury [25]. An animal study conducted by Toledo et al [26] showed better functional results in facial nerve recovery in the group that received topical bFGF compared to the control group on the 6th day, while there was no difference between the two groups on the 16th day.

**PDGF**

PDGF plays an important role in embryonic development, cell proliferation, migration and angiogenesis. PDGF has been shown to be a potent mitogen for fibroblasts, muscle cells and mesenchymal cells [3]. PDGF-β is also a mitogenic factor for Schwann cells with its trophic activity on neurons. The increased expression after peripheral nerve injury supports that it plays a role in peripheral nerve regeneration [15].

**PRP Therapy and Its Effectiveness**

Recent studies have investigated the effect of PRP on peripheral nerve regeneration due to the factors it contains. Ding et al [27] applied local PRP following a crush injury they created in bilateral cavernous nerves of 24 rats in their study. The authors found functional and histological parameters of the PRP group to be significantly better and reported that PRP has a positive effect on cavernous nerve regeneration and functional improvement. The positive effects of PRP were demonstrated in a similar study conducted by Emel [17] et al where crush injury was formed at the sciatic nerve. Farrag et al [28] reported an improved functional outcome with the use of PRP in comparison with fibrin sealant or no bioactive agents on facial nerve regeneration in a rat model. Sarıgüney et al [10] suggested that the PRP following an ideal surgical repair in a peripheral nerve incision model provided a significant improvement in myelin thickness and latency, but had no marked positive effect on axonal regeneration. The authors also reported PRP to be ineffective if surgical repair was inadequate.

Besides studies reporting positive effects, there are also some studies which do not confirm a positive effect of PRP on healing process. Pişkin et al [29] reported that PRP had no positive effect on nerve regeneration in their studies where they reconstructed the nerve lesion with collagen tubes. Welch et al [30] suggested that PRP has no significant effect on healing after direct repair in a nerve transection model.

Despite the presence of animal studies investigating the effects of PRP on peripheral nerve improvement, we did not find any clinical studies on this subject in the literature. Ultrasound guided intraneural PRP injection in a 28-year-old male who had developed drop foot due to peroneal nerve paralysis after multiple ligament injury resulted in partial improvement in clinical and electrophysiological parameters 21 weeks later. The patient was able to walk and run without an orthosis [15].

PRP injection in or around a peripheral nerve plays a role in regeneration. The suggested mechanisms of action in various studies are as follows:

1. It increases the number of regenerating nerve fibers by improving the biological environment and thus supports axonal sprouting and remyelination;
2. It enhances migration of undifferentiated cells at the injury site and induces mitosis and angiogenesis;
3. Another possible effect is that the growth factors has a role in shifting the histological property of extra- and intraneural tissues from “stiff scar tissue or fibrosis” to “bening sof scar tissue” where axonal sprouting and reinnervation is possible [15,31].

In conclusion, PRP treatment has become common in musculoskeletal problems in recent years and has been shown to have positive effects also on nerve regeneration. Controlled long-term studies could be planned for its use in tendon and cartilage damage, chronic wound treatment and also peripheral nerve injury, and this is an open area for future research. PRP treatment seems to have a promising future when accompanied by proper rehabilitation once the ideal PRP preparation technique, correct dose and the correct timing are determined. Further studies are needed to guide the development of standard PRP injection procedures and to decide when they should be used.

*Competing interests*

The authors declare that they have no competing interests.

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*How to cite this article:*
Afsar S,İ, Yemisci O.U, Cetin N. The Role of Platelet-Rich Plasma in Peripheral Nerve Injuries. J Clin Anal Med 2015;6(suppl 6): 905-8.